ORIGINAL RESEARCH

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Long-Term Prognosis After Coronary Artery Calcification Testing in Asymptomatic Patients

A Cohort Study

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Background: The extent of coronary artery calcification (CAC) and near-term adverse clinical outcomes are strongly related through 5 years of follow-up.

Objective: To describe the ability of CAC scores to predict long-term mortality in persons without symptoms of coronary artery disease.

Design: Observational cohort.

Setting: Single-center, outpatient cardiology laboratory.

Patients: 9715 asymptomatic patients.

Measurements: Coronary artery calcification scoring and binary risk factor data were collected. The primary end point was time to all-cause mortality (median follow-up, 14.6 years). Univariable and multivariable Cox proportional hazards models were used to compare survival distributions. The net reclassification improvement statistic was calculated.

Results: In Cox models adjusted for risk factors for coronary artery disease, the CAC score was highly predictive of all-cause mortality ($P < 0.001$). Overall 15-year mortality rates ranged from 3% to 28% for CAC scores from 0 to 1000 or greater ($P < 0.001$). The relative hazard for all-cause mortality ranged from 1.68 for a CAC score of 1 to 10 ($P < 0.001$) to 6.26 for a score of 1000 or greater ($P < 0.001$). The categorical net reclassification improvement using cut points of less than 7.5% to 22.5% or greater was 0.21 (95% CI, 0.16 to 0.32).

Limitations: Data collection was limited to a single center with generalizability limitations. Only binary risk factor data were available, and CAC was only measured once.

Conclusion: The extent of CAC accurately predicts 15-year mortality in a large cohort of asymptomatic patients. Long-term estimates of mortality provide a unique opportunity to examine the value of novel biomarkers, such as CAC, in estimating important patient outcomes.

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A coronary artery calcification (CAC) test is used to estimate cardiovascular prognosis and provides additive information, above and beyond traditional cardiac risk factors, to estimate important clinical outcomes (1, 2). The published data show a strong relationship between the extent of CAC and adverse clinical outcomes across diverse asymptomatic patient subgroups and population cohorts (1–10). However, most risk-stratification evidence on CAC involves short-term prognosis, with few registries reporting follow-up beyond 5 years (1, 11).

For screening with CAC, a large proportion of tested persons is middle-aged and has the possibility for long-term survival. According to published data, CAC incidence increases with age and the potential interaction between CAC and the length of follow-up is important (1, 6, 7). Given the progressive nature of atherosclerotic disease and the prevalence of potentiating cardiac risk factors, an understanding of the long-term sequelae of low- to high-risk CAC scores may prove useful in defining the value of cardiovascular testing for patients of various age groups. Thus, the aim of this report was to describe the prognostic significance of long-term follow-up across an array of CAC scores for asymptomatic patient subgroups of younger and older women and men.

METHODS

Study Population

From 1996 to 1999, primary care physicians referred 9715 patients to 1 outpatient clinic as part of a cardiology outreach screening program in the Tricare Healthcare System. These patients did not have symptoms of coronary artery disease and were from the area surrounding Nashville, Tennessee (86% were white, 8% were African American, 4% were Hispanic, and 2% were Asian). The median annual per capita income was $33 000. Each patient paid $69 out of pocket for the procedure at the time of service.

All patients signed informed consent for the index CAC scan and follow-up procedures; Centennial Medical Center (Nashville, Tennessee) provided institutional approval. Deidentified data were sent to 3 participating institutions (Emory University School of Medicine, Atlanta, Georgia; Cedars-Sinai Medical Center, Los Angeles, California; and Weill Cornell Medical College, New York, New York) for analysis. Institutional review board approval was garnered for data analysis at each institution. Five-year follow-up was previously reported in a subgroup of these patients (3).

Cardiac Risk Factor Data

A detailed history of cardiac risk factors was ascertained at the time of testing, as previously described (3). In addition to age, a medical history of hypertension was collected and defined as having had a pre-

scription for an antihypertensive medication or documented blood pressure 140/90 mm Hg or higher. A history of diabetes was defined as having had a prescription for an antidiabetic medication or a history of elevated blood glucose levels greater than 7 mmol/L (>126 mg/dL). Patients who received a dyslipidemic medication or those with a history of elevated cholesterol levels were classified as dyslipidemic. Patients who had a relative with a history of coronary heart disease (CHD) were considered to have a family history of CHD.

