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Low short-term and long-term cardiovascular and all-cause mortality in absence of coronary artery calcium: A 22-year follow-up observational study from large cohort

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ABSTRACT

Objectives: We sought to evaluate the gender-specific predictive value of coronary artery calcium (CAC) score on all-cause mortality and cardiovascular disease (CVD) mortality in individuals with and without diabetes mellitus (DM).
Background: CAC score is a robust predictor of CVD and all-cause mortality during long-term follow-up in large cohorts in adults with DM. However, less is known about its sex-specific impact on all-cause mortality in DM.
Methods: We evaluated 25,563 asymptomatic participants with no known history of coronary artery disease (CAD) who underwent clinically indicated CAC. 1999 (7.8%) individuals had diabetes. CAC was characterized as an Agatston score of 0, 1–99, 100–300, and ≫300. We evaluated the association between CAC and all-cause mortality and CVD mortality.
Results: Overall, 1345 individuals died (5.3%) from all causes during a mean follow-up of 14.7 ± 3.8 years. CAC score was 0 in 57.5% females and 34.4% of males without DM, while 36.6% females and 20.3% males with DM had CAC-0. The frequency of CAC ≫ 300 was 18% and 36% in females and males with DM, respectively. CAC score of zero was associated with low all-cause mortality event rate in females and males with diabetes (1.7 and 2.5 events per 1000 person-years, respectively). Cardiovascular mortality per 1000 person years was ≪1 in females and males with CAC score of 0 irrespective of their diabetes. Adjusted multivariable analysis, compared to CAC-0, HR for all-cause mortality associated with CAC 1–99, 100–299 and ≫300 were 1.74(95% CI 0.65, 4.63, P-0.20), 5.54(95% CI 2.16, 14.22, P ≪ 0.001) and 5.75(95% CI 2.30, 14.37, P ≪ 0.001) in females with DM respectively; in males with DM HR associated with CAC 1–99, 100–299 and ≫300 were 1.87(95% CI 0.95, 3.66, P-0.06), 2.15(95% CI 1.05, 4.38, P-0.035) and 2.60(95% CI 1.34, 5.0, P-0.004), respectively.
Conclusion: Presence of subclinical atherosclerosis varies among individuals with DM. The absence of CAC was associated with very low cardiovascular as well as all-cause mortality events in all subgroups during long term follow-up.

1. Introduction

Incidence and prevalence of diabetes mellitus (DM) are growing by epidemic proportions in developed and developing countries around the world.[1–3] According to the estimates, 380 million people will be living with diabetes worldwide by 2025.[4] Diabetes is known to be one of the most potent risk factors associated with cardiovascular morbidity and mortality.[1,5] Patients with type 2 diabetes are at 2–4 fold higher risk of cardiovascular mortality compared with patients without diabetes.[1,6,7] Since the original publication by Haffner et al.[8] the concept that diabetes is coronary heart disease (CHD) equivalent has been challenged by several subsequently published studies.[9–11] Coronary artery calcium (CAC) measured by non-contrast computed tomography is a robust marker of subclinical atherosclerosis.[12] Individuals with diabetes have greater extent and prevalence of subclinical atherosclerosis. Nonetheless, a high percentage of adults with diabetes tend to have no coronary calcification or low CAC associated with low event rates.[13,14] Several studies have demonstrated the prognostic value of CAC in reclassifying asymptomatic patients with diabetes.[13,14]

Contrary to the general population without diabetes, but according to some reports, females and males with diabetes have a similar presence of CAC.[15,16] Furthermore, a number of studies have reported diabetes is more strongly associated with cardiovascular (CVD) mortality and

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morbidity in women compared to men. The relative risk for CVD events in women with diabetes being 2 times higher than in similarly affected men.[17] Sex-specific impact of CAC on all-cause mortality in diabetes has not been reported. We sought to evaluate the gender-specific long term prognostic value of CAC in a cohort of 25,663 patients with and without diabetes and followed for up to 22 years.

2. Methods

2.1. Study population

We studied 25,563 consecutive asymptomatic individuals without known coronary artery disease. Mean age of participants was 55.3 + 11 years clinically referred for a CAC scan between July 1992 and December 2014 at our institution (Los Angeles Biomedical Institute at Harbor UCLA Medical Center). We stratified the population in groups by diabetes (1999/25563(7.8%) DM) and gender (women 30.8%). All participants completed a form for CVD risk factors including diabetes, hypertension, hypercholesterolemia, current cigarette smoking, and family history of premature CVD. Individuals with chest pain or prior known CVD (prior coronary revascularization or myocardial infarction) were excluded. This study was approved by the Institutional Review Board of Los Angeles Biomedical Institute at Harbor UCLA Medical Center. Informed consent was obtained from all patients. CVD mortality was defined as death from coronary heart disease, stroke and heart failure.

