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ORIGINAL RESEARCH

Long-Term All-Cause and Cause-Specific Mortality in Asymptomatic Patients With CAC ≥1,000

Results From the CAC Consortium

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ABSTRACT

OBJECTIVES This study thoroughly explored the demographic and imaging characteristics, as well as the all-cause and cause-specific mortality risks of patients with a coronary artery calcium (CAC) score ≥1,000 in the largest dataset of this population to date.

BACKGROUND CAC is commonly used to quantify cardiovascular risk. Current guidelines classify a CAC score of >300 or 400 as the highest risk group, yet little is known about the potentially unique imaging characteristics and mortality risk in individuals with a CAC score ≥1,000.

METHODS A total of 66,636 asymptomatic adults were included from the CAC consortium, a large retrospective multicenter clinical cohort. Mean patient follow-up was 12.3 ± 3.9 years for patients with cardiovascular disease (CVD), coronary heart disease (CHD), cancer, and all-cause mortality. Multivariate Cox proportional hazards regression models adjusted for age, sex, and conventional risk factors were used to assess the relative mortality hazard of individuals with CAC ≥1,000 compared with, first, a CAC reference of 0, and second, with patients with a CAC score of 400 to 999.

RESULTS There were 2,869 patients with CAC ≥1,000 (86.3% male, mean 66.3 ± 9.7 years of age). Most patients with CAC ≥1,000 had 4-vessel CAC (mean: 3.5 ± 0.6 vessels) and had greater total CAC area, higher mean CAC density, and more extracoronary calcium (79% with thoracic artery calcium, 46% with aortic valve calcium, and 21% with mitral valve calcium) than those with CAC scores of 400 to 999. After full adjustment, those with CAC ≥1,000 had a 5.04- (95% confidence interval [CI]: 3.92 to 6.48), 6.79- (95% CI: 4.74 to 9.73), 1.55- (95% CI:1.23 to 1.95), and 2.89-fold (95% CI: 2.53 to 3.31) risk of CVD, CHD, cancer, and all-cause mortality, respectively, compared to those with CAC score of 0. The CAC ≥1,000 group had a 1.71- (95% CI: 1.41 to 2.08), 1.84- (95% CI: 1.43 to 2.36), 1.36- (95% CI:1.07 to 1.73), and 1.51-fold (95% CI: 1.33 to 1.70) increased risk of CVD, CHD, cancer, and all-cause mortality compared to those with CAC scores 400 to 999. Graphic analysis of CAC ≥1,000 patients revealed continued logarithmic increase in risk, with no clear evidence of a risk plateau.

CONCLUSIONS Patients with extensive CAC (CAC ≥1,000) represent a unique very high-risk phenotype with mortality outcomes commensurate with high-risk secondary prevention patients. Future guidelines should consider CAC ≥1,000 patients to be a distinct risk group who may benefit from the most aggressive preventive therapy.
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ABBREVIATIONS AND ACRONYMS

AVC = aortic valve calcium

CAC = coronary artery calcium

CHD = coronary heart disease

CTA = computed tomography angiography

CVD = cardiovascular disease

MVC = mitral valve calcium

PCE = pooled cohort equations

TAC = thoracic artery calcium

Coronary artery calcium (CAC), determined by acquiring cardiac-gated noncontrast computed tomography imaging, is now routinely used to quantify atherosclerotic burden in the coronary arteries. Higher levels of CAC have been strongly associated with an increased risk of coronary heart disease (CHD) and all-cause mortality (1). In fact, most studies have found CAC to be a more robust predictor of coronary events in the asymptomatic primary prevention population than conventional risk scores such as the Framingham Risk Score or the Pooled Cohort Equations (PCE) (2-4). CAC, as a measurement of cumulative subclinical vascular injury, also appears to be an independent predictor of other important clinical outcomes such as stroke, dementia, cancer, and chronic kidney disease (5-7).

Current guidelines classify persons with CAC scores >300 or >400 at the highest risk group for cardiovascular disease (CVD) events, with no further differentiation above that threshold (8-11). To date, few studies have explored the commonly encountered, extensively calcified plaque phenotype of persons with CAC scores ≥1,000. There are few data for the demographic and imaging characteristics of this population, and even fewer long-term data for the relative risks of cause-specific mortality. For example, it remains unclear if these patients constitute a unique population with an extremely high CHD risk or if the extensively calcified nature of their atherosclerosis puts them at high all-cause mortality risk but no higher CHD risk than those with CAC >300 or >400. Prior studies investigating these extensive Agatston scores have been limited by small sample sizes and by studying only all-cause mortality (1,12).

Therefore, the present study sought to comprehensively describe the demographic characteristics, the baseline cardiovascular risk factors, and the computed tomography (CT) imaging features of this unique and clinically important population, as well as to determine the risks for long-term cause-specific long-term mortality. To accomplish this, the CAC Consortium, which is the largest cohort of patients with measured CAC to date, was used (13).

METHODS

STUDY DESIGN AND STUDY POPULATION. Analysis involved 66,636 asymptomatic adults (≥18 years of age) without known CHD, from the multicenter CAC Consortium study, which was designed to study the relationship between clinical CAC scoring and long-term cause-specific mortality. Details for data collection, preparation, and harmonization were published previously (13). In summary, this study collected data from 1991 through 2010, and follow-up data were collected until June 2014. Four medical centers with ≥10 years of experience scanning CAC (according to CAC Consortium study site inclusion criteria) from 3 different states (California, Ohio, and Minnesota) contributed patient data to the CAC Consortium. All CAC scans were clinically indicated and physician-referred. All study participants provided informed consent at the time of CAC scanning. Institutional Review Board approval for coordinating center activities was obtained at the Johns Hopkins Hospital.

