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Absence of Coronary Artery Calcification and All-Cause Mortality

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OBJECTIVES We sought to quantify the mortality rates associated with absent and low positive (CAC 1 to 10) coronary artery calcium (CAC).

BACKGROUND There is increasing interest in the absence of CAC as a "negative" cardiovascular risk factor. However, published event rates for individuals with no CAC vary, likely owing to differences in baseline risk, follow-up period, and outcome ascertainment. The prognostic significance of low CAC (CAC 1 to 10) is not well described.

METHODS Annualized all-cause mortality rates were assessed in 44,052 consecutive asymptomatic patients referred for CAC testing. Mean follow-up of the cohort was 5.6 ± 2.6 years (range 1 to 13 years).

RESULTS A total of 19,898 patients (45%) had no CAC on screening electron beam tomography, whereas 5,388 (12%) had low levels of CAC (CAC 1 to 10), and 18,766 (43%) had CAC >10. There were 104 deaths in those with no CAC (0.52%), 58 deaths in those with CAC 1 to 10 (1.06%), and 739 deaths in those with CAC >10 (3.96%). Annualized all-cause mortality rates for CAC = 0, CAC 1 to 10, and CAC >10 were 0.87, 1.92, and 7.48 deaths/1,000 person-years, respectively. The hazard ratio (HR) for all-cause mortality among CAC 1 to 10 versus CAC = 0 after adjustment for traditional risk factors was 1.99 (95% confidence interval [CI]: 1.44 to 2.75). Smoking (HR: 3.97, 95% CI: 2.75 to 5.41) and diabetes mellitus (HR: 3.36, 95% CI: 2.09 to 5.41) were associated with few events observed in CAC = 0 group.

CONCLUSIONS In appropriately selected asymptomatic patients, the absence of CAC predicts excellent survival with 10-year event rates of approximately 1%. A finding of 0 CAC might be used as a rationale to emphasize lifestyle therapies rather than pharmacotherapy and to forgo repeated imaging studies. Individuals with low CAC score (CAC 1 to 10) are at increased risk above individuals with a 0 score and could be considered a distinct risk group by physicians and investigators. (J Am Coll Cardiol Img 2009;2:692–700) © 2009 by the American College of Cardiology Foundation

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The presence of calcium in coronary arteries is pathognomonic of atherosclerosis, as confirmed by histopathology and intravascular ultrasound studies (1–4). Coronary artery calcium (CAC), detected and quantified with cardiac computed tomography, represents a reliable linear anatomic estimate of total plaque burden (5) and is represented clinically as a "calcium score." Nearly all prospective studies have found moderate-to-high CAC to be an independent and incremental predictor of future cardiovascular events over conventional risk factors and the Framingham Risk Score (6–15). Therefore current guidelines recommend measurement of CAC for further risk stratification of intermediate risk individuals, in whom treatment with long-term aspirin and statin therapy is most uncertain (5,16).

There is increasing interest in the absence of CAC (a calcium score of 0) as a "negative" cardiovascular risk factor (17,18). Absence of CAC might reliably exclude obstructive coronary disease in asymptomatic and selected symptomatic individuals and seems to be associated with a low cardiovascular event rate, suggesting that less aggressive pharmacotherapy might be indicated in this population (19). However, published event rates for individuals with 0 CAC vary, likely owing to differences in baseline risk, follow-up period, as well as outcome ascertainment and verification (18). The characteristics of the few individuals with 0 CAC who subsequently develop cardiovascular events have not been well-described.

Less is known about the prognosis of a low positive CAC score (CAC 1 to 10), because most studies are underpowered to report this as a distinct group. Some studies have reported increased and variable noncalcified soft coronary plaque in patients with low CAC (20). Budoff et al. (13) recently reported a 2.5-fold increased risk with CAC 1 to 10 as compared with 0 CAC, although this difference was not statistically significant after adjusting for conventional risk factors.

To further elucidate the prognosis of absent (0) and low positive (CAC 1 to 10) CAC, we studied a large combined cohort of 44,052 asymptomatic individuals referred for screening electron beam tomography (EBT). We sought to describe the all-cause mortality rate in individuals with 0 CAC as well as the all-cause mortality rate in individuals with low CAC (CAC 1 to 10) in relation to those with no CAC.

