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. Further, diabetes is considered to be a CAD equivalent, 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.

Coronary artery calcium (CAC) scoring by noncontrast computed tomography (CT) is a well-validated tool for the detection of CAD in asymptomatic individuals. Prior studies have observed the presence, extent, and progression of CAC to enable prediction of adverse clinical events among asymptomatic individuals. 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.
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 non-diabetic 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 non-diabetic 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 mm Hg; and (5) family history of premature CAD was defined 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.9

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.

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
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.

Table 1. Clinical Characteristics of the Study Population

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

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

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.
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
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

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td>2.23 (1.84–2.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3.76 (3.05–4.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6.41 (5.20–7.90)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Diabetic vs Nondiabetic Individuals</th>
<th>At 5 Years</th>
<th>At 15 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=9715)</td>
<td>2.63 (1.99–3.49); P&lt;0.001</td>
<td>2.98 (2.54–3.49); P&lt;0.001</td>
</tr>
<tr>
<td>CAC 0 (n=4864)</td>
<td>2.07 (0.95–4.55); P=0.069</td>
<td>2.84 (1.97–4.11); P&lt;0.001</td>
</tr>
<tr>
<td>CAC 1–399 (n=4011)</td>
<td>1.83 (1.21–2.76); P=0.004</td>
<td>2.31 (1.83–2.91); P&lt;0.001</td>
</tr>
<tr>
<td>CAC ≥400 (n=840)</td>
<td>2.11 (1.33–3.37); P=0.002</td>
<td>2.01 (1.51–2.67); P&lt;0.001</td>
</tr>
</tbody>
</table>

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.
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 endpoint 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.

Sources of Funding

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Disclosures

Dr Truong reports grants from NIH, grants from DCRI, grants from ACRIN, grants from St Jude Medical, outside the submitted work. Dr Min is a consultant for Abbott Vascular, HeartFlow, Neograft, MyoKardia, and CardioDx. He is also on the scientific advisory board for Arineta, has ownership in MDDX and Autoplaq, and has a research agreement with GE Healthcare. Dr Min serves on the medical advisory boards of Arineta and CardioDx. Dr Min serves as a consultant to HeartFlow. Dr Truong received grant support from St Jude Medical, American College of Radiology Imaging Network, and Duke Clinical Research Institute. The other authors report no conflicts.

References


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

<table>
<thead>
<tr>
<th></th>
<th>AUC Model 1 †</th>
<th>AUC Model 2†</th>
<th>P Value</th>
<th>NRI</th>
<th>NRI 95% CI</th>
<th>P Value</th>
<th>% of Events Correctly Reclassified Event P Value</th>
<th>% of Nonevents Correctly Reclassified Non-Event P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiabetic</td>
<td>0.688</td>
<td>0.733</td>
<td>&lt;0.001</td>
<td>0.53</td>
<td>0.45–0.60</td>
<td>&lt;0.001</td>
<td>23%</td>
<td>29%</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.694</td>
<td>0.737</td>
<td>0.006</td>
<td>0.50</td>
<td>0.35–0.66</td>
<td>&lt;0.001</td>
<td>33%</td>
<td>17%</td>
</tr>
</tbody>
</table>

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.
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
Valentina Valenti, Bríain ó Hartaigh, Iksung Cho, Joshua Schulman-Marcus, Heidi Gransar, Ran Heo, Quynh A. Truong, Leslee J. Shaw, Joseph Knapper, Anita A. Kelkar, Sebastiano Sciarretta, Hyuk-Jae Chang, Tracy Q. Callister and James K. Min

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