COMPUTED TOMOGRAPHY DATA. Each individual study site performed routine noncontrast cardiac-gated CT scans for the clinical determination of CAC scores. A common standard protocol was used for each scanner technology, and scans were read locally at each center, using the Agatston method (13). Electron beam tomography was used for the CT scans performed at most of the centers (93%), whereas 2 centers (7%), which had more recent CAC data, used multidetector CT. It has been shown that electron beam tomography has no clinically meaningful differences compared with multidetector CT scanners in assessing CAC scores (14).

In addition, data for the total number of vessels with CAC (0 to 4) were available in 54,678 patients (82%), thoracic aortic calcium (TAC) scores in 34,024 patients (51%), aortic valve calcium (AVC) scores in 10,007 patients (15%), mitral valve calcium (MVC) scores in 10,008 patients (15%), and mean density (CT attenuation) of calcified coronary lesions in 20,052 patients (30%). In patients with CAC density data, a summed area of all CAC lesions (in square millimeters) was determined by dividing the total Agatston

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CAC score by the mean density (in Hounsfield units [HU]) divided by 100 (to back-calculate the mean density weighting factor in the Agatston protocol) (15).

MEASUREMENT AND DEFINITION OF BASELINE CHARACTERISTICS AND RISK FACTORS. Participants had baseline characteristics, risk factors, and laboratory data collected at the time of the CAC scan and/or as part of their routine clinical visit. Data for race was available from only a subset of the study population (n = 42,964 [64%]) (Supplemental Table 1). Hypertension was defined as current treatment with antihypertensive medications or prior diagnosis of hypertension. Dyslipidemia was defined as prior diagnosis of dyslipidemia (elevated triglycerides and/or low high-density lipoprotein cholesterol [HDL-C]), a prior diagnosis of hyperlipidemia, or treatment with lipid-lowering medications. If participants had concomitant laboratory data, dyslipidemia was considered present if HDL-C was <50 mg/dl in women and <40 mg/dl in men, and low-density lipoprotein cholesterol (LDL-C) was >160 mg/dl, or fasting triglycerides were >150 mg/dl. Smoking status was defined as current cigarette smoker or not (yes/no). Diabetes was defined as prior diagnosis of diabetes or treatment with antidiabetic drugs. At all centers except for the Columbus, Ohio, site, family history of CHD was determined by presence of a first-degree relative with history of CHD. The Columbus, Ohio, site used a more stringent definition of family history of CHD, which was <55 years of age in male relatives and <65 years of age in female relatives. Multiple imputations were conducted in the instance of partially missing risk factor data (28% of cohort had at least 1 missing data element). The imputation algorithm has been previously validated (13). The PCE were used to calculate 10-year risk of atherosclerotic cardiovascular disease (ASCVD), as previously described (13).

ASCERTAINING OUTCOME. Mortality status was determined by linking to the Social Security Administration Death Master File, using a previously validated algorithm (16). Individual-level causes of death were ascertained by using International Classification of Disease-coded death certificates from the National Death Index. Participants had follow-up data until June 2014. Mean follow-up was 12.3 ± 3.9 years.

STATISTICAL METHODS. CAC scores were divided into CAC 0, CAC 1 to 399, CAC 400 to 999, and CAC ≥1,000. Baseline characteristics were stratified by CAC groups, reporting number (percentage) and mean ± SD as appropriate.

Mortality rates (per 1,000 person-years) were calculated for all-cause and cause-specific mortality. For purposes of comparison, the proportion of a particular cause-specific death was calculated as: $[(N_{\text{cause-specific deaths}})/(N_{\text{total deaths}})]$ for groups with CAC scores 400 to 999 and ≥1,000.

Multivariate-adjusted Cox regression models were used to assess the relative hazards of CAC groups for cause-specific and all-cause mortality compared to that of a reference group with Agatston score of 0. Additionally, for the purposes of specific comparison, the same models were used to assess risk of patients with CAC ≥1,000 compared to a reference group of CAC 400 to 999 (in the CAC ≥400 subset).

For the Cox regression models, an unadjusted model (Model 1) and a fully adjusted model adjusted for age, sex, and conventional cardiovascular risk factors (Model 2) were chosen. We also included Three other models were also included as supplementary analyses (Supplemental Tables 2 and 3), which were: 1) adjusted for age and sex (Model 3); 2) Model 2 additionally was adjusted for race in the race subset (Model 4); and 3) Model 2 was additionally adjusted for study site (Model 5).

To graphically study risks around the CAC threshold score of 1,000, cubic splines were used to study the dose response relationship between CAC score and mortality outcomes in a multivariate model adjusted for age, sex, and conventional risk factors. Knots were placed at CAC intervals of 100 (to capture risk acceleration at low CAC scores) and CAC score of 1,000.

A 2-sided p value <0.05 was considered statistically significant. All analyses were performed using Stata version 14.0 software (Stata Corp., College Station, Texas).

RESULTS

BASELINE CHARACTERISTICS. There were 2,869 patients (4.3% of the study cohort) with CAC scores ≥1,000. These patients tended to be older (66.3 ± 9.7 years of age), more likely to be men (86.3%), and were at higher risk (by number of risk factors, Framingham Risk Score and ASCVD risk score) than those with lower CAC scores (**Table 1**). In the CAC ≥1,000 group, mean age was 66.3 ± 9.7 years, and 27.4% were younger than 60 years of age. In contrast, among those with CAC scores of 400 to 999, 39.0% were younger than 60 years of age.

Men comprised 55.5% of the CAC 0 group, 74.3% of the CAC 1 to 399 group, 82.5% of the CAC 400 to 999 group, and 86.3% of the CAC ≥1,000 group.

