JACC: CARDIOVASCULAR IMAGING
VOL. 3, NO. 12, 2010

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2010.08.018

# Progression of Coronary Artery Calcium Predicts All-Cause Mortality

Matthew J. Budoff, MD,* John E. Hokanson, MPH, PhD,‡ Khurram Nasir, MD, MPH,§ Leslee J. Shaw, PhD,‖ Gregory L. Kinney, PhD,‡ David Chow, BS,* Daniel DeMoss, BS,* Vivek Nuguri, BS,* Vahid Nabavi, BS,* Raghu Ratakonda, BS,* Daniel S. Berman, MD,† Paolo Raggi, MD‖

*Torrance and Los Angeles, California; Denver, Colorado; Pittsburgh, Pennsylvania; and Atlanta, Georgia*

**OBJECTIVES** This study examined a large cohort to assess whether progression of coronary artery calcium (CAC) was associated with all-cause mortality, and which among 3 different methods to assess CAC progression provided the best estimate of risk.

**BACKGROUND** Serial assessment of CAC scores has been proposed as a method to follow progression of coronary artery disease, and it has been suggested that excessive CAC progression may be a useful noninvasive predictor of the patient's risk of future events. However, the optimal method to measure calcium progression has not been well established.

**METHODS** The study sample consisted of 4,609 consecutive asymptomatic individuals referred by primary physicians for CAC measurement with electron beam tomography, who underwent repeat screening. Three general statistical approaches were taken: 1) the absolute difference between follow-up and baseline CAC score; 2) percent annualized differences between follow-up and baseline CAC score; and 3) difference between square root of baseline and square root of follow-up CAC score >2.5 (the "SQRT method").

**RESULTS** The average interscan time was 3.1 years, and there were 288 deaths. Progression of CAC was significantly associated with mortality regardless of the method used to assess progression ($p < 0.0001$). After adjusting for baseline score, age, sex, and time between scans, the best CAC progression model to predict mortality was the SQRT method (hazard ratio [HR]: 3.34; 95% confidence interval [CI]: 2.65 to 4.21; $p < 0.0001$), followed by a >15% yearly increase (HR: 2.98; 95% CI: 2.20 to 4.95; $p < 0.0001$). Progression was very limited and did not predict mortality in patients with baseline CAC = 0.

**CONCLUSIONS** The CAC progression added incremental value in predicting all-cause mortality over baseline score, time between scans, demographics, and cardiovascular risk factors. Serial assessment may have clinical value in assessing plaque progression and future cardiovascular risk. (J Am Coll Cardiol Img 2010;3:1229–36) © 2010 by the American College of Cardiology Foundation

From the *Department of Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California; †Department of Medicine, Cedars Sinai Medical Center, Los Angeles, California; ‡Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Denver, Colorado; §Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and the ‖Department of Medicine, Emory University, Atlanta, Georgia. The authors have reported that they have no relationships to disclose. Pim J. de Feyter, MD, PhD, served as Guest Editor for this article.

Manuscript received May 16, 2010; revised manuscript received July 21, 2010, accepted August 2, 2010.

JACC: CARDIOVASCULAR IMAGING, VOL. 3, NO. 12, 2010
DECEMBER 2010:1229–36

As a sensitive marker of atherosclerosis, coronary artery calcium (CAC) has been proposed as a method to follow progression of coronary artery disease. However, randomized clinical trials that used sequential computed tomography (CT) scanning failed to uniformly demonstrate that CAC can to be used to monitor response to medical therapy for atherosclerosis. In spite of this, 1 trial (1) and a few observations (2–4) have shown that the progression of CAC is a marker of increased risk of future cardiovascular events. Similarly, early trials using quantitative invasive coronary angiography conclusively demonstrated that atherosclerosis progression is a harbinger of adverse outcomes. Hence, excessive CAC progression may be a useful noninvasive predictor of the patient's risk of future events. Nonetheless, the evidence so far accumulated is small (1–4), and little is known of the development of CAC and its significance in subjects without CAC at baseline. Therefore, in this study, we verified the all-cause mortality of patients who underwent at least 2 CT scans for quantification of CAC. We further assessed which of several methods to estimate CAC progression was more accurate to predict mortality, and whether absence of CAC at baseline and its development are independently associated with all-cause mortality.

