

Absence of Coronary Artery Calcium Identifies Asymptomatic Diabetic Individuals at Low Near-Term But Not Long-Term Risk of Mortality

A 15-Year Follow-Up Study of 9715 Patients

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Background—Data regarding coronary artery calcification (CAC) prognosis in diabetic individuals are limited to 5-years follow-up. We investigated the long-term risk stratification of CAC among diabetic compared with nondiabetic individuals.

Methods and Results—Nine thousand seven hundred and fifteen asymptomatic individuals undergoing CAC scoring were followed for a median (interquartile range) of 14.7 (13.9–15.6) years. The incidence density rate and hazard ratios with 95% confidence intervals were used to calculate all-cause mortality. Incremental prognostic utility of CAC was evaluated using the area under the receiver operator characteristic curve and net reclassification improvement. Diabetics (54.7±10.8 years; 59.4% male) comprised 8.3% of the cohort (n=810), of which 188 (23.2%) died. For CAC=0, the rate of mortality was similar between diabetic and nondiabetic individuals for the first 5 years ($P>0.05$), with a nonlinear increased risk of mortality for diabetics after 5 years ($P<0.05$). The adjusted risk of death for those in the highest (CAC>400) versus the lowest (CAC=0) category of CAC increased by a hazards of 4.64 (95% confidence interval =3.74–5.76) and 3.41 (95% confidence interval =2.22–5.22) for nondiabetic and diabetic individuals, respectively. The presence of CAC improved discrimination (area under the receiver operator characteristic curve range: 0.73–0.74; $P<0.01$) and reclassification (category-free net reclassification improvement range: 0.53–0.50; $P<0.001$) beyond conventional risk factors in nondiabetic and diabetic individuals, respectively.

Conclusions—CAC=0 is associated with a favorable 5-year prognosis for asymptomatic diabetic and nondiabetic individuals. After 5 years, the risk of mortality increases significantly for diabetic individuals even in the presence of a baseline CAC=0. (*Circ Cardiovasc Imaging*. 2016;9:e003528. DOI: 10.1161/CIRCIMAGING.115.003528.)

Key Words: calcium score ■ computed tomography ■ coronary artery calcium ■ diabetes mellitus ■ mortality ■ prognosis

Diabetes mellitus is a prominent cause of death in the United States, with the presence of coronary artery disease (CAD) and cerebrovascular events contributing to a substantial portion of mortality among diabetic patients.¹ Further, diabetes is considered to be a CAD equivalent,^{2,3} and the risk of incident adverse clinical events for diabetic individuals is estimated to be similar to nondiabetic individuals considered high-risk by clinical prediction models.^{2,3}

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Coronary artery calcium (CAC) scoring by noncontrast computed tomography (CT) is a well-validated tool for the detection of CAD in asymptomatic individuals.^{4–7} Prior studies have observed the presence, extent, and progression of CAC to enable prediction of adverse clinical events among asymptomatic individuals.^{8–14} Notably, the absence of CAC in asymptomatic individuals—including those with diabetes mellitus—has been associated with a salutary prognosis, although these investigations have been limited to near-term follow-up periods extending to only 5 years.^{15–17}

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To date, evidence is lacking regarding the long-term prognosis of diabetic individuals undergoing CAC scoring, as well as the prognosis of diabetic individuals compared with nondiabetic individuals considered at high cardiovascular risk. In a large prospective observational cohort study, we sought to examine the long-term prognostic utility of CAC for asymptomatic diabetic individuals followed for 15 years (median and interquartile range of follow-up was 14.7 [13.9–15.6] years). As a secondary objective, we investigated whether the prognostic role of CAC for diabetic individuals differed from that for nondiabetic individuals.

Methods

Study Population

The enrollment and follow-up procedures were approved by the institutional review board. The study cohort comprised 9715 (mean age 53.4±10.5, 59.3% male) consecutive asymptomatic individuals without known CAD. All individuals referred by their physicians for electron beam CT underwent CAC testing from a single site (Tennessee Heart and Vascular Institute, Hendersonville, TN). Of those, 810 (mean age 54.7±10.8 years; 59.4% male) individuals were identified as having diabetes mellitus. All screened individuals provided written informed consent, and the study received ethical approval from the appropriate Human Investigations Committee and complies with the Declaration of Helsinki.