TABLE 1 Baseline Characteristics According to Agatston Score Group

	CAC 0 (n = 29,757)	CAC 1 to 399 (n = 29,601)	CAC 400 to 999 (n = 4,409)	CAC ≥1,000 (n = 2,869)
Age, yrs	49.9 ± 9.2	56.5 ± 9.8	63.0 ± 9.4	66.3 ± 9.7
<50	50.2	24.7	6.9	3.7
50-59	36.0	40.6	32.1	23.7
60-69	11.6	24.8	36.4	35.5
70-79	2.0	8.6	20.3	29.2
≥80	0.2	1.2	4.3	7.9
Race (n = 42,964)*				
White	88.7	89.4	90.7	87.6
Asian	4.2	3.5	3.2	4.0
Black	2.2	2.3	1.5	3.1
Hispanic	3.2	3.0	2.8	3.4
Males	55.5	74.3	82.5	86.3
Hypertension	22.8	34.5	46.5	55.4
Smoking	8.9	10.1	11.0	10.2
Diabetes	3.9	7.5	12.8	19.4
Dyslipidemia	48.0	57.9	65.0	67.3
Family history of coronary heart disease	45.6	46.3	46.5	48.5
Risk factors	1.3 ± 0.9	1.5 ± 0.9	1.8 ± 0.9	1.9 ± 0.9
0	21.7	14.6	10.2	7.7
1	39.0	34.5	28.1	23.7
2	29.2	33.6	36.4	36.4
>2	10.2	17.3	25.4	32.2
FRS, % score	7.8 ± 5.9	12.4 ± 9.0	18.0 ± 12.3	21.8 ± 15.0
<10	71.8	48.5	29.8	22.2
10-19	24.3	36.4	36.5	33.8
≥20	3.8	15.1	33.6	44.0
ASCVD risk score†	3.8 ± 4.7	8.6 ± 8.7	15.1 ± 12.0	20.2 ± 14.9
<5	76.9	43.8	16.0	8.6
5-20	21.7	47.5	59.0	52.1
≥20	1.4	8.7	25.0	39.2

Values are mean ± SD or n (%). *Data were available for only a subset of the study population. Detailed data for a number of participants in each subgroup can be found in Supplemental Table 1. †Pooled cohort equations ASCVD risk score.

ASCVD = Atherosclerotic Cardiovascular Disease; CAC = coronary artery calcium score; FRS = Framingham Risk Score.

Generally, with increasing CAC score, the percentage of participants with conventional cardiovascular risk factors increased. The distribution of specific risk factors is shown in Table 1.

Those with CAC scores ≥1,000 had a mean ASCVD PCE risk score of 20.2 ± 14.9%, in contrast to a mean score of 15.1 ± 12.0% for the CAC 400 to 999 group. Although mean risk scores were high in the CAC ≥1,000 group, the distribution (Table 1) indicates that many scores were lower in the range where clinical risk might have been considered uncertain (ASCVD score: 5% to 20%).

IMAGING CHARACTERISTICS. In those with a CAC score ≥1,000, most had 4-vessel CAC (52.4%) (Table 2). Table 2 shows the distribution of imaging characteristics, including extracoronary artery calcium by CAC group. The CAC ≥1,000 group tended to have not only a higher total mean density but also a substantially greater total CAC area than those with lower CAC scores. Additionally, those with extensive CAC ≥1,000 also tended to have more diffuse systemic vascular disease than those with lower CAC scores, with 79.3% having TAC, 45.7% having AVC, and 21.4% having MVC.

ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY BY CAC GROUP. Incidence rates of all outcomes increased across all causes of mortality with increasing CAC scores (Figure 1). Individuals with CAC scores ≥1,000 had approximately twice the mortality rate of those with CAC 400 to 999 across all causes of mortality. For CVD mortality, the mortality rate per 1,000 person-years was 8.0 for those with CAC scores ≥1,000 compared with 3.6 for those with CAC scores of 400 to 999. Similarly for CHD mortality, the mortality rate of the CAC ≥1,000 group was more than twice that of the CAC 400 to 999 group (5.1 vs. 2.1, respectively, per 1,000 person-years).

In those with CAC ≥1,000, the most common cause of death was CVD (42.6%) followed by cancer (24.3%) (Figure 2), whereas CVD death (36.5%) constituted a smaller portion of all deaths in the CAC 400 to 999 score group, followed by cancer (28.0%).

MULTIVARIATE ADJUSTED HAZARD RATIOS. Adjusted for conventional cardiovascular risk factors, those with CAC ≥1,000 had a 5.04- (95% CI: 3.92 to 6.48), 6.79- (95% CI: 4.74 to 9.73), 1.55- (95% CI: 1.23 to 1.95), and 2.89-fold (95% CI: 2.53 to 3.31) risk of CVD, CHD, cancer, and all-cause mortality, respectively (Table 3, A. CAC 0 Reference Group), compared to those with CAC=0.

In a similarly adjusted model, those with CAC scores ≥1,000 had a 1.71- (95% CI: 1.41 to 2.08), 1.84- (95% CI: 1.43 to 2.36), 1.36- (95% CI: 1.07 to 1.73), and 1.51-fold (95% CI: 1.33 to 1.70) increase in CVD, CHD, cancer, and all-cause mortality, respectively (Table 3, B. CAC 400 to 999 Reference Group), compared to those with CAC scores of 400 to 999.

The relationship between CAC score and multivariate adjusted risks of cause-specific and all-cause mortality is displayed graphically in Figure 3. Increasing CAC score above 1,000 led to higher hazard ratios for all causes of mortality (Figure 3). Although the hazard ratio increases with a slightly steeper slope when the CAC score is <1,000, the hazard ratio continues to increase when CAC is ≥1,000, with no apparent upper CAC threshold for this increase of both cause-specific and all-cause mortality.