METHODS

The study cohort consisted of 44,052 consecutive asymptomatic individuals free of known coronary heart disease (CHD) referred for EBT for the assessment of subclinical atherosclerosis. Patients were determined to be free of CHD on the basis of patient history and prior work-up conducted by the referring physician. The dataset for this study represents the combination of data from 3 centers, each representing several sites geographically dispersed throughout the U.S., for which similar methods have been defined for data accumulation. The combined population was predominantly white and middle-aged.

Study participants were referred by their primary physicians on the basis of established cardiovascular risk factors for atherosclerosis and, as such, do not represent a random sample of the general population. All screened individuals provided informed consent to undergo EBT and for the use of their blinded data for epidemiologic research. The general study received approval from the Human Investigations Committee, and separate Committee approval was obtained for the patient interviews, collection of baseline and follow-up data, and corroboration of the occurrence of death.

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium
CHD = coronary heart disease
EBT = electron beam tomography

Risk factor data collection. All study participants were given a questionnaire for the collection of demographic and clinical characteristics as well as baseline cardiovascular risk factors. Cigarette smoking was considered present if a subject was a smoker at the time of scanning. Dyslipidemia was considered to be present for any individual reporting a history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, and/or high triglycerides or current use of lipid-lowering therapy. Study subjects were considered to have diabetes if they reported using oral anti-diabetes medications or insulin. Hypertension was defined as a self-reported history of high blood pressure or use of antihypertensive medication. Family history of CHD was determined by asking patients whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization. Body mass index was calculated for individuals who self-reported a height and weight. Individuals with body mass index $\geq$30 kg/m^2 were considered obese.

EBT screening protocol. All subjects underwent EBT on either a C-100 or C-150 Ultrafast computed tomography scanner (GE-Imatron, South San Fran-

cisco, California). With a tomographic slice thickness of 3 mm, a total of approximately 40 sections were obtained beginning at the level of the carina and proceeding caudally to the level of the diaphragm. Images were obtained with a 100-ms/slice scanning time, with image acquisition electrocardiographically triggered at 60% to 80% of the R-R interval.

A calcified lesion was defined as ≥3 contiguous pixels with a peak attenuation of at least 130 Hounsfield units. Each lesion was then scored with the method developed by Agatston et al. (21).

Follow-up and mortality ascertainment. Patients were followed for a mean of 5.6 ± 2.6 years (range 1 to 13 years). Follow-up was completed in 100% of the patients. The primary end point for the study cohort was mortality from any cause. Ascertainment of mortality was conducted by individuals blinded to baseline historical data and EBT results. The occurrence of death was verified with the Social Security Death Index.

Statistical methods. The baseline characteristics of the study population are presented by pre-specified CAC group (0, 1 to 10, >10) and in aggregate for the entire study population. Age is presented as a continuous measure ± SD, and other risk variables are expressed as proportional frequencies. Age was compared across increasing CAC groups with analysis of variance techniques, and proportional frequencies of other risk variables were compared across increasing CAC groups with chi-square analysis. A p value <0.05 was considered statistically significant.

Annualized all-cause mortality rates were estimated by dividing the number of deaths by the number of person-years at risk. Mortality rates are first expressed for each CAC group and then stratified according to pre-specified age group (<45, 45 to 64, ≥65 years) as well as by presence of individual categorical risk factors.

In addition, survival analysis was conducted with individual subject time-to all-cause mortality data. Curves representing the cumulative probability of survival were generated with Kaplan-Meier estimates. To evaluate the effect of CAC group on all-cause mortality, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with the Cox proportional hazards regression model with CAC = 0 as the reference group. Three hierarchical models were constructed: Model 1: unadjusted; Model 2: adjusted for age and sex; and Model 3: adjusted for age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, and family history of CHD.

Finally, the relationship of individual risk factors with all-cause mortality was tested by adjusting for all risk factors simultaneously in a multivariable Cox regression model. The risk imparted by these factors was modeled both in patients with 0 CAC and in the entire study population.

All statistical analyses were performed with Stata version 8 (STATA Corp., College Station, Texas).

RESULTS

Clinical characteristics of study cohort. The final study population consisted of 44,052 asymptomatic individuals free of known cardiovascular disease at baseline. Average age for the study cohort was 54 ± 10 years, with slightly over one-half being male (54%). A total of 19,898 patients (45%) had no CAC on screening EBT, whereas 5,388 (12%) had low levels of CAC (CAC 1 to 10), and 18,766 (43%) had CAC >10 (Table 1). Overall, with increasing CAC scores, the population was significantly more likely to be male and older, with increased prevalence of smoking, hypertension, diabetes, and dyslipidemia as well as higher likelihood of family history of heart disease (all p < 0.0001).