Risk Factor Collection

Study participants were queried for baseline demographic characteristics and cardiovascular risk factors. The following risk factor definitions were used: (1) cigarette smoking was present if a subject was an active smoker at the time of scanning; (2) 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, high triglycerides, or current use of lipid-lowering therapy; (3) diabetes mellitus was defined as baseline use of antidiabetic medication or had a history of elevated blood glucose measurement of ≥126 mg/dL use; (4) hypertension was defined if a patient was prescribed an antihypertensive medication or had a documented blood pressure ≥140/90 mmHg; and (5) family history of premature CAD was determined by asking individuals whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and coronary revascularization in a male relative <55 years or a female relative <65 years.

Electron Beam CT Image Acquisition

All subjects underwent electron beam CT on either a C-100 or C-150 Ultrafast CT scanner (GE-Imatron, South San Francisco, CA). With a tomographic slice thickness of 3 mm, a total of ≈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 using the method developed by Agatston.¹⁸

Study Outcome

Study participants were followed for 15 years for an end point of all-cause mortality. Ascertainment of mortality status was acquired by individuals masked to baseline historical data and electron beam CT results and was verified using the Social Security Death Index. The Social Security Death Index is a national registry of all deaths that have occurred in the United States, allowing for 100% ascertainment of mortality status among study participants.

Statistical Methods

The chi-square test was used for comparison of categorical variables. Between-group comparisons for continuous variables were computed using the independent samples *t* test or the Mann-Whitney U test as appropriate. Categorical variables are presented as counts with proportions and continuous variables as mean±SD or median (interquartile range), as appropriate. On visual inspection, CAC was non-normally distributed and subsequently transformed using the natural log method. Over the course of the study, annualized and cumulative mortality rates were used to compare survival between groups according to CAC categories. Univariable and multivariable Cox proportional hazard regression models reporting hazard ratios with 95% confidence intervals were performed to examine the risk of death from all causes in the study population, adjusting for age, sex, hypertension, dyslipidemia, smoking, and family history of premature CAD. Specifically, all Cox models were performed for diabetic and nondiabetic individuals and stratified according to the presence or absence, as well as severity, of CAC. A Kaplan–Meier survival curve with log-rank test was used to compare survival rates for diabetic versus nondiabetic individuals, according to CAC scores. We additionally tested the discrimination ability of CAC over and above the conventional cardiovascular risk factors using the area under the receiver operator characteristic curve¹⁹ and the continuous net reclassification improvement (category-free).²⁰ Statistical analyses were performed using STATA version 12 (StataCorp LP, College Station, TX) and SAS version 9.3 software (SAS Institute Inc, Cary, NC). A 2-tailed *P* value <0.05 was considered statistically significant.

Results

Characteristics of the Study Population

Baseline demographics of the study sample are reported in Table 1. Individuals with diabetes mellitus were older and had a higher prevalence of dyslipidemia and hypertension as compared with individuals without diabetes mellitus (all, *P*<0.05). During the study period, 936 deaths occurred. A higher rate of incident mortality was reported among diabetic versus nondiabetic individuals (eg, 188 [23.2%] versus 748 [8.4%], respectively; *P*<0.001). The presence of CAC was higher for diabetic individuals compared with persons without diabetes mellitus (*P*<0.001; Table 1). A higher extent of CAC was observed for individuals with diabetes mellitus compared with nondiabetic individuals (median [interquartile range]: 29 [0–260]) versus 0 [0–60]; *P*<0.001). The prevalence and distribution of CAC categories among diabetic and nondiabetic individuals are shown in Figure 1.

Diabetic Status and Long-Term Mortality Rate

Figure 2 reports the 15-year incidence rates per 1000 person years among diabetic and nondiabetic individuals according to CAC score categories. The mortality rates increased monotonically in accordance with the severity of CAC scores, although the mortality rate tended to be higher overall for diabetic individuals compared with nondiabetic individuals, respectively.