DISCUSSION

This study provides the most extensive description of individuals with extreme CAC scores (CAC ≥1,000) to date. Findings show those with CAC scores ≥1,000 have both a higher area and density of calcification, a more dispersed pattern of calcification in their coronary artery tree (most had 4-vessel disease), with a markedly more diffuse distribution of extracoronary calcification than the other CAC groups. Additionally, this study found that extreme CAC scores (≥1,000) are associated with a substantially increased risk of CVD, CHD, cancer, and all-cause mortality, and importantly, those with CAC scores ≥1,000 are at an almost 2-fold higher risk of CVD mortality than those with CAC scores of 400 to 999 (**Central Illustration**). Although the mortality risk levels off slightly after the CAC score reaches 1,000, risk still increases with no apparent upper CAC threshold for both all-cause and cause-specific mortality.

The few prior smaller studies of CAC patients with scores ≥1,000 explored only all-cause rather than cause-specific mortality or investigated individual coronary endpoints rather than mortality outcomes (1,12). For example, Patel et al. (1) showed that, among 1,593 patients with extensive Agatston scores, increasing CAC led to decreased survival, with continued increased mortality risk past CAC those with scores >2,000 (1). Other prior studies have suggested that, although extensive CAC scores may be associated with higher angina, they are not associated with harder CHD events (12). For example, in the MESA (Multi-Ethnic Study of Atherosclerosis; NCT00005487) study, Coylewright et al. (12) found that, in those with extensive CAC scores, ≥1,000 (n = 257), there was no greater risk of CHD death or myocardial infarction than in those with high CAC scores (n = 420 in the CAC 400 to 999 group). That finding has been interpreted as being consistent with the notion that a denser plaque phenotype may be no riskier than lower CAC scores and could perhaps be protective.

Indeed, with increasing recognition from other imaging modalities, that denser calcified plaque may be more stable, and many have cast doubt on the exceptional risk of extensive CAC scores (CAC score ≥1,000). For example, a seminal paper by Criqui et al. (17) found that, although higher CAC volume led to increased CHD and CVD risk, higher CAC density was actually significantly protective against CHD and CVD risk when CAC volume was kept constant. The protective effect of high-density plaque makes sense because calcified plaque is more stable than low attenuation plaque (predominantly noncalcified) in prior studies using intravascular ultrasonography and CTA (18-21). Because the CAC score is a combination of plaque volume and density, some investigators have speculated that many patients who have extensive CAC scores may simply have higher plaque density yet not more plaque burden, which might actually lower CVD risk (17,18,22,23). Similarly, there has been much discussion about endurance athletes, such as marathon runners, whose higher CAC scores may be driven by higher plaque density, which may be relatively protective (24-28).

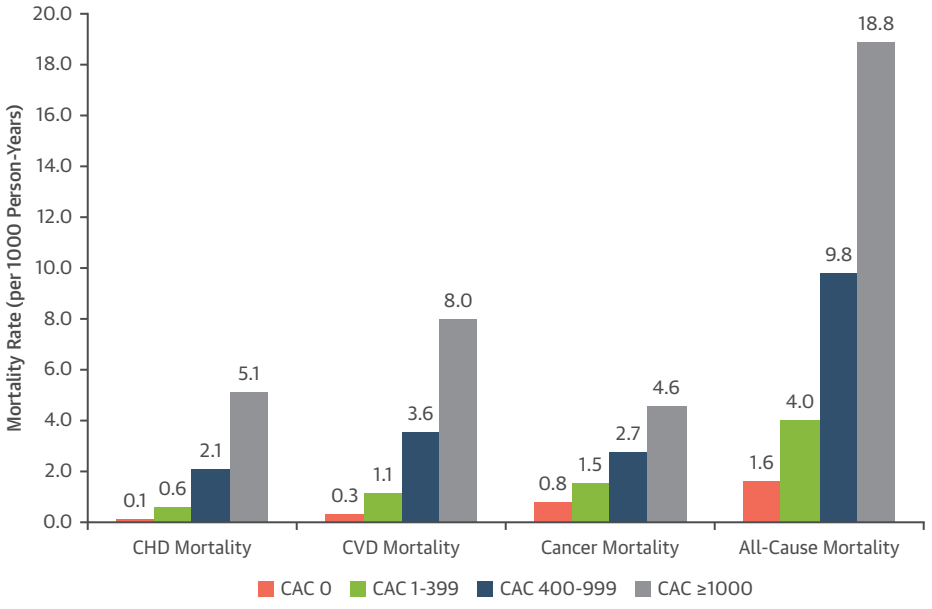
TABLE 2 Imaging Characteristics According to Agatston Score Group