**ABBREVIATIONS AND ACRONYMS**

**CAC** = coronary artery calcium
**CT** = computed tomography
**EBT** = electron beam tomography
**HU** = Hounsfield unit
**MI** = myocardial infarction

## METHODS

The study sample consisted of 4,609 consecutive asymptomatic individuals referred by primary care physicians for CAC measurement with electron beam tomography (EBT), who underwent sequential scans at least 10 months apart. Patients underwent repeat scans, as per their primary physician, to assess change in atherosclerosis risk over time. This study received the approval of the institutional review board.

Patients with a history of coronary artery disease (i.e., admission to the hospital for chest pain, acute coronary syndrome, or myocardial infarction [MI], as well as prior coronary revascularization) were excluded. Also, patients suffering an interim event between scans were excluded. Subjects were given a risk-factor questionnaire to assess ethnicity and cardiovascular risk factors at baseline and follow-up. The presence and number of risk factors for each subject was calculated based on the National Cholesterol Education Program guidelines (5). Risk factors included: age (men age >45 years of age, women >55 years of age), current cigarette smoking, diabetes mellitus, history of premature coronary artery disease in first-degree relatives (men <55 years of age, women <65 years of age), hypertension, and hypercholesterolemia. Current cigarette smoking was defined as any cigarette smoking in the past month. Hypertension was defined by current use of antihypertensive medications or known and untreated hypertension. Hypercholesterolemia was defined as use of cholesterol-lowering medications or, in the absence of cholesterol-lowering medication use, as having a total serum cholesterol >200 mg/dl. Statin use was recorded at the time of scanning at both baseline and follow-up.

**Imaging methods.** All study subjects underwent 2 EBT scans using an Imatron C-300 computed tomography scanner (GE Imatron, South San Francisco, California). Thirty to forty 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 per tomographic slice, and total radiation dose was 0.6 mSv per scan.

**Calcium scoring.** All scans were analyzed with a commercially available software package (Neo Imagery Technologies, City of Industry, California). An attenuation threshold of 130 Hounsfield units (HU) and a minimum of 3 contiguous pixels were utilized for identification of a calcific lesion. Each focus exceeding the minimum criteria was scored using the algorithm developed by Agatston et al. (6), 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 anatomical sites (left main, left anterior descending, left circumflex, and right coronary artery) (7).

**Follow-up data collection.** Epidemiologic methods for follow-up included ascertainment of death by individuals who were blinded to historical and CAC score results (8,9). The occurrence of all-cause death was verified with the National Death Index (10). Individuals who underwent cardiovascular screening were followed for a mean of 5.4 ± 3.4 years after the second scan (range 1.0 to 16.0 years). Follow-up was completed in 100% of pa-

tients; there were 4,609 asymptomatic subjects in this sample.

**Statistical analysis.** Categorical variables comparing CAC patient subsets with historical variables were compared using 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 using a Cox proportional hazards model. The exposure variable is the progression of CAC score from baseline to follow-up scan. A priori methods for assessing progression were established. Three general approaches were taken: 1) the difference between follow-up and baseline absolute CAC score; 2) annualized percent differences between follow-up and baseline CAC score; and 3) previously established cut points for progression of CAC. Specifically:

Differences:

1. the absolute difference between the second and first measure of coronary calcium [$CAC_{(follow\text{-}up)} - CAC_{(baseline)}$],
2. the square root transformed difference [$\sqrt{CAC}_{(follow\text{-}up)} - \sqrt{CAC}_{(baseline)}$] (the "SQRT method") (11),
3. the natural logarithm plus 25 difference [(ln $CAC_{(follow\text{-}up)}$ + 25) − (ln $CAC_{(baseline)}$ + 25)]. (the "MESA method") (12),
4. the percent change [$(CAC_{(follow\text{-}up)} - CAC_{(baseline)})/CAC_{(baseline)}$].

Annualized differences:

The preceding 4 quantitative exposure variables divided by the time (in years) between the first and the second scan.

Pre-defined cut points:

1. a square root transformed difference $> 2.5$ (the difference beyond measurement error),
2. an annualized percent change $>15\%$.

