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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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Abstract

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 diabetics, compared to non-diabetic individuals.

Methods and Results—9715 asymptomatic individuals undergoing CAC scoring were followed for a median (IQR) of 14.7 (13.9–15.6) years The incidence density rate and hazard ratios (HR) with 95% confidence intervals (95%CI) were used to calculate all-cause mortality. Incremental prognostic utility of CAC was evaluated using the area under the receiver operator
characteristic curve (AUC) and net reclassification improvement (NRI). 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 non-diabetic individuals for the first 5 years (p>0.05), with a non-linear 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%CI=3.74–5.76) and 3.41 (95%CI=2.22–5.22) for non-diabetic and diabetic individuals, respectively. The presence of CAC improved discrimination (AUC range: 0.73–0.74, P<0.01) and reclassification (category-free NRI range: 0.53–0.50, P<0.001) beyond conventional risk factors in non-diabetic and diabetic respectively.

Conclusions—CAC=0 is associated with a favorable 5-year prognosis for asymptomatic diabetic and non-diabetic individuals. After 5 years, the risk of mortality increases significantly for diabetic individuals even in the presence of a baseline CAC=0.

Keywords
coronary artery calcium; calcium score; computed tomography; diabetes mellitus; prognosis; mortality

Diabetes 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 non-diabetic individuals considered high-risk by clinical prediction models.

Coronary artery calcium (CAC) scoring by non-contrast 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—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 to non-diabetic individuals considered 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 (IQR) 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 computed tomography (EBCT) 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. 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 employed: 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 was defined as baseline use of anti-diabetic 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 anti-hypertensive medication or had a documented blood pressure ≥140/90 mmHg 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/or coronary revascularization in a male relative <55 years or a female relative <65 years.

EBCT Image Acquisition

All subjects underwent EBCT on either a C-100 or C-150 Ultrafast CT scanner (GE-Imatron, South San Francisco, California). With a tomographic slice thickness of 3 mm, a total of approximately 40 sections were obtained beginning at the level of the carina and proceeding caudally to the level of the diaphragm. Images were obtained with a 100-ms/slice scanning time, with image acquisition electrocardiographically triggered at 60%–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 endpoint of all-cause mortality. Ascertainment of mortality status was acquired by individuals masked to baseline historical data and EBCT 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 employed 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 (IQR), 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 (HR) with 95% confidence intervals (95% CI) were performed to examine the risk of death from all causes in the study population, adjusting for age, gender, hypertension, dyslipidemia, smoking, and family history of premature CAD. Specifically, all Cox models were performed for diabetic and non-diabetic 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 employed to compare survival rates for diabetic versus non-diabetic 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 curve (AUC)\(^{19}\) and the continuous net reclassification improvement (NRI, 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 two-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 were older and had a higher prevalence of dyslipidemia and hypertension as compared with individuals without diabetes (all, P<0.05). During the study period, 936 deaths occurred. A higher rate of incident mortality was reported among diabetic versus non-diabetic individuals (e.g., 188 [23.2%] vs. 748 [8.4%], respectively; P<0.001). The presence of CAC was higher for diabetic individuals compared with persons without diabetes (P<0.001) (Table 1). A higher extent of CAC was observed for individuals with diabetes compared with non-diabetic individuals (median [IQR] 29 [0–260]) vs. 0 [0–60], P<0.001). The prevalence and distribution of CAC categories among diabetic and non-diabetic 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 non-diabetic 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 non-diabetic 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 non-diabetic 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 non-diabetic individuals (2.6% vs. 1.2%, P=0.06). Beyond 5 years of follow-up, diabetic individuals experienced a higher rate of mortality when compared with non-diabetic 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 non-diabetic individuals (HR for CAC>400: 3.41 vs. 4.64) (Table 2).

Table 3 reports the long-term comparison of risk of mortality of diabetic individuals versus non-diabetics at 5 and 15 years according to categories of CAC. Overall, diabetic individuals experienced a higher risk of mortality compared with non-diabetic 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 non-diabetic individuals was similar (P= 0.088). At 15 years the concomitant presence of diabetes 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 non-diabetic individuals. The addition of CAC to CAD risk factors further improved reclassification similarly for non-diabetic and diabetic individuals (NRI 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 non-diabetic individuals. In keeping with prior studies, the presence and severity of CAC were more common among diabetic individuals compared to non-diabetic individuals; a finding that was associated with an increased risk of mortality. Across the two groups, increasing CAC severity was linked to higher mortality rates, and was associated with greater relative risk of mortality for diabetic individuals compared to non-diabetic. Indeed, in each increasing CAC group, the presence of diabetes was associated with a 25–33% higher relative risk of mortality when compared to non-diabetic 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 non-diabetic individuals in
the 5-year near-term period, but then increased disproportionately after that. Importantly, this non-linear 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 non-diabetic individuals. The presence of CAC was associated with an instantaneous increase in mortality rates for both non-diabetic 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 non-diabetic individuals—in particular, for those individuals with a CAC=0—by examining the prognosis based upon CAC beyond 5 years, before which comparable survival rates have been observed. Specifically, we observed similar rates of mortality up to 5 years for individuals with CAC=0, irrespective of diabetes status, but noted a significantly higher risk of mortality beyond this time point for diabetic individuals over non-diabetic 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 explanations are manifold. These include, among others, the higher CAC progression rates in diabetic individuals compared with non-diabetics. 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. Thus, an increased risk of mortality based upon CAC conversion may, in part, explain the non-linear 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 non-diabetic individuals. Further, the importance of CAC for improving discrimination and reclassification beyond conventional risk factors was higher in non-diabetic individuals. This observation appears plausible in light of the late systemic complications and non-cardiac comorbidities beyond cardiovascular events that are associated with diabetes, 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 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.