2.2. Non-contrast computed tomography image

All participants underwent either electron beam computed tomography (EBCT) with an Imatron C-150XL Ultrafast-computed tomography scanner (GE-Imatron, South San Francisco, CA) or multi-detector 64-slices coronary computed tomography (CT) (Lightspeed VCT, General Electric Healthcare Technologies, Milwaukee, WI). To capture the entire coronary tree, each scan extended from 1 cm below the carina to the bottom of the heart. Scan parameters included as follows: prospective electrocardiogram-triggering (typically 60–80% of the R–R interval for EBCT, 65–80% for multi-detector CT), 35 cm field of view, 512 × 512 matrix size, and a peak tube voltage of 120 kVp. Slice thickness was 3 mm. Dedicated workstation (AW Volume ShareTM, GE Medical Systems, Milwaukee, WI) was utilized to perform CAC measurements, and CAC was quantified using the Agatston score.[18]

2.3. Statistical analysis

Continuous variables are stated as the mean + SD. Categorical variables were compared using Pearson x2 tests. All-cause death was defined as the endpoint of this current study and verified using linkage with the Social Security Death Index through December 2014. A full Social Security Death Index search was fully performed utilizing the patients' name and date of birth in all of the patients. CAC was categorized into four groups: 0, 1–100, 100–300, and ≥300 Agatston units. The prevalence of CAC was assessed by diabetes and gender groups. The mortality risk was analyzed across all CAC categories by diabetes and gender groups. To investigate the association of CAC and mortality, Kaplan–Meier models were calculated. We also calculated multivariable Cox Proportional hazards models adjusted for age, hypertension, hyperlipidemia, diabetes, current smoking and family history among CAC groups by DM and gender. The mortality event rates per 1000 person-years were assessed among diabetes and gender group based on CAC categories. P values, 0.05 were considered statistically significant. Furthermore, we assessed continuous net reclassification improvement. All statistical calculations were performed using SAS (Version 9.3, SAS Inc., Cary, NC) for Windows.

3. Results

3.1. Baseline characteristics

Baseline demographics of the study are presented in Table 1. Mean follow-up was 14.7 ± 3.8 years. Males and females with DM had a higher prevalence of hypertension and had higher BMI compared to males and females without diabetes respectively ($P \ll 0.05$). A higher rate of mortality was reported among those with diabetes versus those without diabetes (e.g., 175 (12.7%) versus 781 (4.8%) for males and 66(10.6%) vs. 323(4.4%) for females, respectively $P \ll 0.001$).

3.2. Prevalence of CAC

Fig. 1 shows the prevalence of CAC categories by diabetes and gender. The prevalence of CAC = 0 was in 36.6% of females with diabetes and 20.3% in males with diabetes. Similarly, the prevalence of CAC ≫ 300 was higher in DM male as compared to diabetic females (33.7 vs. 18.7%) (Fig. 1).

3.3. Mortality rate and diabetes

There were 66 (10.6%) and 175(12.7%) all-cause mortality events in females and males with diabetes, respectively. During a follow-up of up to 22 years, the all-cause mortality rate was low in patients with CAC-0, 2.4% and 2% in females and males without diabetes, respectively. Mortality was 2.6% and 3.9% in females and males with diabetes. The long-term mortality rate increased progressively with each CAC category (1–99,100–299, and ≫300) (Fig. 2).

As expected patients with DM had higher all-cause mortality per CAC category, for example, DM females with CAC score ≫ 300 had 21.62 all-cause mortality events per 1000 person-years and DM male with CAC ≫300 (15.73; 12.85–19.26) while all-cause mortality per 1000 person-years in females and males without diabetes and CAC ≫ 300 were 13.6(11.04–16.85) and 8.8 (7.89–9.78) (Fig. 3). Further analysis of short term 5-year mortality showed similar trends as long term mortality per 1000 person years (Fig. 4).