CAC Image Acquisition and Interpretation

All patients had CAC imaging using electron beam tomography or multislice computed tomography. The correlation between CAC measurements derived from electron beam tomography with multislice computed tomography was high ($r = 0.99$; $n = 100$), consistent with previous reports (12, 13). Prior reports have detailed our methods for measuring CAC (3, 7, 9, 11). The CAC score was calculated using the method of Agatston and colleagues (14) and grouped as 0, 1 to 10, 11 to 99, 100 to 399, 400 to 999, and 1000 or greater (3).

Follow-up Methods

Long-term follow-up was undertaken in a consecutive series of 9715 patients. Survival status was obtained by querying the National Death Index, a central computerized index of death record information from the National Center for Health Statistics (15). Follow-up status was ascertained through 1 May 2014. Mean follow-up for surviving patients was 14.6 years (range, 12.9 to 16.8). During this observational period, 936 patients were confirmed as dead.

Statistical Analysis

The CAC subgroups with binary risk factor variables were compared by using chi-square analysis. The continuous measures with binary variables, such as age, were compared by using *t* tests or analyses of variance statistics, where appropriate.

The primary end point of this analysis was time to all-cause mortality. Univariable and multivariable Cox proportional hazards models were used to estimate the relationship and added value of cardiac risk factors and CAC scores. Unadjusted, overall survival curves were plotted by the CAC subgroups. Hazard ratios and 95% CIs were calculated from the Cox model. Adjusted models included the CAC score and cardiac risk factor variables, including hypertension, diabetes, dyslipidemia, age, sex, and family history of CHD. The proportional hazards assumption was evaluated by assessing the constancy of the parallel plotted lines in the log–log graph and tested on the basis of Schoenfeld residuals. When we included a variable representing equipment use (electron beam tomography vs. multislice computed tomography), the prognostic models did not change. We examined the goodness of fit of the multivariable models using the Hosmer–Lemeshow test on the basis of quantiles of risk, including the cardiac risk factor model and the combined risk factor and CAC model; both were nonsignificant ($P > 0.80$).

EDITORS' NOTES

Context

Clinicians use coronary artery calcification scores to predict the risk for myocardial infarction from coronary artery disease. The score also predicts all-cause mortality, but more is known about the accuracy of its short-term predictions than its long-term predictions.

Contribution

The study found that the score accurately predicted all-cause mortality at 15 years in asymptomatic patients.

Caution

The study was limited to a single center.

Implication

Coronary artery calcification scores may help motivate patients with high scores to adopt healthier lifestyles and may help researchers stratify study patients more effectively.

The net reclassification improvement (NRI) statistic was calculated, including the percentage of deaths and survivors correctly reclassified when comparing 2 models (model 1 with available cardiac risk factor variables, including age, sex, hypertension, diabetes, dyslipidemia, cigarette smoking, and a family history of CHD, and model 2 with the cardiac risk factor variables and the CAC score) using the methods of Pencina and colleagues (16, 17). Although no specific cut points for 15-year mortality are established, we evaluated 2 sets of cut points for the NRI corresponding to 7.5% to 22.5% mortality (18, 19) and alternatively used cut points of less than 10%, 10% to 19.9%, and 20% or greater (19–21). From model 1, we calculated the predicted probability of 15-year mortality and then categorized a variable on the basis of quartile measurements. The quartiles of predicted mortality were compared by cardiac risk factors using chi-square analysis.

Statistical analysis was done using Stata, version 13.0 (StataCorp); SAS, version 9.2 (SAS Institute); and SPSS, version 22.0 (IBM SPSS).

Role of the Funding Source

This study received no external funding.

RESULTS

Cardiac Risk Factors and CAC Descriptive Statistics

In Table 1, the differences across cardiac risk factors were reported by quartiles of 15-year predicted mortality. Patients in the lower quartiles of predicted mortality were generally middle-aged, were less often female, and had a higher prevalence of dyslipidemia and family history of CHD. By comparison, the patients in the higher quartiles of predicted mortality were older; were more often female; and had a greater prevalence of hypertension, diabetes, and smoking.