Table 1. Baseline Characteristics of Study Population

Variable	Total (n = 44,052)	CAC = 0 (n = 19,898; 45%)	CAC 1 to 10 (n = 5,388; 12%)	CAC >10 (n = 18,766; 43%)	p Value
Age (yrs)	54 ± 10	50 ± 10	52 ± 10	59 ± 10	<0.0001
Sex (male)	54%	52%	57%	55%	<0.0001
Current smoker	14%	12%	11%	17%	<0.0001
HTN	34%	26%	32%	42%	<0.0001
DM	5%	3%	5%	9%	<0.0001
Hyperlipidemia	30%	24%	27%	36%	<0.0001
Family history of heart attack	37%	35%	36%	40%	<0.0001

p value for trend across coronary artery calcium (CAC) [score] categories.
DM = diabetes mellitus; HTN = hypertension.

Table 2. All-Cause Mortality Rates by CAC Scores in Overall Population

	No. of Patients	No. of Events	Rate/1,000 Person-Yrs at Risk	95% CI for Rate
CAC = 0	19,898 (45%)	104 (0.52%)	0.87	0.72–1.05
CAC 1 to 10	5,388 (12%)	58 (1.06%)	1.92	1.48–2.48
CAC >10	18,766 (43%)	739 (3.96%)	7.48	6.95–8.04
Total	44,052 (100%)	901 (2.05%)	3.62	3.39–3.89

CAC = coronary artery calcium; CI = confidence interval.

All-cause mortality rates and CAC. Overall, there were 901 deaths (2.05%) in the total study population over a mean follow-up of 5.6 ± 2.6 years (range 1 to 13 years). There were 104 deaths in those with no CAC (0.52%), 58 deaths in those with CAC 1 to 10 (1.06%), and 739 deaths in those with CAC >10 (3.96%). The annualized mortality rate increased from 0.87 deaths/1,000 person-years (95% CI: 0.72 to 1.05) to 1.89 deaths/1,000 person-years (95% CI: 1.46 to 2.45) and to 7.48/1,000 person-years (95% CI: 6.95 to 8.04) for those with CAC = 0, CAC 1 to 10, and CAC >10, respectively (Table 2). Cumulative survival for the 3 groups was 99.5%, 98.9%, and 96.1% (Fig. 1). Survival curves according to CAC scores in women and men are shown in Figures 2 and 3, respectively.

Table 3 provides unadjusted and multivariable adjusted HRs for all-cause mortality in patients with low CAC (CAC 1 to 10) and CAC >10 in relation to those with no CAC. In unadjusted analysis, CAC 1 to 10 was associated with greater than two-fold increased risk of death from any cause (HR: 2.19, 95% CI: 1.57 to 2.99) as compared with those with a CAC score of 0. After adjustment for age and sex (Model 2), the HR was slightly attenuated to 2.02 but remained highly significant (95% CI: 1.47 to 2.79, $p < 0.0001$). The increased risk in patients with CAC 1 to 10 persisted after adjustment for age, sex, hypertension, smoking, diabetes, dyslipidemia, and family history of CHD (Model 3: HR: 1.99, 95% CI: 1.45 to 2.75). Patients with CAC >10 had in excess of an 8-fold increased unadjusted risk of death compared with individuals with a CAC score of 0 (HR: 8.48, 95% CI: 6.82 to 10.29); this was attenuated to a 5-fold and 3-fold increase in Models 2 and 3, respectively. In addition, for comparison purposes the HRs for all-cause mortality among those with CAC scores of 101 to 400 and >400 as compared with CAC = 0 in Model 3 were 5.56 (95% CI: 4.27 to 7.21) and 9.65 (95% CI: 7.46 to 12.5), respectively.