The primary outcome was mortality verified from the National Death Index. Cox proportional hazard modeling was performed as implemented in SAS software (version 9.2, SAS Institute, Cary, North Carolina). Covariates included in all models were baseline CAC score, age, and sex. The length of time between the 2 scans was included as a covariate in models other than those using annualized difference in progression of CAC. Hazard ratios (HR) and 95% confidence intervals (CI) are presented for continuous variables, for 1 SD of continuous variables (standardized HR), and for the pre-defined cut points. Standardized hazard ratios allow for direct comparison of the effect size of the different continuous exposure methods. Model comparisons for different approaches for assessing progression of CAC scores within each study group used the Akaike information criterion for non-nested models. A lower Akaike information criterion indicates a better fit to the data. We then tested the best fitting models by adding cardiovascular disease risk factors (hypertension, diabetes, smoking, premature family history, and hypercholesterolemia) to assess for further adjustment of the hazard ratios.

To facilitate data interpretation and verification of proportional hazards assumptions, CAC scores were classified into the following categories: 0, 1 to 10, 11 to 100, 101 to 400, and $\geq 400$ (no identifiable plaque, minimal plaque, mild plaque, moderate plaque, and extensive atherosclerotic plaque burden, respectively) (13).

## RESULTS

The majority of patients (72.9%) were men, and the mean age was 60.1 ± 10.8 years. The mean interscan period (scan 1 to scan 2) was 3.1 ± 2.0 years (range 1 to 16 years). The prevalence of cardiovascular risk factors was high: current tobacco use: 6.2%; diabetes: 7.1%; high blood pressure: 23.6%, hypercholesterolemia: 41.2%; family history of coronary artery disease: 40.4%. The CAC score was a strong independent predictor of mortality (chi-square = 51.02, $p < 0.0001$). Mortality significantly increased with increasing CAC score.

There were 288 deaths among the 4,609 individuals in the full cohort (Table 1). A priori analyses were planned for all patients (Table 1), patients with baseline CAC score $>0$ (n = 2,866, 236 deaths) (Table 2), and those with baseline CAC score $>30$ (n = 2,183, 204 deaths) (Fig. 1).

For comparison purposes, subgroups were also examined: patients with baseline CAC = 0, the corollary of Table 2 (n = 1,743, 52 deaths) (Table 3), and those with baseline CAC $\leq 30$, the corollary of Table 3 (n = 2,426, 84 deaths).

Progression of CAC was significantly associated with mortality regardless of the method used to assess progression ($p < 0.0001$). Standardized HRs ranged from 1.12 (95% CI: 1.09 to 1.15) for annualized absolute CAC score increase, to 1.49 (95% CI: 1.39 to 1.59) for the MESA method. The best model to predict mortality, however, was the SQRT method (HR: 3.34, 95% CI: 2.65 to 4.21, $p < 0.0001$), followed by the method that uses an

**Table 1. Relationship Between Progression of Coronary Calcium and Mortality in the Full Cohort With No Exclusions (n = 4,609, 288 Deaths)**

| | HR (95% CI) | Standardized HR (95% CI) | p Value | AIC (Model Fit) |
|---|---|---|---|---|
| Absolute difference | 1.00 (1.00–1.00) | 1.21 (1.17–1.25) | <0.0001 | 4,424.570 |
| √ transformed difference >2.5 | 3.34 (2.65–4.21) | | <0.0001 | 4,382.633 |
| √ transformed difference | 1.09 (1.07–1.10) | 1.36 (1.30–1.43) | <0.0001 | 4,388.108 |
| Ln transformed + 25 difference | 2.73 (2.32–3.22) | 1.49 (1.39–1.59) | <0.0001 | 4,388.861 |
| % change | Cannot be calculated: % change = ∞ for baseline = 0 with any change. | | | |
| % change >15% | Cannot be calculated: % change = ∞ for baseline = 0 with any change. | | | |

Hazard ratio (HR) is the effect size for 1 unit change in the progression variable. Standardized HR represents the effect size for 1 SD of the progression variable. A lower Akaike information criterion (AIC) denotes a better model fit. Models are adjusted for baseline coronary calcium, age, sex, and the length of time between the 2 scans.
CI = confidence intervals; Ln = natural log.

annualized increase in CAC score >15% in those with baseline CAC >30 (HR: 2.98, 95% CI: 2.20 to 4.95, $p < 0.0001$), after controlling for baseline CAC, age, sex, and follow-up time between scans.

The effect of progression of CAC in individuals with CAC >0 at baseline is presented in Table 2. There were 236 deaths among 2,866 individuals. As in the full cohort, all methods for assessing progression of CAC were significantly related to mortality. The best model was again based on the SQRT method (HR: 3.66, 95% CI: 2.82 to 4.74, $p < 0.001$).