Kaplan–Meier survival curves are reported in Figure 3. Irrespective of diabetic status, the presence of CAC was associated with worse prognosis (*P*<0.001). Figure 4 describes the 15-year trend of cumulative mortality rates among diabetic and nondiabetic individuals across the varying CAC categories. Over the course of the study period, the rate of events increased according to diabetic status and CAC. During the initial 5 years, in the absence of CAC, diabetic individuals

Table 1. Clinical Characteristics of the Study Population

	Overall (N=9715)	Nondiabetic N=(8905)	Diabetic (N=810)	P Value
Age, y	53.4±10.5	53.3±10.5	54.7±10.8	<0.001
Men, n (%)	5765 (59.3)	5284 (59.3%)	481 (59.4%)	<0.001
Hypertension, n (%)	4220 (43.4%)	3719 (41.8%)	501 (61.9%)	<0.001
Dyslipidemia, n (%)	6077 (62.6%)	5540 (62.2%)	537 (66.3%)	<0.001
Family history of premature CAD, n (%)	6672 (68.7%)	6140 (69.0%)	532 (65.7%)	0.006
Current smoker, n (%)	3817 (39.3%)	3473 (39.0%)	344 (42.5%)	<0.001
CAC>0, n (%)	4851 (49.9%)	4316 (48.5%)	535 (66.1%)	0.07
Death event, n (%)	936 (9.6%)	748 (8.4%)	188 (23.2%)	<0.001
Mortality rate per 1000 person years	6.9 (6.5–7.4)	6.0 (5.6–6.5)	18.0 (15.6–20.8)	<0.001

CAC indicates coronary artery calcification; and CAD, coronary artery disease.

experienced a similar low rate of events when compared with nondiabetic individuals (2.6% versus 1.2%, $P=0.06$). Beyond 5 years of follow-up, diabetic individuals experienced a higher rate of mortality when compared with nondiabetic individuals irrespective of CAC scores (all $P<0.05$).

All-Cause Mortality, CAC Score, and Diabetic Status

When stratified by CAC score, the adjusted risk of mortality increased incremental to higher CAC (all $P<0.005$), with higher CAC scores conferring less associated relative risk for mortality for diabetic versus nondiabetic individuals (hazard ratio for CAC>400: 3.41 versus 4.64; Table 2).

Table 3 reports the long-term comparison of risk of mortality of diabetic individuals versus nondiabetics at 5 and 15 years according to categories of CAC. Overall, diabetic individuals experienced a higher risk of mortality compared with nondiabetic individuals, with a similar relationship observed when stratifying the study cohort by CAC categories. For CAC=0, at 5 years, the risk of mortality for diabetic individuals compared with nondiabetic individuals was similar ($P=0.088$). At 15 years, the concomitant presence of diabetes mellitus and CAC was associated with an almost 2.5-fold increased risk of death. This disparity in mortality risk

associated with diabetic status attenuated with each increasing CAC category of 1–399 and ≥400.

Long-Term Discrimination and Reclassification

When added to the individual cardiovascular risk factors, CAC improved long-term discrimination of mortality beyond the established risk factors alone for diabetic and nondiabetic individuals. The addition of CAC to CAD risk factors further improved reclassification similarly for nondiabetic and diabetic individuals (net reclassification improvement 0.53 and 0.50, respectively; $P<0.001$; Table 4).

Discussion

In the present study, we examined the long-term prognosis of asymptomatic diabetic individuals according to CAC prevalence severity and compared their risk with nondiabetic individuals. In keeping with prior studies, the presence and severity of CAC were more common among diabetic individuals compared with nondiabetic individuals; a finding that was associated with an increased risk of mortality. Across the 2 groups, increasing CAC severity was linked to higher mortality rates and was associated with greater relative risk of mortality for diabetic individuals compared with nondiabetic individuals.

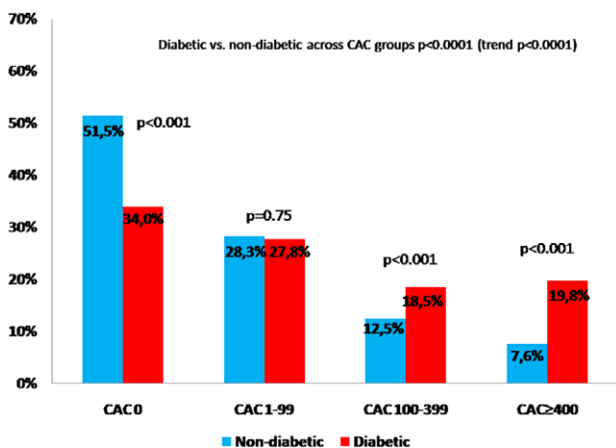


Figure 1. Severity of coronary artery calcification (CAC) among asymptomatic nondiabetic and diabetic individuals.