Imaging Characteristics 1	CAC 0 (n = 26,531)	CAC 1 to 399 (n = 22,572)	CAC 400 to 999 (n = 3,329)	CAC ≥1,000 (n = 2,246)
Number of vessels with CAC	0 ± 0	1.9 ± 0.9	3.2 ± 0.7	3.5 ± 0.6
0	100.0	0.0	0.0	0.0
1	0.0	42.6	0.7	0.0
2	0.0	31.6	12.1	3.7
3	0.0	20.7	53.5	43.9
4	0.0	5.2	33.7	52.4
Imaging Characteristics 2	**CAC 0 (n = 16,250)**	**CAC 1 to 399 (n = 14,214)**	**CAC 400 to 999 (n = 2,147)**	**CAC ≥1,000 (n = 1,413)**
TAC	11.7	39.1	67.3	79.3
TAC 1-399	10.7	30.9	39.4	33.1
TAC 400-999	0.6	4.7	12.4	15.1
TAC ≥1,000	0.4	3.6	15.6	31.1
Imaging Characteristics 3	**CAC 0 (n = 4,842)**	**CAC 1 to 399 (n = 3,842)**	**CAC 400 to 999 (n = 739)**	**CAC ≥1,000 (n = 584)**
AVC	4.1	16.6	39.5	45.7
AVC 1-399	3.7	15.4	32.6	36.8
AVC 400-999	0.2	0.5	3.5	6.2
AVC ≥1,000	0.1	0.7	3.4	2.7
Imaging Characteristics 4	**CAC 0 (n = 4,842)**	**CAC 1 to 399 (n = 3,843)**	**CAC 400 to 999 (n = 739)**	**CAC ≥1,000 (n = 584)**
MVC	1.4	6.6	19.4	21.4
MVC 1-399	1.2	4.9	13.7	14.4
MVC 400-999	0.2	1.0	3.2	2.4
MVC ≥1,000	0.0	0.7	2.4	4.6
Imaging Characteristics 5	**CAC 0 (n = 9,678)**	**CAC 1 to 399 (n = 8,575)**	**CAC 400 to 999 (n = 1,159)**	**CAC ≥1,000 (n = 640)**
Estimated total area, mm^2	0 ± 0	37.5 ± 41.9	254.1 ± 70.3	691.6 ± 365.8
Total mean density, HU	0 ± 0	201.5 ± 45.7	251.9 ± 35.1	272.7 ± 34.8
130-199	0.0	53.0	2.9	0.2
200-299	0.0	43.7	88.1	79.5
300-399	0.0	3.3	9.0	20.2
≥400	0.0	0.1	0.0	0.2

Values are mean ± SD or %.

AVC = aortic valve calcium; MVC = mitral valve calcium; TAC = thoracic artery calcium; other abbreviations as in Table 1.

FIGURE 1 Mortality Rate Per 1,000 Person-Years for CVD, CHD, Cancer, and All-Cause Mortality by CAC Score Group



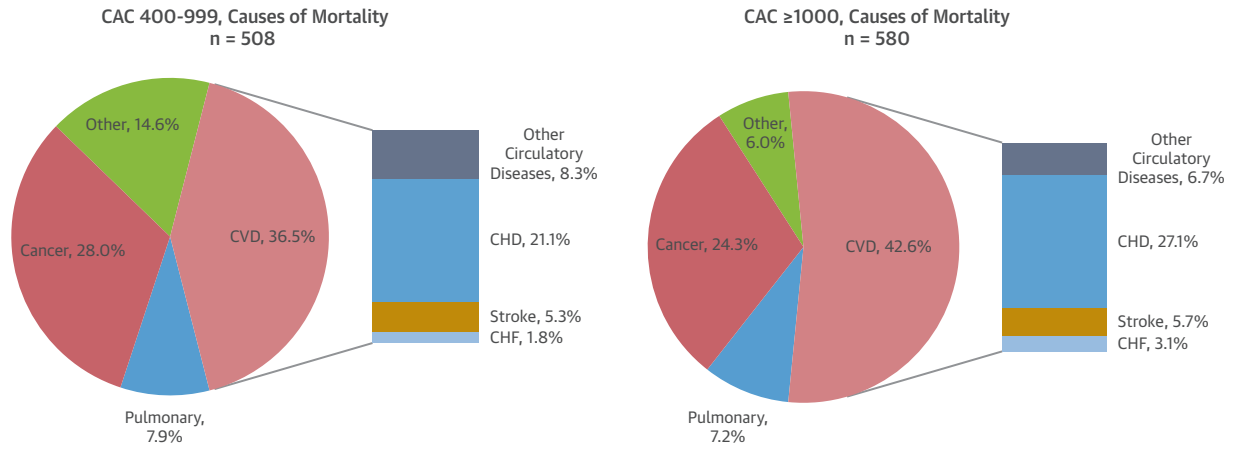
Incidence rates increased for all-cause and cause-specific mortality with increasing CAC scores. Particularly those with CAC score ≥1,000 had a 5.1, 8.0, 4.6, and 18.8 mortality rate per 1,000 person-years for CHD, CVD, cancer, and all-cause mortality, respectively. In contrast, those with CAC scores from 400 to 99 had a 2.1, 3.6, 2.7, and 9.8 mortality rate per 1,000 person-years for CHD, CVD, cancer, and all-cause mortality, respectively. *A version of this figure including error bars for 95% confidence interval can be found in Supplemental Figure 1. CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease.

However, the present study shows that those with CAC scores ≥1,000 constitute a distinct population of patients who are at a significantly higher risk of CVD, CHD, cancer, and all-cause mortality than those with CAC scores 400 to 999. Furthermore, not only did these patients have markedly higher CAC burden (CAC area), they also had more extracoronary calcium, such as TAC, AVC, and MVC, than patients with lower CAC. Therefore, it appears that patients with extreme CAC scores have a higher total burden of both coronary and extracoronary atherosclerosis than those with just high CAC scores (CAC sores of 400 to 999). The most likely reason why the present data contradict those of the prior study by Coylewright et al. (12) has to do with statistical power. Although the analysis of the MESA study by Coylewright et al. (12) had just 257 patients with CAC scores ≥1,000 (too few to show a difference in CHD mortality), the cohort in the present study included 2,869 patients with CAC scores ≥1,000, which is 10-fold more than the number in the MESA cohort, with longer follow-up (12).