3.4. Cardiovascular mortality

Cardiovascular mortality followed the similar pattern as all-cause mortality. Mortality increased with increased calcium score categories. Cardiovascular mortality events were very low (≪1 per 1000 person years) in females and males with CAC-0 regardless of their diabetes status (Fig. 5). Additionally, CVD mortality data by age (less than and above 60 years) is presented (Fig. 6).

3.5. All-cause mortality stratified by gender and diabetes

In multivariable analysis adjusted for age, gender, hyperlipidemia, family history, BMI and smoking, HR increased with increasing CAC categories across all groups. At 22 years, patients with diabetes had higher risk of all-cause mortality events. Diabetic females and males with CAC ≫ 300 had an almost 6- and 3-fold increased risk of all-cause mortality compared to males and females with no coronary calcification, respectively (HR for CAC ≫ 300, DM Male-2.60, DM female-5.75 (Fig. 7)).

3.6. Long-term reclassification

For all-cause mortality, net reclassification improvement with the addition of CAC for Non-DM male and DM male was (0.39 and 0.44, $P \ll 0.05$; Table 2). The highest reclassification was for diabetic females (0.73, $P \ll 0.05$). There was no significant reclassification for non-DM women.

Table 1
Study population characteristics.

	Total	Non DM male (16300)	DM male (1378)	Non DM female (7264)	DM female (621)
	25,563	16,300	1378	7264	621
Age (years)	55.27 ± 10.9	54.1 ± 10.9	58.7 ± 10.9*	56.9 ± 10.7	60.0 ± 10.4**
Hypertension	8264(32%)	4935(30.3)	648(47.0)*	2338(32.2)	343(55.2)**
Hyperlipidemia	15,081(59%)	9551(58.6)	819(59.4)	4304(59.3)	407(65.5)*
Current smoking	2372(9%)	1570(9.6%)	162(11.8%)**	583(8.0%)	57(9.2%)
Family history	13,278(52%)	7828(48.0%)	640(46.4%)	4460(61.4%)	350(56.4%)*
BMI	27.90 ± 4.87	27.2 ± 4.1	29.5 ± 5.8*	26.1 ± 5.5	30.8 ± 7.5**
CAC-0 (n, %)	10,281(40%)	5600 (34.4%)	280(20.3%)	4174(57.5%)	227(36.6%)
CAC-1–99	8602(34%)	5927(36.4%)	430(31.2%)	2044(28.1%)	201(32.4%)
CAC-100–299	2935(11%)	2081(12.8%)	204(14.8%)	573(7.9%)	77(12.4%)
CAC ≫ 300	3745(15%)	2692(16.5%)	464(33.7%)	473(6.5%)	116(18.7%)

* P ≪ 0.05.
** P ≪ 0.001 for comparison with patients without diabetes.

4. Discussion

In the present study, we stratified asymptomatic individuals by diabetes and gender. We examined the long-term prognosis according to CAC prevalence. Extent and prevalence of CAC were higher in males both with and without diabetes compared to females in both groups. Mortality rates increased across all groups with increasing CAC. CAC score of zero was associated with very low short-term and long-term CVD and all-cause mortality in non-diabetic and diabetic males and females. Earlier, diabetes was considered as coronary risk equivalent, denoting a 10-year risk of having cardiovascular event ≫20% for every diabetic patient.[5] Nonetheless, several populations based studies have provided different results.[10,11,19,20] In a meta-analysis of 13 studies involving 45,108 patients, Bulugahapitiya et al.[9] showed that patients with diabetes without prior MI had 43% lower risk of coronary heart disease events as compared to patients with previous MI but without diabetes.

Large population-based studies have shown that a significant proportion of adults with diabetes have CAC scores of zero.[13,14,21] Raggi et al.[21] documented in their research, 39% of individuals with diabetes had CAC score of zero. A recent study from MESA with long-term follow-up (10 years) showed that 37.3% of individuals with diabetes had CAC score of 0 at baseline, associated with a low 10-year event rate of 3.7%.[13] Our results are consistent with the above-mentioned studies, females and males with diabetes with CAC-0 had ≪1 CVD mortality events per 1000 person-years over long term follow-up respectively.