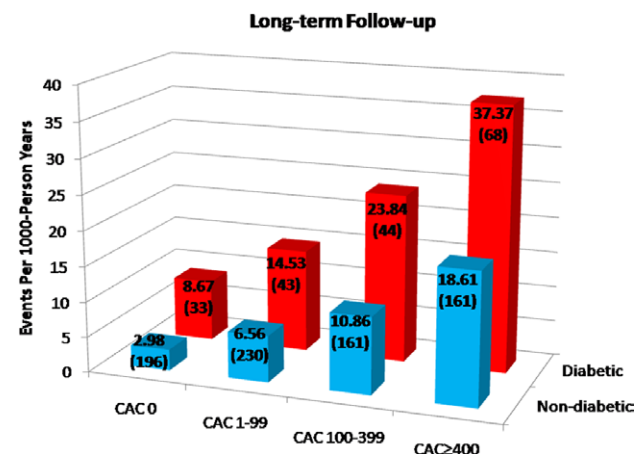


Figure 2. Mortality rate over 15-year follow-up according to the severity of coronary artery calcification (CAC) among nondiabetic and diabetic individuals.

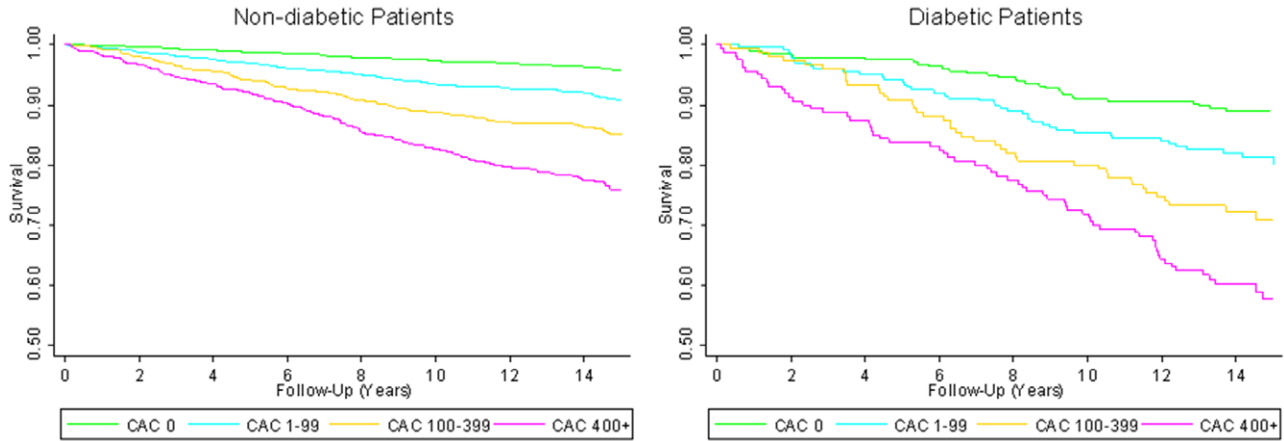


Figure 3. Kaplan–Meier survival curves in diabetic and nondiabetic individuals according to coronary artery calcium (CAC) scores.

Indeed, in each increasing CAC group, the presence of diabetes mellitus was associated with a 25% to 33 higher relative risk of mortality when compared with nondiabetic state. Intriguingly, however, we noted a temporal relationship for mortality for diabetic individuals, wherein the rates of mortality for diabetic individuals linearly tracked with those of nondiabetic individuals in the 5-year near-term period, but then increased disproportionately after that. Importantly, this nonlinear increase in mortality was most evident for DM individuals with a CAC=0.