Table 1. Cardiac Risk Factor Prevalence Across Quartiles of Predicted 15-y Mortality in 9715 Asymptomatic Patients*

Variable	Patients, *n*	Predicted 15-y Mortality Quartile, %				*P* Value
		<3.2% (*n* = 2428)	3.2%–5.8% (*n* = 2429)	5.9%–10.1% (*n* = 2429)	>10.1% (*n* = 2429)	
Age						<0.001
<40 y	752	21.4	6.6	2.7	0.3	–
40–49 y	2914	51.2	38.0	21.4	9.4	–
50–59 y	3423	26.7	40.6	43.5	30.1	–
60–69 y	1898	0.7	13.4	26.4	37.5	–
70–79 y	659	0	1.3	5.7	20.1	–
≥80 y	69	0	0	0.2	2.6	–
Women	3950	39.0	39.2	41.0	43.4	0.005
Hypertension	4220	12.6	37.6	50.8	72.7	<0.001
Dyslipidemia	6077	70.9	65.3	59.7	54.4	<0.001
Diabetes	810	0.2	1.7	5.1	26.3	<0.001
Current smoker	3817	9.1	30.5	49.7	67.8	<0.001
Family history of CHD	6672	80.5	72.5	63.4	58.4	<0.001

CHD = coronary heart disease.
* Percentages may not sum to 100% due to rounding.

In Table 2, we report the frequency of risk factors across the CAC subgroups. Patients with higher-risk CAC scores were more often older; were less likely to be female; and had a greater prevalence and extent of cardiac risk factors, such as hypertension, diabetes, and smoking.

Unadjusted All-Cause Mortality

Overall mortality was 3%, 6%, 9%, 14%, 21%, and 28%, respectively, for CAC subgroups with scores of 0, 1 to 10, 11 to 100, 101 to 399, 400 to 999, and 1000 or greater ($P < 0.001$). The relative hazard for all-cause death was 1.68, 2.91, 4.52, 5.53, and 6.26, respectively ($P < 0.001$). Within each of the estimated predicted mortality quartiles (Figure), survival worsened in a generally proportional manner in the subgroups with increasing CAC scores ($P < 0.001$ for all 4 patient subgroups).

In Cox models adjusting for CAD risk factors, the CAC score was highly predictive of time to all-cause mortality ($P < 0.001$). A graded or proportional relationship between risk and CAC extent was seen at 10 and 15 years of follow-up.

NRI With CAC Over and Above the CAD Risk Factors

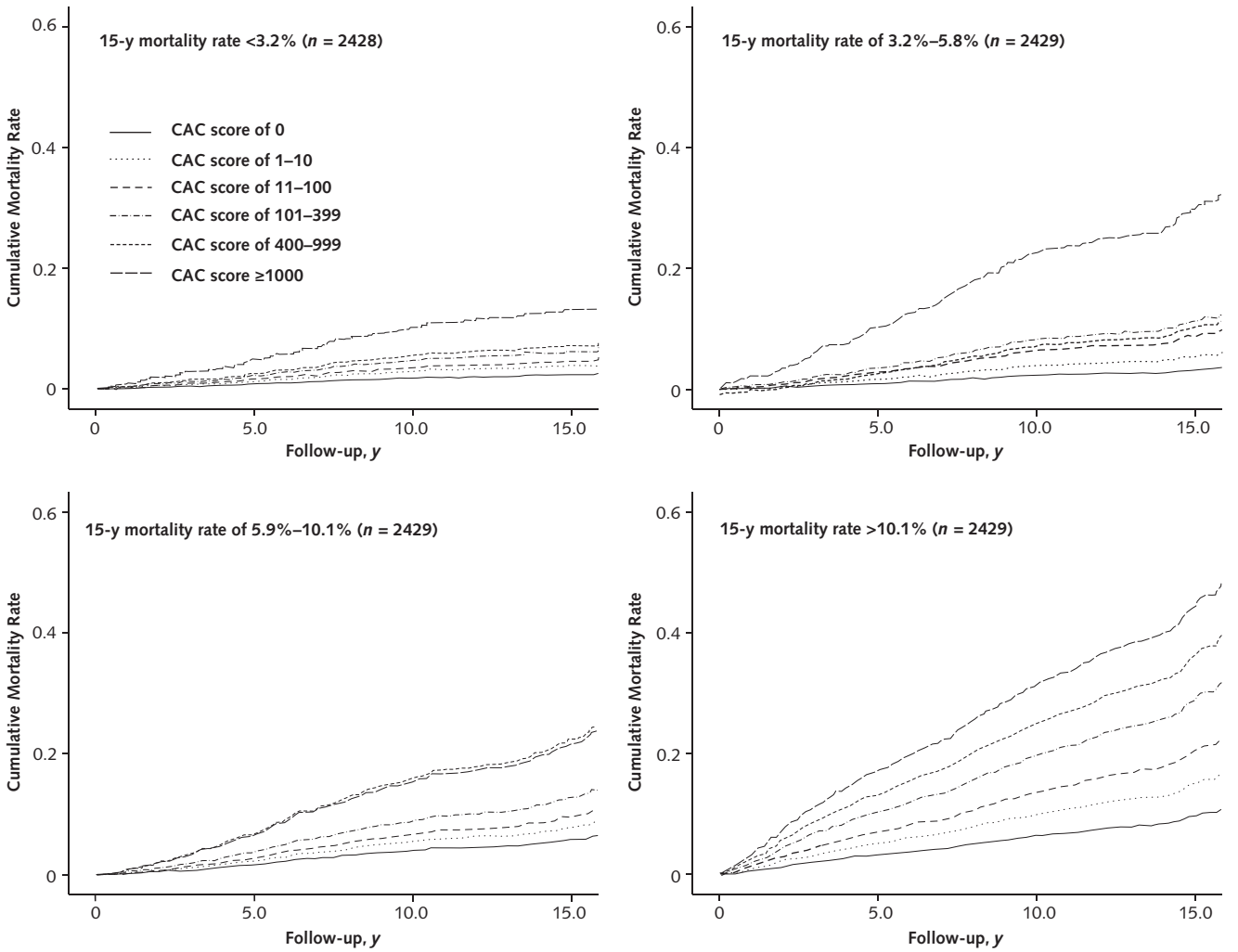
For cut points ranging from less than 7.5% to 22.5% or greater, the categorical NRI was 0.21 (95% CI, 0.16 to 0.32), with 27.9% of patients who died correctly reclassified by the model with CAC added (Table 3). However, the model with CAC incorrectly reclassified 7.4% of survivors to a higher-risk category than the model with cardiovascular risk factors alone. Use of an alternative set of cut points (<10% to ≥20%) resulted in a slight increase in the NRI (0.239), with 34.7% of