The same concept held true in individuals with a baseline CAC >30 (n = 2,183, 204 deaths), where, though all methods were predictive, the SQRT method provided the best fit of the data with a HR = 3.28 (95% CI: 2.48 to 4.32, $p < 0.001$). In secondary analyses, we examined the progression of CAC in individuals who had no detectable CAC at the baseline visit (n = 1,743, 52 deaths during follow-up) (Table 3). There was no significant relationship between development of CAC and mortality in these individuals.

Among individuals with baseline CAC score ≥30, progression of CAC was significantly associated with mortality. In this subgroup, the MESA method provided the best fit of the data (HR: 2.85; 95% CI: 2.20 to 3.70; $p < 0.001$).

Adjusting for cardiovascular disease risk factors did not appreciably alter the relationship between CAC progression and mortality. Progression adjusted for baseline CAC, age, sex, and time between scans yielded a HR = 3.34 (95% CI: 2.65 to 4.21). Further adjustment adding hypertension, hypercholesterolemia, diabetes, family history, and smoking resulted in HR = 3.32 (95% CI: 2.62 to 4.20, $p < 0.0001$). Similarly, HR did not change significantly for models of prediction including baseline CAC >0 (HR: = 3.62, 95% CI: 2.78 to 4.70, $p < 0.0001$) or CAC >30 (HR: 3.22, 95% CI: 2.43 to 4.27, $p < 0.0001$).

We further examined the combined effect of the presence of coronary calcium at baseline and progression of coronary calcium. Having CAC at baseline and significant progression of CAC was a significant predictor of future mortality (HR: 5.15, 95% CI: 3.67 to 7.22, $p < 0.0001$) (Table 4). Adjusting for cardiovascular disease risk factors did not appreciably alter the relationship between CAC progression and mortality (HR: 5.33, 95% CI: 3.74 to 7.60, $p < 0.0001$). Having baseline CAC without significant progression was marginally associated with mortality (HR: 1.42, 95% CI: 0.99 to 2.02, $p = 0.054$). Those without CAC at baseline but with significant progression of CAC did not have an increase in the rate of mortality ($p = 0.97$).

**Table 2. Relationship Between Progression of Coronary Calcium and Mortality in the Individuals With Baseline Coronary Calcium >0 (n = 2,866, 236 Deaths)**

| | HR (95% CI) | Standardized HR (95% CI) | p Value | AIC (Model Fit) |
|---|---|---|---|---|
| Absolute difference | 1.00 (1.00–1.00) | 1.25 (1.19–1.29) | <0.0001 | 3,426.888 |
| √ transformed difference >2.5 | 3.66 (2.82–4.74) | | <0.0001 | 3,378.945 |
| √ transformed difference | 1.08 (1.07–1.09) | 1.42 (1.34–1.49) | <0.0001 | 3,394.080 |
| Ln transformed + 25 difference | 2.60 (2.19–3.09) | 1.56 (1.44–1.69) | <0.0001 | 3,395.578 |
| % change | 1.00 (1.00–1.00) | 1.08 (1.02–1.14) | <0.0056 | 3,471.104 |
| % change >15% | 3.27 (2.43–4.41) | | <0.0001 | 3,407.634 |

HR is the effect size for 1 unit change in the progression variable. Standardized HR represents the effect size for 1 SD of the progression variable. A lower AIC denotes a better model fit. Models are adjusted for baseline coronary calcium, age, sex, and the length of time between the 2 scans.
Abbreviations as in Table 1.

Progression in the setting of increasing baseline CAC using set cut points (1 to 10, 11 to 100, 101 to 400, and >400) was associated with increasing risk of all-cause mortality (Fig. 2).

## DISCUSSION

This is the first large study following patients for 1 to 16 years and submitted to repeat CT scans, demonstrating incremental increase in mortality with progression of CAC over baseline score, time between scans, demographics, and cardiovascular risk factors. The CAC score in itself, as shown in multiple studies before, is a strong independent predictor of mortality. Because CAC can be located and quantified, changes over time can be analyzed so that progression or regression can be determined. At the moment, this is one of the few techniques that enables research to study this important question, as outcome may be related more to the continuous observation of changes over time than a single determination once in a lifetime. The observation that progression of CAC is associated with an adverse outcome extends prior reports linking CAC progression to coronary syndromes (1–3).