Risk factors and all-cause mortality in individuals with no CAC. Increasing age remained a risk factor for all-cause mortality in patients with no CAC. Patients age <45 years and 45 to 64 years had a low mortality rate (0.67 and 0.77 deaths/1,000 person-years, respectively), whereas patients 65 and older were at increased risk of death (2.22 deaths/1,000 person-years). Presence of hypertension, diabetes, and dyslipidemia as well as smoking status also remained risk factors for all-cause mortality in patients with no coronary calcium. The highest mortality rate among individuals with CAC score of 0 was observed in those with diabetes (3.72 deaths/1,000 person-years vs. 0.81 deaths/1,000 person-years in those without diabetes) and smokers (3.31 deaths/1,000 person-years vs. 0.67 deaths/1,000 person-years for nonsmokers). Despite no coronary calcium, study subjects with a family history of CHD had a slightly increased all-cause mortality compared with those without such a family history (Table 4).

After adjusting for all risk factors simultaneously in a multivariable model, age, smoking, diabetes mellitus, and family history of heart disease remained significant predictors of all-cause mortality in patients with no CAC. These same 4 risk factors were significant predictors of all-cause mortality in

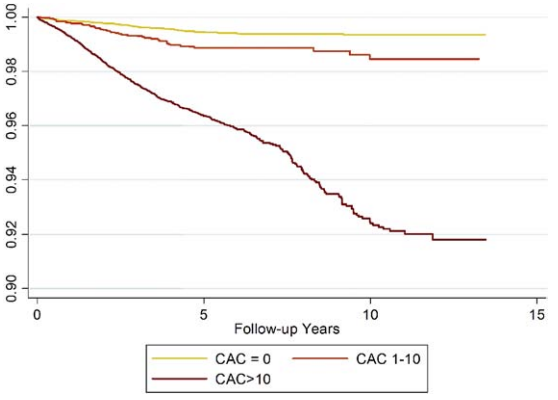

Figure 1. Kaplan-Meier Survival Curve According to CAC Scores (Total Population)

Kaplan-Meier survival curve according to coronary artery calcium (CAC) scores (total population) demonstrating a low mortality rate among those with CAC = 0 as well as higher event rate with presence of low to high CAC scores.

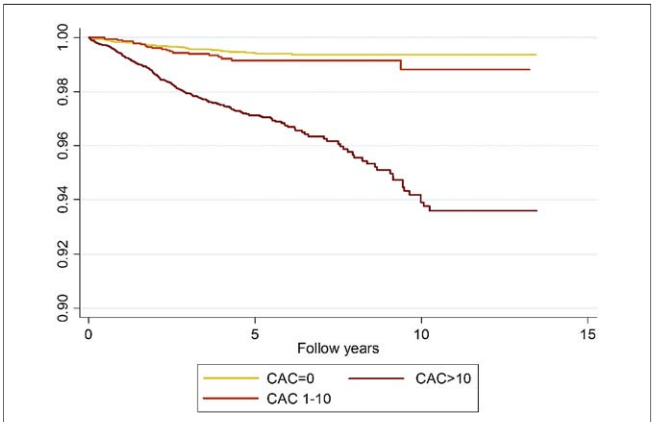

Figure 2. Kaplan-Meier Survival Curve According to CAC Scores (Women)

Kaplan-Meier survival curve according to coronary artery calcium (CAC) scores (women) demonstrating a low mortality rate among those with CAC = 0 as well as higher event rate with presence of low to high CAC scores.

the overall cohort, with similar point estimates of risk. Smoking (HR: 3.97, 95% CI: 2.75 to 5.41) and diabetes mellitus (HR: 3.36, 95% CI: 2.09 to 5.41) in particular were associated with the highest increases in risk (Table 5).

DISCUSSION

In this combined cohort of 44,052 asymptomatic middle-age patients free of known coronary artery disease, a CAC score of 0 was associated with excellent survival, with all-cause mortality rates of 0.87/1,000 person-years (<1% 10-year risk or <0.1%/year). Conventional cardiovascular risk factors, particularly smoking and diabetes mellitus, are associated with a higher relative risk of mortality in patients with no CAC, although absolute event rates remain low. Individuals with low CAC scores (CAC 1 to 10) had a nearly 2-fold increased mortality compared with those with no CAC despite risk factor adjustment, suggesting that patients with low CAC represent a distinct risk group. However, mortality rates in individuals with low CAC scores remained low (<5% 10-year risk, <0.5%/year), and this group remained a low overall risk with traditional Framingham risk stratification.