Table 2. Cardiac Risk Factor Prevalence Across CAC Score Subgroups*

Variable	Patients, *n*	CAC Score Subgroup, %						*P* Value
		0 (*n* = 4864)	1–10 (*n* = 903)	11–100 (*n* = 1856)	101–399 (*n* = 1252)	400–999 (*n* = 562)	≥1000 (*n* = 278)	
Age								<0.001
<40 y	752	10.1	8.2	5.7	4.2	2.8	4.3	–
40–49 y	2914	33.4	32.7	27.6	25.3	21.7	15.1	–
50–59 y	3423	32.7	35.4	39.8	38.3	35.9	33.1	–
60–69 y	1898	16.6	17.9	20.1	24.2	27.9	34.9	–
70–79 y	659	6.5	5.3	6.0	7.5	10.7	10.1	–
≥80 y	69	0.6	0.4	0.8	0.6	0.9	2.5	–
Women	3950	42.1	41.0	38.6	39.2	39.1	36.7	0.049
Hypertension	4220	36.8	45.3	47.5	51.0	58.2	62.9	<0.001
Dyslipidemia	6077	57.8	67.3	66.1	68.4	70.1	65.1	<0.001
Diabetes	810	5.7	8.5	8.1	11.8	17.3	22.7	<0.001
Current smoker	3817	33.6	39.0	41.4	49.7	51.4	53.6	<0.001
Family history of CHD	6672	69.7	67.0	68.5	69.1	66.2	60.8	0.024
15-y predicted mortality quartile								<0.001
<3.2%	2428	31.7	24.9	20.0	16.9	10.0	8.3	–
3.2%–5.8%	2429	26.6	26.6	26.3	20.3	18.5	16.5	–
5.9%–10.1%	2429	23.1	25.5	27.5	27.5	27.4	23.0	–
>10.1%	2429	18.5	23.0	26.1	35.3	44.1	52.2	–

CAC = coronary artery calcification; CHD = coronary heart disease.
* Percentages may not sum to 100% due to rounding.

Figure. Cumulative incidence of all-cause mortality by CAC across 15-y predicted mortality quartiles.



All *P* values are <0.001. CAC = coronary artery calcification.

deaths correctly reclassified but −10.8% of survivors misclassified (Table 4).