Prior smaller studies have suggested this effect. Raggi et al. (14) followed 269 asymptomatic subjects for 2.5 years after being submitted to sequential CT scans; of the 22 cardiovascular disease events, 20 occurred in patients with progression of CAC and 2 among patients without progression ($p < 0.01$). Another study of 225 subjects followed for an average of 3 years after the repeat CT scan, those with new cardiac events had a significantly greater annual change in CAC score than those who did not experience events (35% vs. 22%, $p = 0.04$) (15). Moreover, 78% of patients with events had >20% annual progression versus 37% of those not experiencing events ($p < 0.001$).

Among 817 asymptomatic subjects submitted to sequential CT scans approximately 2 years apart, mean absolute and percent changes in CAC score were 147% and 47%, respectively, in those who developed an MI after the second scan, compared with 63% and 26% in those without events ($p < 0.001$ and $p = 0.01$, respectively) (3). In another EBT study of 495 asymptomatic subjects receiving statins and submitted to more than 1 CT scan, ≥15% CAC progression was associated with a 17.2-fold (95% CI: 4.1 to 71.2) increased risk of MI when compared with patients without CAC progression ($p < 0.0001$) (4). These relatively small studies suggested that continued accumulation of CAC in asymptomatic individuals is associated with increased risk of future MI.

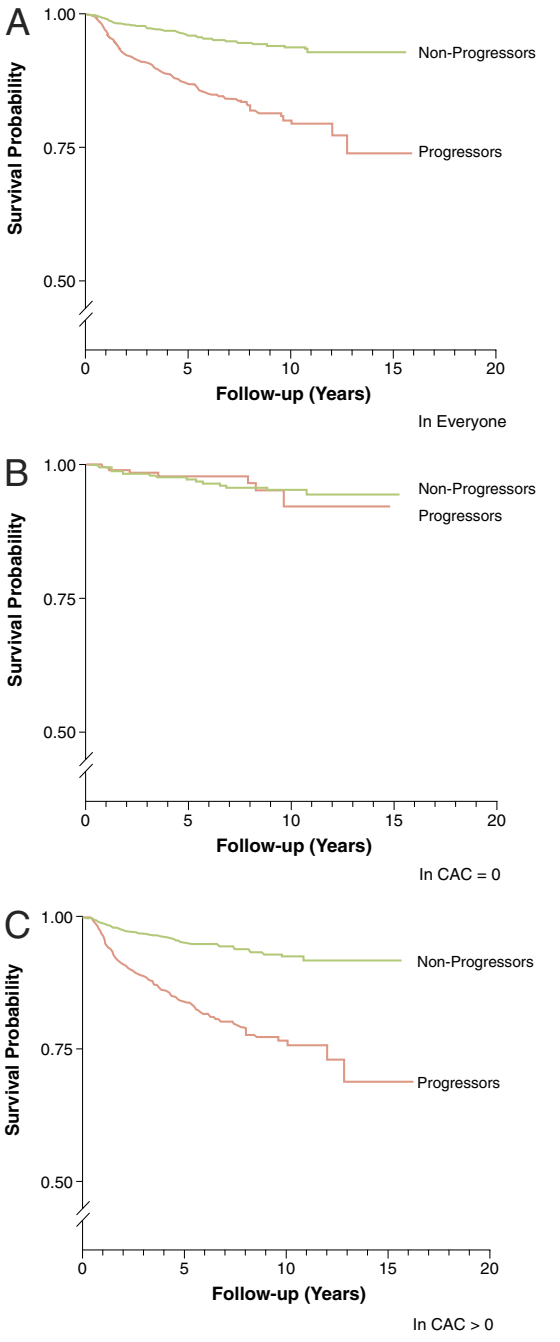


**Figure 1. Survival Curves Demonstrating Time to All-Cause Mortality**

Cox proportional hazards survival curves demonstrating time to all-cause mortality for patients with a yearly change using survival curve of progression based on our best fitting model of square root >2.5 according to baseline calcium score: **(A)** outcomes in all participants, **(B)** outcomes in those with coronary artery calcium = 0, and **(C)** survival in participants with coronary artery calcium >0. CAC = coronary artery calcium.