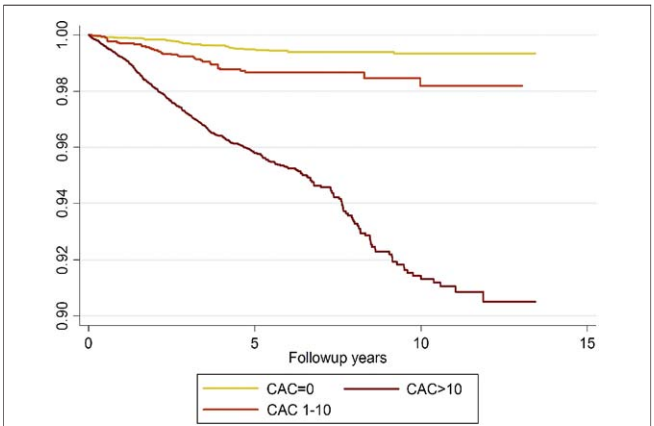

Figure 3. Kaplan-Meier Survival Curve According to CAC Scores (Men)

Kaplan-Meier survival curve according to coronary artery calcium (CAC) scores (men) demonstrating a low mortality rate among those with CAC = 0 as well as higher event rate with presence of low to high CAC scores.

This cohort represents the largest follow-up dataset yet studied for the occurrence of all-cause death after CAC scanning. The size of this study population, with over 25,000 patients with CAC scores between 0 and 10 and over 900 all-cause deaths, lends considerable statistical power to the evaluation of the long-term prognosis of both 0 CAC and the smaller low-CAC group. The end point, all-cause mortality, frees this investigation of the bias imparted by the ascertainment and verification of cardiovascular events (22,23).

Implications for no CAC. The very low mortality rates observed for individuals without CAC in this study are similar to event rates observed in other studies of middle-aged asymptomatic patients. Arad et al. (11) reported an event rate equivalent to 1/1,000 person-years, Taylor et al. (12) demonstrated an event rate equivalent to 0.6/1,000 person-years, whereas Raggi et al. (8) demonstrated an event rate equivalent to 1.1 events/1,000 person-years. Shaw et al. (24) observed 39 events during a mean follow-up of 5 years in a large series of 5,067 patients with no CAC, equivalent to a crude annualized event rate of 1.5 events/1,000 person-years.

LaMonte et al. (25) observed 15 events during a mean follow-up of 3.5 years among 2,692 individuals with no CAC, equivalent to 1.6 events/1,000 person-years. Recently Detrano et al. (14), publishing from the MESA (Multiethnic Study of Atherosclerosis) cohort, reported 8 major cardiac events over 3.7 years among 3,409 patients without CAC, equivalent to an event rate of 0.6/1,000 person-years. In 1 of the largest studies previously published, Budoff et al. (13) reported a cumulative 12-year survival of 99.4% amongst 11,046 patients with no CAC, resulting in an event rate of approximately 0.6/1,000 person-years.

The present study adds to the growing published data supporting no CAC as an important "negative risk factor" for major cardiovascular outcomes in "asymptomatic intermediate risk patients." In addi-

tion to a very low overall event rate in middle-aged patients, CAC score of 0 has been shown to discriminate lower risk groups in the elderly (15).

Individuals with no CAC are also extremely unlikely to have obstructive coronary disease. In a pooled analysis of 10,355 symptomatic patients who underwent coronary angiography (1,941 with no CAC), the presence of any CAC had a sensitivity of 98% and a negative predictive value of 93% for detection of clinically significant coronary stenosis (19). These data are consistent with direct pathologic comparisons (26).

No CAC is also associated with a very low risk of cardiac ischemia. In 9 studies examining 4,870 patients referred for perfusion stress testing (1,225 with no CAC), just 6% had evidence of ischemia (19). Finally, in 3 studies totaling 431 patients presenting to the emergency room with chest pain, negative cardiac biomarkers, and equivocal electrocardiography findings (183 with no CAC), a CAC score of 0 had a 99% predictive value for ruling out acute coronary syndrome (19).

However, attention must be paid to the underlying risk of a population when considering the value of a CAC score of 0; the few studies that reported higher event rates in patients with no CAC considered higher-risk sub-groups. For example, Schenker et al. (27) reported a 16% incidence of inducible ischemia in patients with no CAC undergoing positron emission tomography/computed tomography. All patients in this study were symptomatic, including 34% with either dyspnea or classic exertional angina. Recently, Henneman et al. (28) noted a 70% prevalence of obstructive coronary disease as seen by computed tomography angiography in patients without CAC presenting to the emergency room with high suspicion of acute coronary syndrome. In accordance with Bayes theorem and current clinical guidelines, the value of a CAC score of 0 as a "negative risk factor" lies in the intermediate-risk primary prevention population rather than high-risk populations.