Some studies suggest that women with diabetes are considered to be at higher risk of developing atherosclerotic cardiovascular disease as compared to men. In a sub analysis of Framingham Heart Study, Sundar et al.[19] demonstrated, men and women with diabetes without established CHD had HR of 2.1 and 3.5 for CHD death, respectively as compared to HRs of 1.9 and 4.2 for future CHD death in men and women with established CHD but without diabetes. In an INTERHEART study, diabetes was associated with a 4-fold increase in the risk of developing CHD in women as compared two fold increased risk in male diabetics.[22] In a meta-analysis which included 850,000 individuals, females with diabetes had 44% higher relative risk for CVD than in similarly affected men.[23] Our data were consistent with this concept; specifically, females with diabetes had the highest risk of long term mortality with increasing CAC as compared to men. Previously some reports have also shown that unlike the general population, males and females with diabetes have similar prevalence and extent of coronary artery calcification supporting the concept that DM obliterates the well-established benefit of women over men in the extent of CAC and atherosclerosis burden.[24,25] Khaleeli et al.[15] reported there was no

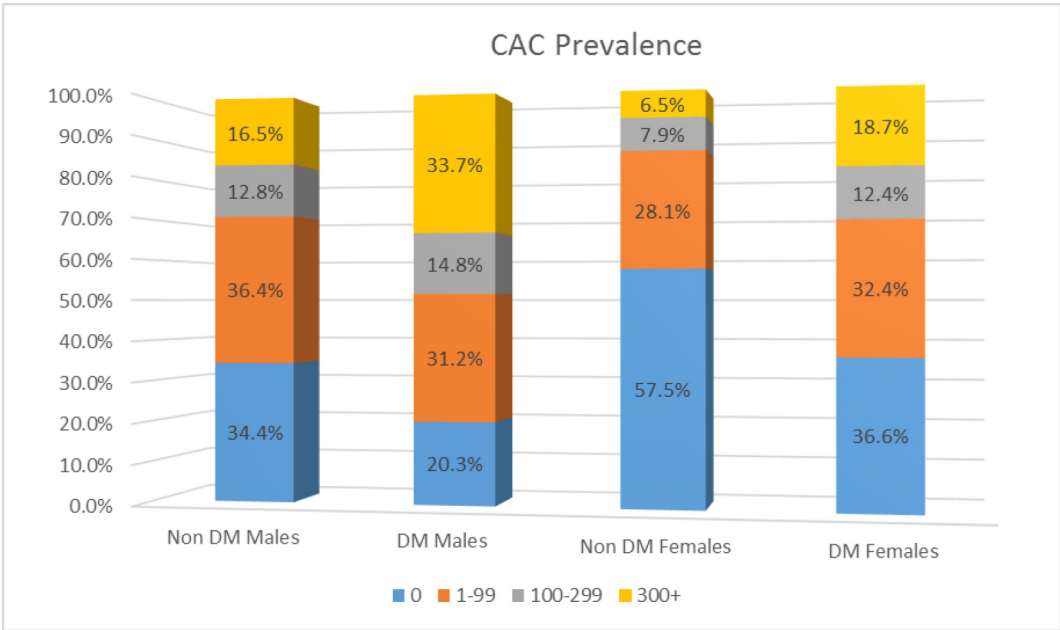

Fig. 1. Prevalence of CAC among males and females with and without DM.