**Table 3. Relationship Between Progression of Coronary Calcium and Mortality in Individuals With Baseline Coronary Calcium = 0 (n = 1,743, 52 Deaths)**

| | HR (95% CI) | Standardized HR (95% CI) | p Value | AIC (Model Fit) |
|---|---|---|---|---|
| Absolute difference | 0.99 (0.97–1.03) | 0.99 (0.75–1.32) | 0.9605 | 707.492 |
| $\sqrt{}$ transformed difference >2.5 | 0.95 (0.43–2.10) | | 0.8914 | 707.476 |
| $\sqrt{}$ transformed difference | 0.93 (0.77–1.12) | 0.89 (0.65–1.20) | 0.4423 | 706.841 |
| Ln transformed + 25 difference | 0.82 (0.23–2.92) | 0.96 (0.72–1.27) | 0.7595 | 707.396 |
| % change | Cannot be calculated: % change = ∞ for baseline = 0 with any change. | | | |
| % change > 15% | Cannot be calculated: % change = ∞ for baseline = 0 with any change. | | | |

HR is the effect size for 1 unit change in the progression variable. Standardized HR represents the effect size for 1 SD of the progression variable. A lower AIC denotes a better model fit. Models are adjusted for baseline coronary calcium, age, sex, and the length of time between the 2 scans.
Abbreviations as in Table 1.

One large prospective study using CT to measure progression of CAC has also been reported. This prospective observational study evaluated 4,613 asymptomatic persons aged 50 to 70 years with EBT screening for CAC at baseline and again at 2 years and the follow-up lasted 4.3 years (1). This study demonstrated that the median (interquartile range) CAC scores increased by 4 (0, 38) units from baseline to follow-up in subjects who did not sustain a coronary event at any time during the study. In contrast, median (interquartile range) CAC scores increased by 247 (40, 471) units in subjects who experienced a first coronary disease event after the follow-up scan ($p < 0.0001$). Multivariable logistic regression analyses demonstrated that age ($p = 0.03$), male sex ($p = 0.04$), low-density lipoprotein cholesterol ($p = 0.01$), high-density lipoprotein cholesterol ($p = 0.04$), and 2-year change in CAC score ($p < 0.0001$) were significantly associated with subsequent coronary artery disease events. The MESA (Multi-Ethnic Study of Atherosclerosis) (12) is following patients after a second CAC screen, and will assess subsequent cardiovascular events; however, results are still 1 to 2 years away.

**Table 4. Relationship Between the Combined Effects of the Presence of Baseline CAC With Significant Progression of CAC Compared With Those Without Either Baseline or Progression of CAC and Mortality in the Full Cohort With No Exclusions (n = 4,609, 288 Deaths)**

| | HR (95% CI) | p Value |
|---|---|---|
| Baseline and progression | 5.15 (3.67–7.22) | <0.0001 |
| Baseline only | 1.42 (0.99–2.02) | 0.055 |
| Progression in CAC = 0 | 0.94 (0.44–2.15) | 0.97 |
| Age | 1.05 (1.04–1.06) | <0.0001 |
| Sex | 1.38 (1.04–1.83) | 0.03 |
| Time between scans | 0.95 (0.89–1.01) | 0.13 |

Progression of coronary calcium was defined as $\sqrt{}$ transformed difference >2.5 based on the best fitting model.
CAC = coronary artery calcium; other abbreviations as in Table 1.

Baseline 0 scores were not predictive of progression or all-cause mortality in this study. This further validates the concept that a baseline 0 score has a significant warranty period for both future cardiovascular events and progression of atheroscle-