In the appropriately selected non–high-risk patient, the absence of CAC could potentially be used as a rationale to emphasize lifestyle therapy, scale back on costly preventive pharmacotherapy, and refrain from frequent cardiac imaging and testing. Given the low 1% 10-year risk in this population, a drug that produces a 30% relative risk reduction would have to be given to over 300 patients for 10 years to prevent 1 death (number needed to treat, approximately 333 for 10 years). In addition, recent data suggest that repeat CAC imaging could be delayed in this population for perhaps 5 years. Gopal et al. (29) showed that in 710 physician-referred patients with no CAC at baseline, less than one-half developed CAC, whereas just 4% developed CAC scores >50 at 5 years' follow-up. In the MESA cohort, only 16% of individuals with no CAC developed some degree of CAC at median follow-up of 41 months (30).

However, it is important to keep in mind that even in the absence of CAC, relatively more events occur among those with higher risk especially in diabetic patients and smokers, who are at increased risk for in-situ thrombosis and coronary vasospasm that can be independent of coronary atherosclerosis. This scenario is analogous to the elevation of cardiac enzymes in the face of a "clean" coronary

Table 3. All-Cause Mortality (HR, 95% CI) for All-Cause Mortality With Low CAC (CAC 1 to 10) and CAC >10 Compared With CAC = 0

	CAC = 0	CAC 1 to 10	CAC >10
Model 1	1 (ref)	2.19 (1.57–2.99)	8.38 (6.82–102.9)
Model 2	1 (ref)	2.02 (1.47–2.79)	4.96 (4.02–6.11)
Model 3	1 (ref)	1.99 (1.45–2.75)	4.08 (3.30–5.04)

Model 1: unadjusted; Model 2: age-, sex-adjusted; Model 3: age-, sex-, hypertension-, smoking-, diabetes mellitus–, hyperlipidemia-, and family history of coronary heart disease–adjusted.
CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio.

Table 4. All-Cause Mortality Rates by Absence and Presence of CHD Risk Factors Among Those With CAC = 0

	Rate/1,000 Person-Yrs at Risk	95% CI for Rate
Age, yrs		
<45	0.67	0.45–1.01
45–64	0.77	0.59–1.00
≥65	2.22	1.49–3.32
Sex		
Female	0.91	0.69–1.20
Male	0.84	1.63–1.10
Hypertension		
No	0.75	0.61–0.95
Yes	1.69	1.14–2.50
Smoking		
No	0.67	0.53–0.84
Yes	3.31	2.31–4.74
Diabetes mellitus		
No	0.81	0.66–0.99
Yes	3.72	1.94–7.16
Hyperlipidemia		
No	0.70	0.56–0.89
Yes	1.72	1.23–2.40
Family history of CHD		
No	0.63	0.48–0.82
Yes	1.59	1.20–2.10

CHD = coronary heart disease; CI = confidence interval.

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Table 5. Relationship of Risk Factors With All-Cause Mortality in Overall Population and Those With CAC = 0

	Overall HR (95% CI)	CAC = 0 HR (95% CI)
Age/10 yrs	1.67 (1.46–1.90)	1.63 (1.38–1.93)
Male	1.15 (0.84–1.57)	0.91 (0.62–1.33)
Hypertension	1.32 (0.91–1.89)	1.04 (0.64–1.68)
Smoking	3.97 (2.75–5.41)	3.63 (2.28–5.75)
Diabetes mellitus	3.36 (2.09–5.41)	2.51 (1.24–5.05)
Hyperlipidemia	0.95 (0.66–1.37)	1.24 (0.78–1.96)
Fam history of CHD	1.57 (1.11–2.20)	1.53 (1.00–2.34)

All risk factors adjusted in the multivariate Cox regression models simultaneously. Abbreviations as in Table 3.

angiogram. However, apart from this reason, another potential mechanism could be that those with risk factors such as diabetes and smoking even in the presence of CAC are more likely to develop incident CAC during follow-up, as shown by Kronmal et al. (30), and thus might explain the increased risk of outcomes in longer-term follow-up. Further studies assessing whether this increased risk of development of new CAC in these low-risk individuals will further shed light on the higher risk seen with risk factors such as diabetes mellitus and smoking even in the absence of CAC at baseline.