Guidelines from organizations such as the American College of Cardiology (ACC) and American Heart Association (AHA) currently describe the highest risk group for coronary events and mortality as patients with CAC scores >300 or >400 (8-11). The present data argue that those with extensive CAC scores (≥1,000) represent a distinct group of patients at the highest risk for all-cause mortality and cardiovascular mortality. The present analyses indicate a potential for future guidelines to recognize asymptomatic patients with extensive Agatston scores (CAC ≥1,000) as a distinct group in whom targeted and more aggressive treatment should be considered.

For example, many current recommendations in preventive cardiology include goals for LDL lowering and blood pressure reduction, among other modifiable risk factors (29-32). Specifically, a reduction of approximately 38 mg/dl (1 mmol/l) of LDL-C has been found to reduce the risk of cardiovascular mortality and nonfatal infarctions by 20% to 25% (33,34); and the newest evidence from the IMPROVE-IT (Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin [Ezetimibe/Simvastatin] vs Simvastatin [P04103] (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; NCT00202878), FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects

FIGURE 2 Causes of Mortality for CAC Score 400 to 999 and CAC Score ≥1,000 Groups



In both of the CAC groups, the leading cause of death was CVD (CAC scores: 400 to 999 = 36.5%; CAC scores ≥1,000 = 42.6%), followed by cancer (CAC scores of 400 to 999 = 28.0%; CAC scores ≥1,000 = 24.3%). CHD mortality, as a subset of CVD mortality, constituted 21.1% of deaths in the CAC score 400 to 999 group and 27.1% of deaths in the CAC score ≥1,000 group. CHF = congestive heart failure; other abbreviations as in Figure 1.

With Elevated Risk; NCT01764633), and ODYSSEY-OUTCOMES (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; NCT01663402) clinical trials suggest that combining statins with nonstatins, such as ezetimibe or PCSK9 inhibitors, can significantly reduce CVD outcomes, even in patients who are taking maximally tolerated intensive statin therapy (35-38).

Guidelines from medical societies, particularly the American Association of Clinical Endocrinologists (AACE), have begun recommending very low LDL-C goals (<55 mg/dl) in those who are at "extreme risk" (35,39). Based on the present data, the authors argue that many patients with CAC scores ≥1,000 are at extreme risk and can be considered for the most aggressive therapies, including nonstatin lipid-lowering therapies such as ezetimibe or PCSK9 inhibitors. For example, in the FOURIER trial, which enrolled stable secondary prevention patients for a median of 2.2 years after their last CVD event, the annualized cardiovascular death rate (0.77%/year) in the placebo group was lower than the CVD mortality rate these authors observed in asymptomatic primary prevention patients with CAC scores ≥1,000 (8.0 per 1,000 patient-years, or 0.80%/year) (36). Such data from those with CAC scores ≥1,000 help to blur the lines between primary and secondary prevention (40). In addition, prior data suggest a high risk of ischemia in those patients (41), arguing for taking a more thorough history to ensure that they are truly asymptomatic.

TABLE 3 Hazard Ratios for All-Cause and Cause-Specific Mortality by CAC Score Group

CAC 0 Reference Group

Model 1-Unadjusted HRs

Agatston Score	Cause of Mortality, HR (95% CI)			
	CVD	CHD	Cancer	All-Cause
0	Ref.	Ref.	Ref.	Ref.
1-399	3.49 (2.85-4.27)	4.14 (3.05-5.63)	1.96 (1.70-2.26)	2.50 (2.28-2.75)
400-999	10.85 (8.63-13.64)	14.86 (10.64-20.74)	3.52 (2.88-4.30)	6.07 (5.39-6.83)
≥1,000	24.23 (19.49-30.12)	36.26 (26.44-49.73)	5.87 (4.80-7.18)	11.64 (10.38-13.05)

Model 2-Fully Adjusted HRs*

Agatston Score	Cause of Mortality, HR (95% CI)			
	CVD	CHD	Cancer	All-Cause
0	Ref.	Ref.	Ref.	Ref.
1-399	1.77 (1.43-2.18)	1.99 (1.45-2.74)	1.09 (0.94-1.27)	1.37 (1.24-1.52)
400-999	3.09 (2.41-3.97)	3.90 (2.72-5.59)	1.19 (0.95-1.48)	1.98 (1.73-2.25)
≥1,000	5.04 (3.92-6.48)	6.79 (4.74-9.73)	1.55 (1.23-1.95)	2.89 (2.53-3.31)

CAC 400-999 Reference Group

Model 1-Unadjusted HRs*

Agatston Score	Cause of Mortality, HR (95% CI)			
	CVD	CHD	Cancer	All-Cause
400-999	Ref.	Ref.	Ref.	Ref.
≥1,000	2.23 (1.84-2.70)	2.43 (1.90-3.11)	1.65 (1.31-2.09)	1.91 (1.69-2.15)