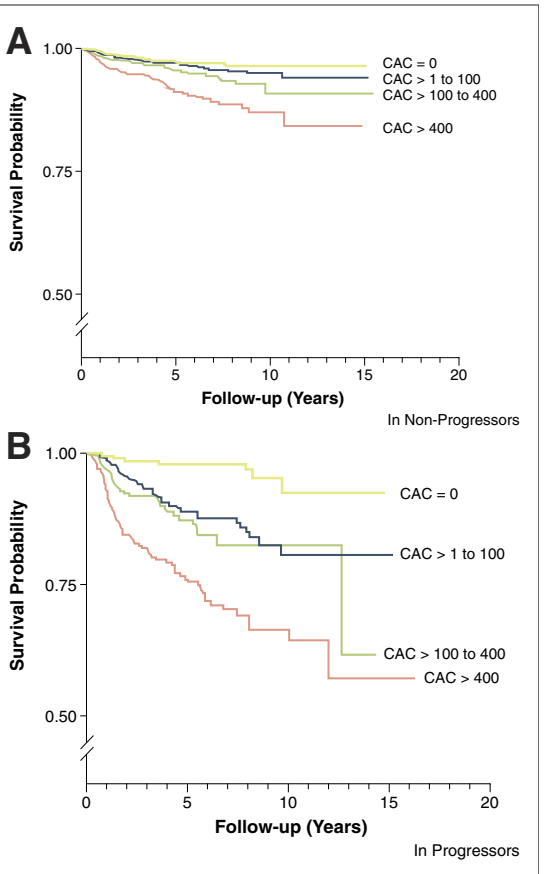


**Figure 2. Survival Curves Demonstrating Time to All-Cause Mortality for Nonprogressors and Progressors**

Cox proportional hazards survival curves demonstrating time to all-cause mortality for patients with a yearly change using survival curve of progression based on our best fitting model of square root >2.5 according to baseline calcium score: **(A)** nonprogressors and **(B)** outcomes in progressors. CAC = coronary artery calcium.

rosis (16,17). Min et al. (16) have suggested a 0 calcium score affords at least a 5-year warranty period, and our study strongly supports that evidence with even longer follow-up and interscan periods.

Our study provides strong confirmatory evidence that CAC progression is associated with future cardiovascular events and, as radiation doses are being reduced to a minimum, that may be a useful tool in the prevention armamentarium to assess atherosclerosis progression noninvasively. Measuring CAC progression requires sequential CT scans, with a cumulative radiation exposure. Prior reports have raised concern about the excess risk of cancer with such an approach (18). However, such predictions are outdated as current gating technology reduces the radiation dose substantially, with an expected dose of <1 mSv per scan (7). Further advances have reduced the CAC dose to as low as 0.6 mSv, lower than screening mammography (19).

Strengths of this study include its large sample size and long follow-up. In addition, the scans were read in the same CT reading center that interprets the MESA and multiple other National Institutes of Health epidemiologic studies, with standardized protocols for acquisition and interpretation of CAC scans (20).

Prior event studies of CAC progression have reported on different techniques to assess progression. In this analysis, we compared previously reported techniques to determine the best predictor of outcomes with CAC progression. All methods for assessing progression of CAC were significantly related to mortality except in individuals with no detectable CAC at baseline (score = 0). Multiple studies have demonstrated the very low event rates in persons without CAC (score = 0) (17,21). In general, a square root transformed difference of >2.5 provided the best fit of the data. This (20) and other methods (21) account for interscan variability in CAC. This was true in the full cohort, among those with baseline CAC >0, and in those with a baseline CAC >30, or 3 pre-defined subgroups. The HRs for this cut point were 3.34 (95% CI: 2.65 to 4.21) in the full cohort, 3.66 (95% CI: 2.82 to 4.74) in those with baseline coronary calcium >0, and 3.28 (95% CI: 2.48 to 4.32) in those with CAC >30. These analyses indicate that regardless of cut points, progression of CAC is related to a >3-fold increase in mortality. The greatest risk was a combination of moderate (>100) or severe (>400) CAC score and progression (Fig. 2). This supports the hypothesis that whereas CAC represents lifetime accumulation of atherosclerosis and scarring after plaque rupture (22,23), progression demonstrates the quiescence or activity of the atherosclerotic pathway and is an independent predictor of survival.

**Study limitations.** The cardiovascular risk factors were taken by survey, rather than measured. Nonetheless, the prevalence of hypercholesterolemia, hypertension, and diabetes mellitus in our population was similar to that observed in other large, population-based studies of coronary heart disease (24). Additionally, the National Death Index obtained for this study did not include 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 coronary heart disease deaths has been reported to be approximately one-third of death from all causes (25).

This is a single-center study, using the same CT reading center as used in multiple National Institutes of Health–sponsored studies. Reproducibility of CAC scanning and scoring from this laboratory has been previously reported (26,27). We used a minimum interscan time of 10 months. Only 311 patients had follow-up <1 year. There is no difference if different time cut points are used. We used 10, 12, and 18 months as minimum without affecting overall results, just lowering sample size (data not shown).

## CONCLUSIONS

The progression of CAC adds significant incremental prediction ability of all-cause mortality, after adjustment for time between scans, demographics, risk factors, and baseline CAC scores. It appears that persons with scores >30 can be assessed for progression of CAC, and this adds incremental information regarding future prognostic risk. Though use of repeat CT testing to estimate an individual's risk associated with CAC "change" appears to be of value, a better understanding of what therapies may be of benefit and how clinicians should use these data in clinical practice remains to be determined.