The present study is the first to describe risk factors for the few events that occur in patients with no CAC. Contrary to a prior report (31), diabetes and smoking are associated with the limited mortality observed in individuals with no CAC. This might be due to mechanisms separate from the genesis of atherosclerotic plaque, including impaired endothelial function, prothrombotic state, and increased vasospasm. Although absolute mortality rates remain low (3 to 4 deaths/1,000 person-years, equivalent to 3% to 4% 10-year risk), risk in these patients warrants further study, and these patients should continue close follow-up and pharmacotherapy according to present guidelines.

Implications for low CAC score (CAC 1 to 10). To our knowledge, this is the first study to confirm a robust increased risk in patients with low positive CAC. Budoff et al. (13) recently reported an unadjusted relative risk of 2.5 with CAC 1 to 10, although this difference was not statistically significant after adjusting for cardiovascular risk factors.

Recent computed tomography angiography data suggest a mechanism for the observed increased risk. Cheng et al. (20) scanned 554 low- to intermediate-risk outpatients and expressed the prevalence of noncalcified coronary artery plaque (NCAP) as a function of CAC. Compared with patients with no CAC, individuals with low CAC (CAC 1 to 10) had marked increased rate of NCAP (65% vs. 7%), including NCAP causing >50% luminal obstruction (9% vs. 1%). The authors hypothesize a threshold effect, consistent with prior histopathology data, whereby a significant burden of NCAP might need to be present before intimal hydroxyapatite accumulates.

Clinicians and future investigators should, on the basis of the results of the present study, refrain from merging no CAC and low CAC into a single group. For some patients, including younger individuals and women, a low absolute CAC score might indeed represent a high percentile. Dedicated studies, stratified by age and sex, are needed to better define the risk in patients with low CAC.

Study limitations. There are a few limitations to this study. First, all patients were referred for CAC screening and therefore do not represent a random sample of the population. In general, patients referred for CAC scans might be at higher risk compared with age-matched patients from the general population. If this were the case in the present study, the finding of excellent survival amongst patients with no CAC could be considered even more striking. Comparison with published data reveals that our observed CAC frequency and distribution is similar to that seen in 2 large population-based epidemiologic studies—MESA and CARDIA (Coronary Artery Risk Development in Young Adults) (32).

A second potential weakness is the self-reporting of risk factors. Data gathered by self report is limited by patient recall and thus subject to recall bias. However, patient reporting of hypertension has been validated as an acceptable way to assess risk factor data (33). Although the lack of a continuous risk variable might decrease the precision of point estimates of risk, the use of categorical risk factor data has been validated as an approach to clinical risk stratification (34).

Our models do not include the cause of death, and as such, our models might be based on mortality unrelated to atherosclerotic disease. However, all-cause mortality is an appropriate end point to follow, because when one accounts for both cardiac and systemic forms of the disease, nearly three-fourths of all deaths have been related to atherosclerosis (23). Furthermore, this end point is unaffected by the reporting and misclassification bias potentially introduced by a physician's filing of a death report (22).

Finally, more detailed conclusions in our study are not possible due to the lack of cardiovascular-specific mortality data. Although CHD remains the most common killer in industrialized countries, it is not possible to ascertain the proportion of deaths that are cardiovascular in origin. Although CAC is presumed to influence mortality mainly via cardiovascular mechanisms, other risk factors such as smoking and diabetes contribute to all-cause mortality via additional noncardiovascular mechanisms (i.e., lung disease and kidney dysfunction). Therefore it is not possible in this study to conclude that smoking and diabetes cause excess cardiovascular deaths in the no CAC population.

CONCLUSIONS

We conclude that, in appropriately selected asymptomatic patients, absence of CAC predicts excellent survival with 10-year event rates of approximately 1% (<0.1%/year). On the basis of this finding, in conjunction with published reports supporting incremental improved risk assessment when CAC is added to conventional risk factors, a finding of no CAC might allow shifting of these patients into lower risk groups. As such, physicians might consider emphasizing appropriate lifestyle therapy, using less pharmacotherapy, and ordering less costly cardiac imaging studies in these patients. Patients who smoke and have diabetes, however, should be treated according to existing guidelines. Individuals with low positive CAC (CAC 1 to 10) are at increased risk compared with those with a CAC score of 0 and should be considered a distinct albeit low-risk group by physicians and investigators.

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