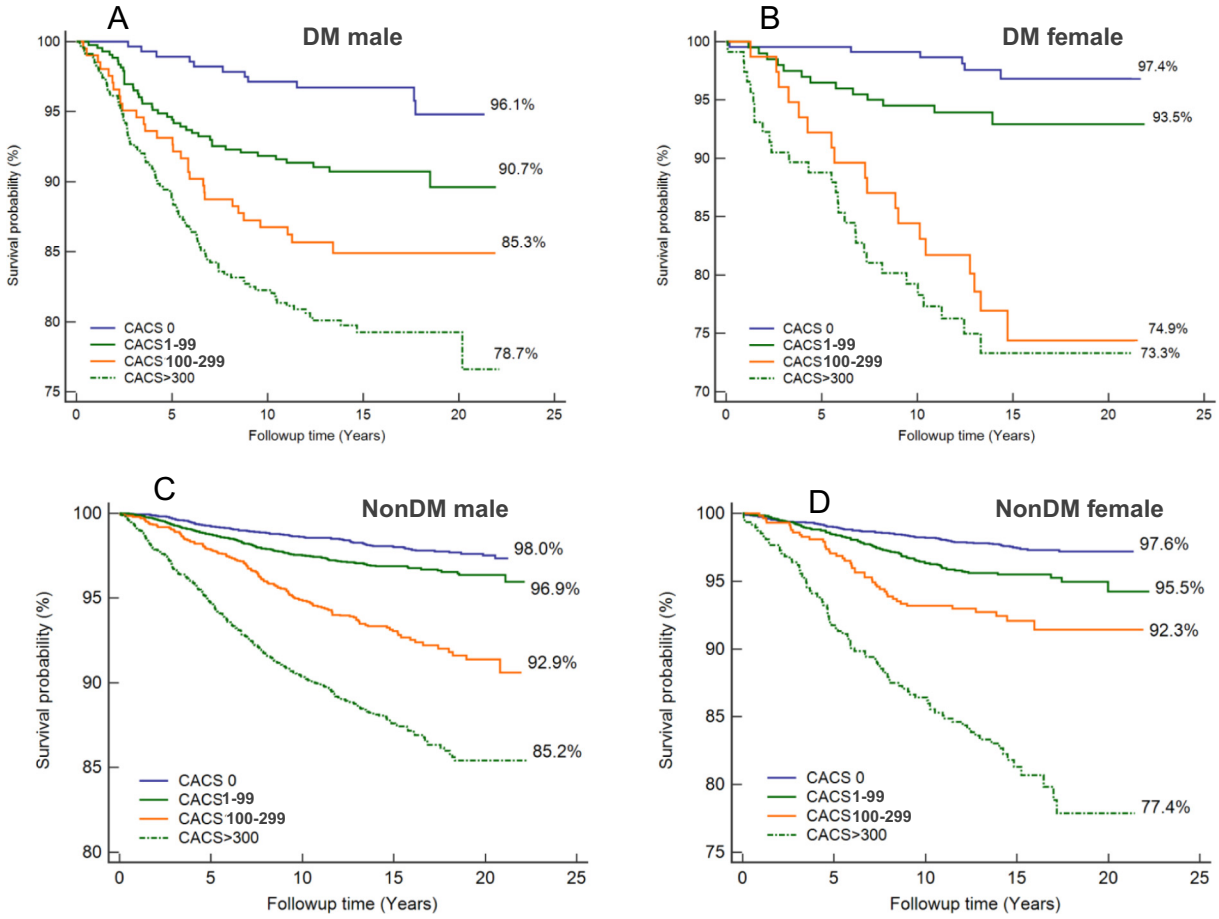

Fig. 2. (A) Kaplan-Meier analysis for all cause mortality among males with DM (B) Kaplan-Meier analysis for all cause mortality among females with DM (C) Kaplan-Meier analysis for all cause mortality among males without DM (D) Kaplan-Meier analysis for all cause mortality among females without DM.

significant difference in coronary calcification between men and women with diabetes. In another study, Mielke et al.[16] performed EBCT in 3389 patients with diabetes. They showed that women with diabetes had greater plaque burden when compared to men with a history of diabetes.[16] However, in our data, higher percentage of females with diabetes had CAC-0 as compared to male diabetics