**Reprints requests and correspondence:** Dr. Matthew Budoff, Los Angeles Biomedical Research Institute, 1124 West Carson Street, Torrance, California 90502. *E-mail: mbudoff@labiomed.org.*

## REFERENCES

1. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005; 46:158–65.
2. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. J Am Coll Cardiol 2005; 46:166–72.
3. Raggi P, Cooil B, Shaw L, et al. Progression of coronary calcification on serial electron beam tomography scanning is greater in patients with future myocardial infarction. Am J Cardiol 2003;92:827–9.
4. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol 2004;24:1272–7.
5. Expert Panel on Detection, Evaluation, and Treatment of High Blood Pressure Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
6. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
7. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography, a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006;114:1761–91.
8. Shaw LJ, Hachamovitch R, Peterson ED, et al. Using an outcomes-based approach to identify candidates for risk stratification after exercise treadmill testing. J Gen Intern Med 1999;14:1–9.
9. Shaw LJ, Peterson ED, Kesler KL, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. Circulation 1998;98: 1622–30.
10. Centers for Disease Control and Prevention. National Death Index. Available at: http://www.cdc.gov/nccdphp/burdenbook2004/Section01/tables.htm. Accessed December 31, 2009.
11. Hokanson JE, MacKenzie T, Kinney G, et al. Evaluating changes in coronary artery calcium: an analytical approach that accounts for inter-scan variability. AJR Am J Roentgenol 2004;182:1327–32.
12. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects—results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;29;115:2722–30.
13. Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. Mayo Clin Proc 1999;74:243–52.
14. Raggi P, Cooil B, Ratti C, Callister TQ, Budoff M. Progression of coronary artery calcium and occurrence of myocardial infarction in patients with and without diabetes mellitus. Hypertension 2005;46:238–43.
15. Budoff MJ, Raggi P. Coronary artery disease progression assessed by electron beam tomography. Am J Cardiol 2001;88:46E–50E.
16. Min JK, Lin FY, Gidseg DS, et al. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan. what is the "warranty period" for remaining normal? J Am Coll Cardiol 2010;55: 1110–7.
17. Blaha M, Budoff MJ, Shaw LJ, et al. Absence of coronary artery calcification and all-cause mortality. J Am Coll Cardiol Img 2009;2:692–700.
18. Kim KP, Einstein AJ, Berrington de Gonzalez A. Coronary artery calcification screening: estimated radiation dose and cancer risk. Arch Intern Med 2009;169:1188–94.
19. Nakazato R, Dey D, Gutstein A, et al. Coronary artery calcium scoring using a reduced tube voltage and radiation dose protocol with dual-source computed tomography. J Cardiovasc Comput Tomogr 2010;3:394–400.
20. Budoff MJ, Nasir K, McClelland RL, et al. Coronary calcium predicts events better with absolute calcium scores than age-sex-race percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2009;53: 345–52.
21. Budoff MJ, McClelland RL, Nasir K, et al. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2009; 158:554–61.
22. Budoff MJ, Yu D, Nasir K, et al. Diabetes and progression of coronary calcium under the influence of statin therapy. Am Heart J 2005;149:695–700.
23. Bielak LF, Sheedy PF, Peyser PA. Coronary artery calcification measured at electron-beam CT: agreement in dual scan runs and change over time. Radiology 2001;218:224–9.
24. Arnett DK, McGovern PG, Jacobs DR Jr., et al. Fifteen-year trends in cardiovascular risk factors (1980–1982 through 1995–1997): the Minnesota Heart Survey. Am J Epidemiol 2002; 156:929–35.
25. National Center for Chronic Disease Prevention and Health Promotion. The Burden of Chronic Diseases as Causes of Death, United States. [Online report]. 2004. Available at: http://www.cdc.gov/nccdphp/burdenbook2004/Section01/tables.htm. Accessed December 31, 2009.
26. Budoff MJ, McClelland RL, Chung H, et al. Reproducibility of coronary artery calcified plaque with cardiac 64-MDCT: the Multi-Ethnic Study of Atherosclerosis. AJR Am J Roentgenol 2009;192:613–7.
27. Lu B, Zhuang N, Mao SS, et al. EKG-triggered CT data acquisition to reduce variability in coronary arterial calcium score. Radiology 2002; 224:838–44.

**Key Words:** atherosclerosis progression ■ coronary artery calcium ■ mortality ■ outcomes.