Our present findings confirm prior investigations which have observed worsened prognosis associated with CAC>0 for both diabetic and nondiabetic individuals. The presence of CAC was associated with an instantaneous increase in mortality rates for both nondiabetic and diabetic individuals, with

mortality rates increasing proportionally with CAC severity. The predictive value of CAC was further complemented by a high discriminatory value of CAC, as well as a robust marker for correct reclassification of at-risk individuals. Yet, our study extends our understanding of the pathogenic process in diabetic and nondiabetic individuals—in particular, for those individuals with a CAC=0—by examining the prognosis based on CAC beyond 5 years, before which comparable survival rates have been observed.²¹ Specifically, we observed similar rates of mortality ≤5 years for individuals with CAC=0, irrespective of diabetes mellitus status, but noted a significantly higher risk of mortality beyond this time point for diabetic individuals over nondiabetic individuals with CAC=0. The mechanisms involved in the adverse prognosis after 5 years in diabetic patients with CAC=0 are unclear, but the potential

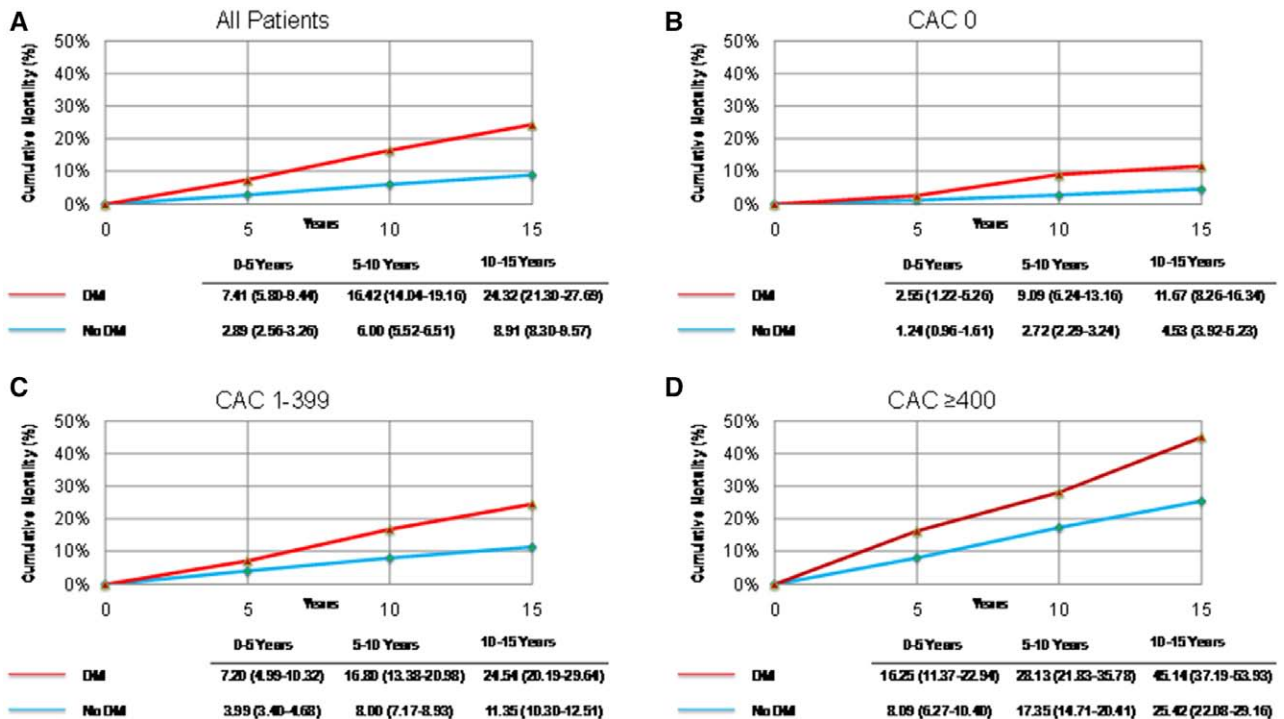


Figure 4. Cumulative mortality rate over 15 years of follow-up among diabetic and nondiabetic individuals stratified by coronary artery calcification (CAC) score (A), CAC=0 (B), CAC 1–399 (C), and CAC ≥ 400 (D).