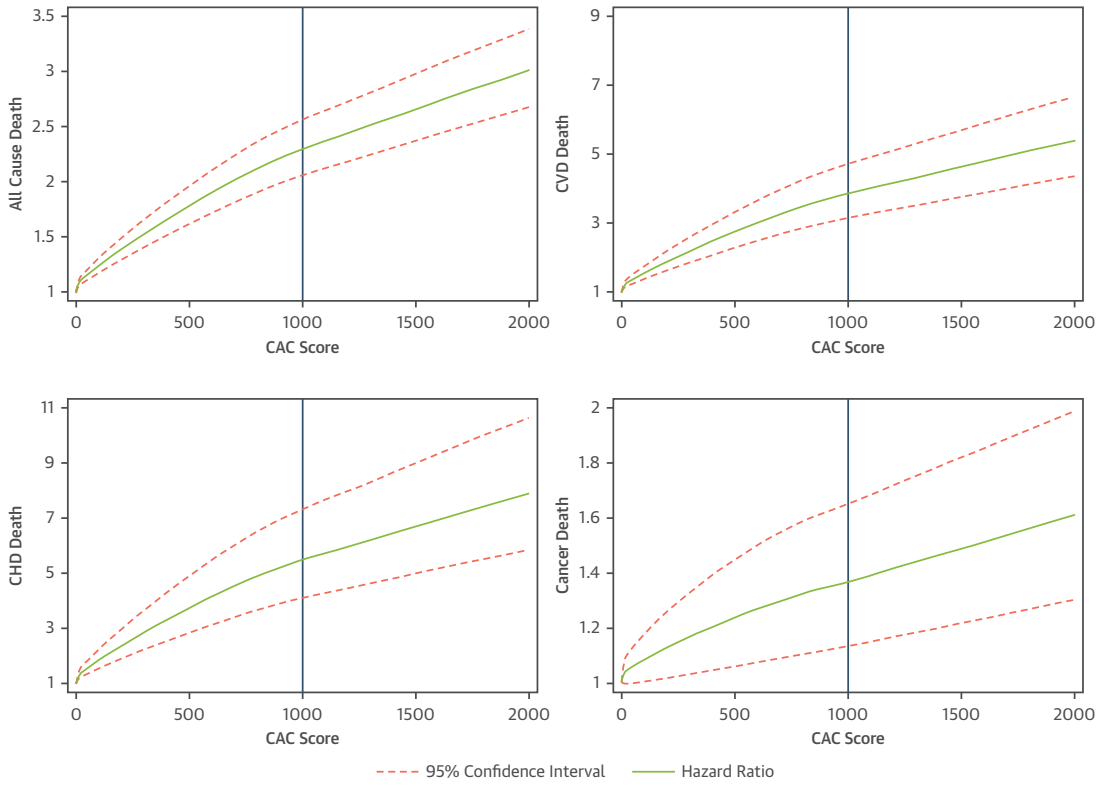
Model 2-Fully Adjusted HRs

Agatston Score	Cause of Mortality, HR (95% CI)			
	CVD	CHD	Cancer	All-cause
400-999	Ref.	Ref.	Ref.	Ref.
≥1,000	1.71 (1.41-2.08)	1.84 (1.43-2.36)	1.36 (1.07-1.73)	1.51 (1.33-1.70)

*Adjusted for age, sex, hypertension, dyslipidemia, smoking, diabetes, and family history of CHD.

CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; Ref. = reference; other abbreviation as in Table 1.

FIGURE 3 Adjusted Hazard Ratios and 95% CI for CVD, CHD, Cancer, and All-Cause Mortality by Continuous CAC Score