DISCUSSION

The past several decades have seen reports on the prognostic value of CAC scores, with most publications having a limited duration of follow-up (1, 3, 5, 7, 10, 11, 22). Challenges remain in understanding the link between an index CAC scan to more lengthy follow-up because the duration of expected life-years affects the prognostic significance of low- and high-risk test results. The current findings support effective long-term (that is, approximately 15-year) mortality stratification and risk reclassification based on CAC measurements. Risk estimations projecting through approximately 15 years more closely approach the concept of lifetime risk projections (23). Thus, an understanding of the long-term sequelae of low- to high-risk CAC scores may be useful in defining the effect of cardiovascular screening on life expectancy estimates among patients of various ages.

The Framingham risk score is a well-established method for estimating 10-year CHD risk, whereas we applied CAC scoring to estimate 15-year all-cause mortality. A reasonable question is whether overlap exists between these scores. Age is strongly related to CAC, with incidence increasing in older patients; however, our data note substantive risk reclassification (that is, NRI >0.20) in patients with CAC and risk factors beyond age and other cardiac risk factors. Accordingly, the extent of CAC as a risk marker and subcomponent of atherosclerotic disease represents the cumulative exposure of cardiac risk factors and other novel contributors.

In addition, several patterns emerged from the NRI analyses. Based on clinical risk factors in a model, most patients had either low or intermediate risk, with a few categorized as clinically high-risk. For survivors, a large proportion of low- to intermediate-risk patients (based

Table 3. NRI for Adding CAC Score to a Model With Cardiac Risk Factors, Including Age, Sex, Hypertension, Dyslipidemia, Diabetes, and Cigarette Smoking, by Cut Point*

Variable	Cut Point			Total, %
	<7.5%	7.5%–22.4%	≥22.5%	
Nonevents (*n* = 8779)				
<7.5%	5279 (60.10)	1499 (17.10)	4 (0.05)	77.30
7.5%–22.4%	940 (10.70)	866 (9.90)	125 (1.40)	22.00
≥22.5%	0 (0)	39 (0.40)	27 (0.30)	0.70
Total, %	70.80	27.40	1.80	100
Events (*n* = 936)				
<7.5%	280 (30.00)	265 (28.30)	1 (0.10)	58.30
7.5%–22.4%	86 (9.20)	197 (21.00)	82 (8.70)	39.00
≥22.5%	0 (0)	1 (0.10)	24 (2.60)	2.70
Total, %	28.30	48.20	23.50	100

Categorical NRI (95% CI)	*P* Value	Deaths Correctly Reclassified, %	Survivors Correctly Reclassified, %
0.205 (0.164–0.319)	<0.001	27.9	7.4

CAC = coronary artery calcification; NRI = net reclassification improvement.
* Values are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100% or the total indicated due to rounding.

on the risk factor model) were incorrectly reclassified as higher risk when CAC was added to the Cox model. For the model containing CAC, nearly 40% of all nonsurviving patients in the low- to intermediate-risk categories were reclassified to a higher risk status.

The use of all-cause mortality as an end point, particularly for longer follow-up, expands the evidence base for a novel biomarker, such as CAC, beyond the traditional cardiovascular disease outcomes. Although calcification is a disease-specific marker of the burden of subclinical atherosclerosis, our prognostic models estimating all-cause mortality may be indicative of its predictive value as a global measure of vascular health. In the assessment of biomarkers, researchers have argued for the use of all-cause mortality as a summary measure of consequential disease-specific mortality and potential harm induced after diagnostic testing (24–26). Evidence herein suggests that low- to high-risk CAC scores broadly categorize patient mortality risk and may be beneficial across patient subgroups in which global risk scores are less accurate (1, 2, 27).

Among patients without CAC, the 15-year all-cause mortality rate was 3%. By comparison, the 5-year rate of cardiac events was less than 0.5% in several reports and roughly equal to population-based risk estimates (22, 28–30). As follow-up lengthened, all-cause mortality rates increased: Patients with a CAC score of 0 had a mortality rate of 0.7% at 7 years (11). The incident mortality curves revealed very low mortality through 5 years, but mortality seemed to increase substantively between 5 and 15 years of follow-up. In our registry, the lengthy follow-up and higher mortality rate (3%) may have captured the progressive nature of atherosclerosis or other competing risks (such as diabetes-related complications) among incident all-cause deaths. In our cohort, many of the patients without CAC

Table 4. NRI for Adding CAC Score to a Model With Cardiac Risk Factors, Including Age, Sex, Hypertension, Dyslipidemia, Diabetes, and Cigarette Smoking, by Alternative Cut Points*