**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/or 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 employed death from any cause as the primary endpoint in this study. However, we believe that mortality for all-causes is the most relevant endpoint that can be evaluated in epidemiological studies.23

While 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.

**CONCLUSION**

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

**Acknowledgments**

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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 Technologies, 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.

**Relationship with Industry Policy:** 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.
REFERENCES


Clinical Perspective

Diabetes is a prominent cause of death in the United States, with atherosclerosis the major precipitant of coronary artery disease (CAD) and stroke in diabetic individuals. Coronary artery calcium (CAC) scoring by computed tomography is a well-validated tool for detection of CAD in asymptomatic individuals. Prior investigations have documented a comparable 5-year mortality rate among individuals with and without diabetes 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, 9,715 individuals with (n=810) and without (n=8905) diabetes 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 non-diabetic 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-years follow-up for diabetic versus non-diabetic 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.
Figure 1.
Severity of coronary artery calcification among asymptomatic non-diabetic and diabetic individuals.
Figure 2.
Mortality rate over 15 years follow-up according to the severity of coronary artery calcification among non-diabetic and diabetic individuals.
Figure 3.
Kaplan Meier survival curves in diabetic and non-diabetic individuals according to coronary artery calcium (CAC) scores.
Figure 4.
Cumulative mortality rate over 15 years of follow-up among diabetic and non-diabetic individuals stratified by coronary artery calcification (CAC) score (A) CAC=0, (B) CAC 1–399, and (C) CAC ≥400.
Table 1

Clinical characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=9715)</th>
<th>Non-diabetic (N=8905)</th>
<th>Diabetic (N=810)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</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>

CAD: coronary artery disease; CAC: coronary artery calcification
Table 2
Long-term univariable and multivariable hazard ratios for 15-years all-cause mortality as stratified by diabetic status and coronary artery calcium score

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC 0 (n=4589)</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td>CAC 1–99 (n=2520)</td>
<td>2.23 (1.84–2.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAC 100–399 (n=1116)</td>
<td>3.76 (3.05–4.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAC ≥400 (n=680)</td>
<td>6.41 (5.20–7.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC 0 (n=275)</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td>CAC 1–99 (n=225)</td>
<td>1.70 (1.08–2.68)</td>
<td>0.02</td>
</tr>
<tr>
<td>CAC 100–399 (n=150)</td>
<td>2.83 (1.80–4.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAC ≥400 (n=160)</td>
<td>4.46 (2.94–6.78)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multivariable model adjusted for age, gender, hypertension, dyslipidemia, smoking, family history of premature coronary artery disease
Table 3

Long-term comparison of risk of mortality of diabetic patients when compared with non-diabetic individuals according to coronary artery calcium categories.

<table>
<thead>
<tr>
<th>Diabetic vs non-diabetic individuals</th>
<th>At 5-years</th>
<th>At 15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>Overall (n=9715)</td>
<td>2.63 (1.99–3.49) p&lt;0.001</td>
<td>2.13 (1.60–2.83) 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>2.00 (0.90–4.42) p=0.088</td>
</tr>
<tr>
<td>CAC 1–399 (n=4011)</td>
<td>1.83 (1.21–2.76) p=0.004</td>
<td>1.62 (1.08–2.45) p=0.021</td>
</tr>
<tr>
<td>CAC ≥400 (n=840)</td>
<td>2.11 (1.33–3.37) p=0.002</td>
<td>1.88 (1.17–3.02) p=0.009</td>
</tr>
</tbody>
</table>

Adjusted model included: age, sex, hypertension, dyslipidemia, smoking and familiar history of premature coronary artery disease. Abbreviations as in Table 2.
Table 4

Long-term discrimination and reclassification improvement for all-cause mortality by coronary artery calcium among non-diabetic 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</th>
<th>Event P Value</th>
<th>% of Nonevents correctly reclassified</th>
<th>Non-Event P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic</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>&lt;0.001</td>
<td>29%</td>
<td>&lt;0.001</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>&lt;0.001</td>
<td>17%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

‡ Individual cardiovascular risk factors alone including age, gender, hypertension, dyslipidemia, smoking, family history of premature coronary artery disease

§ Model 1+ logCAC

AUC: area under the curve; NRI: net reclassification improvement; CI: confidence interval