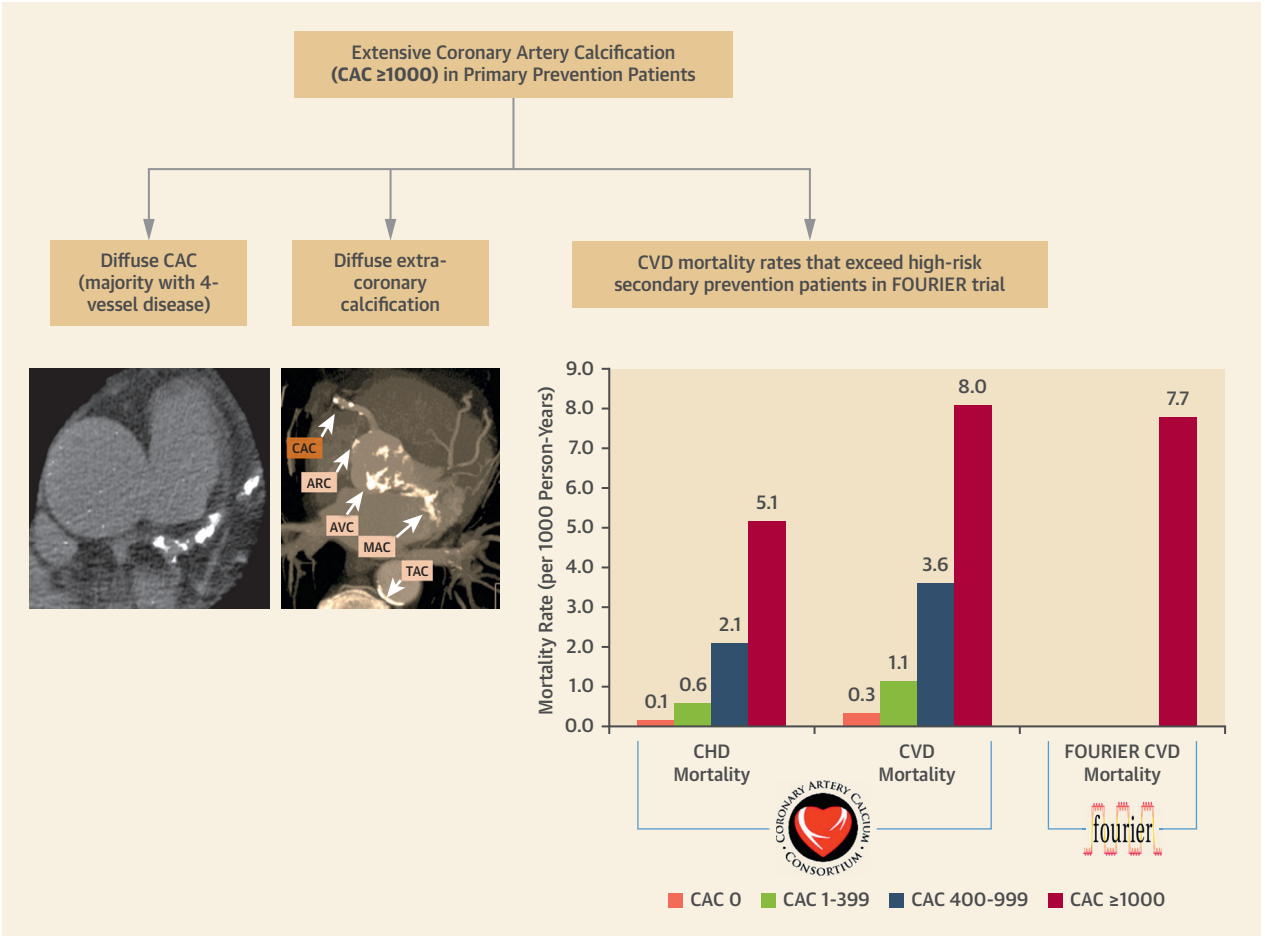


Cubic splines were used to study the relationship between CAC score and mortality outcomes, with hazard ratios adjusted for age, sex, and conventional risk factors. Knots were placed at CAC scores of 100 and 1,000. With increasing CAC score, mortality risk continues to increase logarithmically for all-cause and cause-specific mortality, with no apparent plateau in risk. CI = confidence interval; other abbreviations as in Figure 1.

Patients who are truly asymptomatic should be managed with preventative risk-reducing medications only.

STUDY LIMITATIONS. First, because the CAC Consortium data consist of patients referred for CAC screening, these patients may not be representative of the general population. First, however, previous studies indicate that the CAC Consortium contains patients with characteristics that are generally similar to those of participants in the Framingham Heart Study and MESA studies (13,42). Second, data for covariates such as diabetes, hypertension, and dyslipidemia relied in part on self-reports, and furthermore, these data were adjusted in analytical models rather than reporting of actual blood pressure and lipid profiles. Therefore the models used may be subject to some residual confounding. Third, data for race and advanced imaging characteristics was available only from a subset of the study cohort. However, these data were missing at random relative to CAC scores and outcomes, and therefore, the present authors expect differential bias in analyses using these data points. Fourth, creatinine measurements or information on chronic kidney disease (CKD) was not available in the population analyzed for the present study. Thus, the present authors were unable to adjust for kidney function in this analysis. However, none of these patients had end-stage renal disease at baseline, and through the review of the source populations from which the CAC Consortium was derived, it was expected <1% would have advanced CKD (CKD 3B or above). Fifth, CAC scans were not read at a central laboratory but rather at 4 different centers as part of the clinical workflow. However, the site-specific reading of CAC scores adds generalizability to clinical practice, as these scans closely resemble those done routinely in the community. Sixth and finally, a key limitation is that the present authors did not have data for the follow-up treatment

CENTRAL ILLUSTRATION **Understanding Extensive CAC (CAC Score ≥1,000) in Primary Prevention Patients**



Peng, A.W. et al. J Am Coll Cardiol Img. 2019;■(■):■–■.

Primary prevention patients with extensive CAC (CAC ≥1,000) are unique in their burden of coronary and extra-coronary disease and in their long-term outcomes. Those with CAC ≥1,000 can be found on imaging to have a dispersed pattern of calcification in their coronary artery tree (the majority with 4-vessel disease) and diffuse extra-coronary calcification (TAC, AVC, and MVC). In addition, their annualized CVD mortality rates exceed those of high-risk secondary prevention patients from the FOURIER trial (0.80%/year vs. 0.77%/year). AVC = aortic valve calcium; CAC = coronary artery calcium; CVD = cardiovascular disease; MVC = mitral valve artery; TAC = thoracic artery calcium.

of patients after they received their CAC scores. Those with CAC scores ≥1,000 were most likely treated aggressively; however, such treatment would bias the present results to the null, making the findings even more significant and powerful.

CONCLUSIONS

A study of the largest sample of patients with CAC scores ≥1,000 yet assembled shows that patients with extensive CAC are unique in their burden of coronary and extracoronary disease and in their long-term outcomes. The present data argue for consideration of patients with CAC scores ≥1,000 as a distinct group with CVD mortality greater than that of contemporary secondary prevention trials like FOURIER.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with extensive CAC scores (CAC ≥1,000; 4.3% of our population) have distinct imaging characteristics, with higher area and density of CAC, nearly ubiquitous multivessel disease, and characteristically diffuse extracoronary calcification (TAC, MVC, and AVC). Furthermore, they are unique in their high risk of all-cause and cause-specific mortality, with CAC ≥1,000 patients showing 50% increased risk of CVD mortality compared to those with CAC scores of 400 to 999, independent of conventional CVD risk factors. Furthermore, risk continues to climb logarithmically with higher CAC scores above 1,000, with no clear evidence of a risk plateau. Present data show that these patients have CVD mortality greater than that of secondary prevention trials (such as FOURIER), lending them a unique risk status that may inform intensity of preventive therapy.

TRANSLATIONAL OUTLOOK: Identification of asymptomatic patients with CAC scores ≥1,000 is important in clinical practice, given their very high risk of mortality. More studies comparing outcomes in CAC ≥1,000 patients to routine secondary prevention patients are needed to further inform treatment guidelines. In addition, future randomized controlled trials of aggressive preventative therapies, for example, PCSK9 inhibitors and anti-inflammatory drugs, in patients with CAC scores ≥1,000, may prove helpful to evaluate the benefits of such treatment in this unique group. Last, it may be important to update current guidelines reflecting the best practices in this distinct group of patients with CAC scores ≥1,000.

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KEY WORDS cardiovascular imaging, coronary artery calcium, high risk, primary prevention, risk scoring

APPENDIX For supplemental tables and a figure, please see the online version of this paper.