Table 2. Long-Term Univariable and Multivariable Hazard Ratios for 15-Year All-Cause Mortality as Stratified by Diabetic Status and Coronary Artery Calcium Score

	Univariable		Multivariable	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Nondiabetic				
CAC 0 (n=4589)	1.00 (Ref.)		1.00 (Ref.)	
CAC 1–99 (n=2520)	2.23 (1.84–2.70)	<0.001	2.04 (1.68–2.47)	<0.001
CAC 100–399 (n=1116)	3.76 (3.05–4.64)	<0.001	3.11 (2.51–3.84)	<0.001
CAC ≥400 (n=680)	6.41 (5.20–7.90)	<0.001	4.64 (3.74–5.76)	<0.001
Diabetic				
CAC 0 (n=275)	1.00 (Ref.)		1.00 (Ref.)	
CAC 1–99 (n=225)	1.70 (1.08–2.68)	0.02	1.69 (1.07–2.66)	0.03
CAC 100–399 (n=150)	2.83 (1.80–4.44)	<0.001	2.38 (1.51–3.77)	<0.001
CAC ≥400 (n=160)	4.46 (2.94–6.78)	<0.001	3.41 (2.22–5.22)	<0.001

Multivariable model adjusted for age, sex, hypertension, dyslipidemia, smoking, family history of premature coronary artery disease. CAC indicates coronary artery calcification; CI, confidence interval; and HR, hazard ratio.

explanations are manifold. These include, among others, the higher CAC progression rates in diabetic individuals compared with nondiabetic individuals.²² Notably, these present study findings are in direct accordance with previous reports published by our group regarding the warranty period of a CAC=0, whereby conversion of a CAC from 0 to >0 occurs after 4 years in diabetic individuals.²² Thus, an increased risk of mortality based on CAC conversion may, in part, explain the nonlinear risk observed in this study for CAC=0. Given the observational nature of this study, this premise should be considered speculative with future studies necessary to substantiate this claim.

These data underscore the adverse prognosis associated with the diabetic state but suggest a differential risk of increasing CAC severity between diabetic and nondiabetic individuals. Further, the importance of CAC for improving discrimination and reclassification beyond conventional risk factors was higher in nondiabetic individuals. This observation appears plausible in light of the late systemic complications and noncardiac comorbidities beyond cardiovascular events that are associated with diabetes mellitus, which could have affected diabetic individuals' survival in a

manner independent of CAD and CAC. Conversely, in those who are affected by CAD risk factors, CAC may impart a greater risk to cardiac mortality and, thus, overall mortality in a population generally free of other systemic metabolic diseases.

To our knowledge, this study is the first to demonstrate that CAC is associated with an increased risk of long- but not short-term mortality independently of diabetes mellitus status. Remarkably, CAC screening appeared to be an efficacious and practical tool for distinguishing diabetic patients at higher risk of death within 5 years. Several clinical considerations can be speculated from this finding. In diabetic patients, CAC screening may prove useful for identifying individuals with poor short-term prognosis who subsequently might benefit from an early and more intensive pharmacological hypoglycemic treatment. Conversely, in the absence of CAC, these subjects may receive milder treatment, coupled with lifestyle modifications, as well as frequent re-evaluation of glycemic blood value and other potential risk factors. However, future prospective studies are needed to investigate the therapeutic implication of CAC screening in patients with diabetes mellitus.

Table 3. Long-Term Comparison of Risk of Mortality of Diabetic Patients When Compared With Nondiabetic Individuals According to Coronary Artery Calcium Categories

Diabetic vs Nondiabetic Individuals	At 5 Years		At 15 Years	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Overall (n=9715)	2.63 (1.99–3.49); P<0.001	2.13 (1.60–2.83); P<0.001	2.98 (2.54–3.49); P<0.001	2.47 (2.10–2.90); P<0.001
CAC 0 (n=4864)	2.07 (0.95–4.55); P=0.069	2.00 (0.90–4.42); P=0.088	2.84 (1.97–4.11); P<0.001	2.53 (1.74–3.69); P<0.001
CAC 1–399 (n=4011)	1.83 (1.21–2.76); P=0.004	1.62 (1.08–2.45); P=0.021	2.31 (1.83–2.91); P<0.001	2.07 (1.64–2.62); P<0.001
CAC ≥400 (n=840)	2.11 (1.33–3.37); P=0.002	1.88 (1.17–3.02); P=0.009	2.01 (1.51–2.67); P<0.001	1.88 (1.41–2.51); P<0.001

Adjusted model included: age, sex, hypertension, dyslipidemia, smoking, and familiar history of premature coronary artery disease. CAC indicates coronary artery calcification; CI, confidence interval; and HR, hazard ratio.