Variable	Cut Point			Total, %
	<10.0%	10.0%–19.9%	≥20.0%	
Nonevents (*n* = 8779)				
<10.0%	6810 (77.6)	1137 (13.0)	65 (0.7)	91.3
10.0%–19.9%	324 (3.7)	221 (2.5)	125 (1.4)	7.6
≥20.0%	28 (0.3)	29 (0.3)	40 (0.5)	1.1
Total, %	81.6	15.8	2.6	100
Events (*n* = 936)				
<10.0%	456 (48.7)	252 (26.9)	30 (3.2)	78.8
10.0%–19.9%	30 (3.2)	62 (6.6)	74 (7.9)	17.7
≥20.0%	1 (0.1)	0 (0)	31 (3.3)	3.4
Total, %	52.0	33.5	14.4	100

Categorical NRI (95% CI)	*P* Value	Deaths Correctly Reclassified, %	Survivors Correctly Reclassified, %
0.239 (0.204–0.275)	<0.001	34.7	−10.8

CAC = coronary artery calcification; NRI = net reclassification improvement.
* Values are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100% or the total indicated due to rounding.

were younger but had a sizeable burden of cardiac risk factors. Although it cannot be quantified, failure to document CAC may affect patient behaviors, such as smoking cessation, or treatment adherence for hypertension, diabetes, or dyslipidemia. Thus, even for patients who are free of CAC on the index examination, guideline-directed treatment and lifestyle-modification approaches remain mainstays of clinical practice for effective long-term risk reduction in patients with cardiac risk factors.

Previous findings also highlighted the excess hazard for worsening clinical outcomes among persons with high CAC scores. At 5 years of follow-up, incident cardiac death or myocardial infarction rates among patients with high CAC scores (300 to 400 and higher) ranged from 4% to 9% (22, 31). In the current report, CAC scores of 400 or greater had a 15-year all-cause mortality rate that exceeded 20%, confirming the importance of length of follow-up in defining substantively higher-risk status. In fact, on the basis of 5-year estimates, 1 in 20 persons with a CAC scan indicating high-risk would be expected to have a cardiac event. By comparison, through 15 years of follow-up, 1 in 5 patients with high-risk CAC scans had died, reflecting progressive disease and perhaps nonlinear risk that may only be found through more lengthy follow-up. These data are consistent with some reports that note that high-risk subclinical atherosclerosis at an index examination progresses to a greater extent than that noted for persons with lower CAC scores (8).

Despite evidence of increased risk, current effectiveness evidence does not support targeted treatment of patients with high-risk CAC scores to improve outcomes. In addition, definitive strategies for confirmatory testing after high-risk CAC findings have yet to be defined (32, 33). Data do support improved patient adherence, and in 1 trial the average change in the Framingham risk score 4 years after CAC scanning was lower than that in enrollees randomly assigned to usual care without CAC scanning (34). It may seem reasonable to emphasize expected long-term risk during patient interactions that may promote improved adherence and lifestyle-modifying behaviors. Care should also be taken to uncover previously undocumented symptoms that, in the setting of elevated CAC, would prompt symptom-guided evaluation and management.

Our study had a long follow-up with clinical outcome data available only on all-cause mortality. Because we are presenting observational data, causality with regard to influencing outcome cannot be inferred. With longer-term follow-up, competing risks remain an important consideration in prognostic modeling. Information of specific causes of death and other end points may have improved the precision of the prognostic models, although the misclassification rate has been noted to be a disadvantage for cardiac-specific mortality models (26). There is a lag in reporting deaths to the National Death Index, which may have precipitated underreporting of all-cause mortality. Only binary risk factor data were available, and the lack of continuous data on blood pressure, glucose, and cholesterol measurements likely resulted in an overestimation of the added value of CAC scoring. Other cardiac risk factors, such as chronic kidney disease, were not available for inclusion in our prognostic modeling. All patients were self-identified as being asymptomatic, but it is possible that a subgroup of patients had infrequent, atypical, or self-diagnosed noncardiac symptoms and sought evaluation for cardiac risk.

For asymptomatic patients, long-term mortality estimates allow for calculation of projected premature mortality and provide insight into the societal benefit of CAC scanning. This benefit may offset the minimal projected risk for cancer after exposure to ionizing radiation with CAC scanning, with an estimated cancer risk for approximately 12 out of 10 000 screened patients (35). These data show that testing for subclinical atherosclerosis that includes CAC scoring may provide guidance about risk over a 15-year follow-up. The current report details a critical finding and may prompt additional explorations to develop therapeutic strategies aimed at improving outcomes particularly for patients with high-risk CAC scans.

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