Table 4. Long-Term Discrimination and Reclassification Improvement for All-Cause Mortality by Coronary Artery Calcium Among Nondiabetic and Diabetic Individuals

	AUC Model 1*	AUC Model 2†	P Value	NRI	NRI 95% CI	P Value	% of Events		% of Nonevents	
							Reclassified	Event P Value	Reclassified	Non-Event P Value
Nondiabetic	0.688	0.733	<0.001	0.53	0.45–0.60	<0.001	23%	<0.001	29%	<0.001
Diabetic	0.694	0.737	0.006	0.50	0.35–0.66	<0.001	33%	<0.001	17%	<0.001

AUC indicates area under the curve; CI, confidence interval; and NRI, net reclassification improvement.

*Individual cardiovascular risk factors alone, including age, sex, hypertension, dyslipidemia, smoking, family history of premature coronary artery disease.

†Model 1+ logCAC.

Limitations

This study is not without limitations. Despite the large study sample, long-term follow-up, and prospective evaluation of study individuals, the single-center design of the current study limits the generalizability afforded by multicenter trials. Further, CAC, the baseline therapy, and the effects of CAC scoring on incident changes to medical therapy and lifestyle modification are not known in this study, and their mitigating effects to reduce (or increase) mortality rates is unknown. However, we think that this aspect likely contributed to an under-, rather than over-estimation, of the effect of the current study findings.

In addition, CAC and clinical risk assessment were determined at the time of scanning and only once. Thus, the extent to which the time-varying nature of CAC progression, post-CAC therapies, and behavioral modifications could have affected the present study results is unknown. Further, prior smoking history and smoking intensity as measured by pack years were not available. We used death from any cause as the primary end point in this study. However, we believe that mortality for all causes is the most relevant end point that can be evaluated in epidemiological studies.²³

Although this enabled 100% follow-up and preclusion from ascertainment bias, cause-specific mortality could not be obtained, and it remains possible that our study findings could be diluted, thereby reducing the apparent strength of CAC findings to prognosticate, discriminate, and reclassify risk.

Conclusions

CAC provides incremental prognostic utility for prediction of mortality for diabetic and nondiabetic individuals, with a CAC=0 associated with reduced risk of death. A temporal relationship exists for diabetic individuals with a CAC=0, with a nonlinear increased risk of mortality after 5 years.

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Disclosures

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CLINICAL PERSPECTIVE

Diabetes mellitus is a prominent cause of death in the United States, with atherosclerosis being the major precipitant of coronary artery disease and stroke in diabetic individuals. Coronary artery calcium (CAC) scoring by computed tomography is a well-validated tool for detection of coronary artery disease in asymptomatic individuals. Prior investigations have documented a comparable 5-year mortality rate among individuals with and without diabetes mellitus in the absence of any CAC. Yet, information regarding near- (5-year) and long-term (15-year) prognostication of CAC=0 among diabetic individuals remains sub-optimal at present. In the current study, 9715 individuals with (n=810) and without (n=8905) diabetes mellitus followed for 15 years underwent screening for CAC. During the initial 5 years of study follow-up, the risk of mortality appeared similar among diabetic and nondiabetic persons in the absence of CAC. Beyond initial 5-year follow-up, there was a persistent rise in near- and long-term adverse prognosis according to the presence and severity of CAC, irrespective of diabetic status. Direct comparisons of the risk of death according to CAC categories displayed higher adjusted risks at both 5- and 15-year follow-up for diabetic versus nondiabetic persons, though the long-term findings were more pronounced. In summary, CAC may prove useful for identifying diabetic individuals prone to a greater burden of mortality and may facilitate therapeutic decision-making within a clinical setting. Forthcoming studies assessing the CAC therapeutic approach in diabetic individuals now appear warranted.

Absence of Coronary Artery Calcium Identifies Asymptomatic Diabetic Individuals at Low Near-Term But Not Long-Term Risk of Mortality: A 15-Year Follow-Up Study of 9715 Patients

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