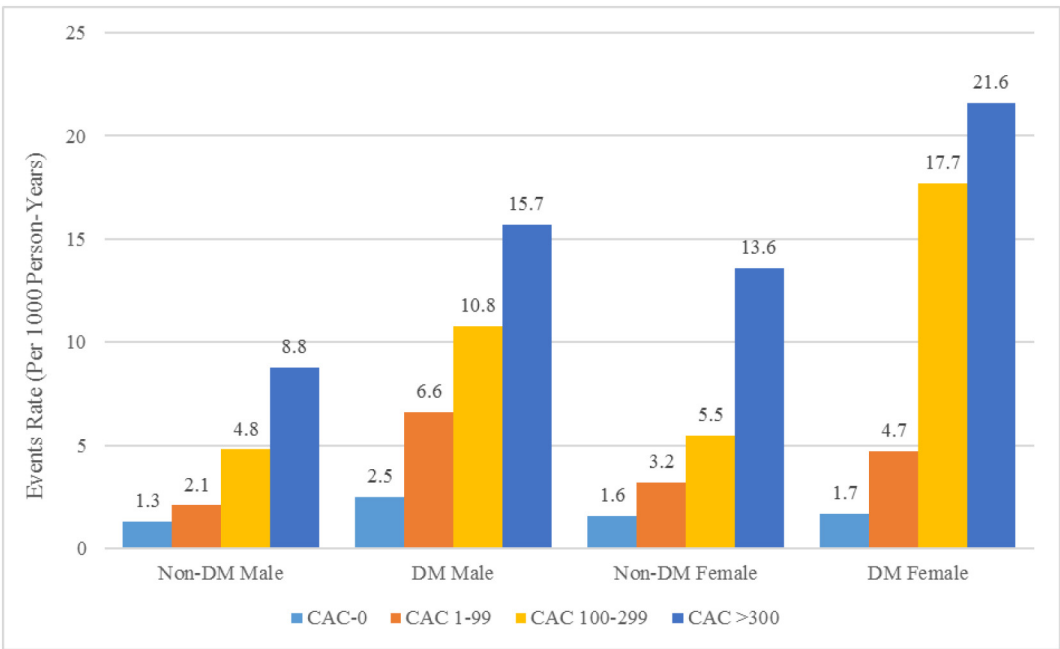

Fig. 3. Annualized mortality risk per 1000 person-years stratified by CAC categories among males and females with and without diabetes.

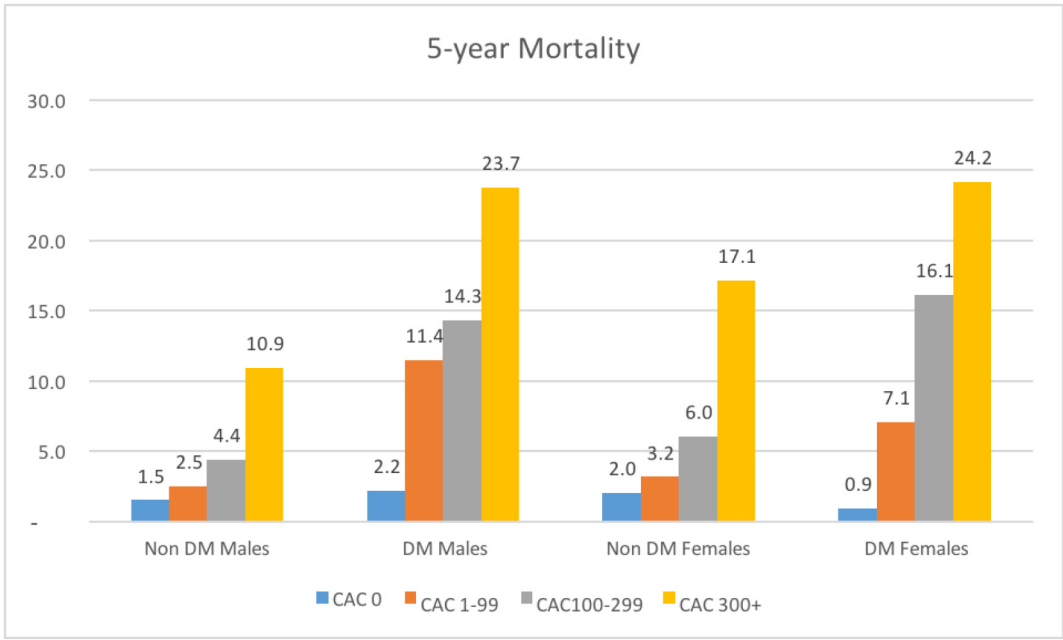

Fig. 4. Annualized short-term all-cause mortality risk per 1000 person-years stratified by CAC categories among males and females with and without diabetes.

(36.6 vs 23.3%). Similarly, less females with diabetes had CAC ≫300 in our study as compared diabetic males (18.7% vs 33.7%). Similarly, Heinz Nixdorf Recall study, more women (39.3%) as compared to men (13.4%) with diabetes had CAC score of 0, absence of CAC was associated with low short term risk of death (1% at 5 years).[26]

ACC/AHA guidelines recognize the value of CAC in reclassifying patients who will potentially benefit from statin therapy.[27] Furthermore, new guidelines also recommend withholding statin therapy in patients with CAC scores of zero in general population given the extremely low event rate in those with no coronary calcification.[27] Though, it says "CAC scores of zero in patients with diabetes mellitus may still be association with substantial 10-year risk".[27] There is significant variation in prevalence and extent of CAC in individuals with diabetes.[13,14,21] CAC potentially could reclassify significant number of individuals with diabetes at risk for CVD event. In a recent report from MESA, for incident CHD Net reclassification index (NRI) using CAC score was 0.23(95% CI, 0.10–0.37) in individuals with diabetes over 10-year follow-up.[13] Valenti el al[14] reported category-free NRI for all-cause mortality of

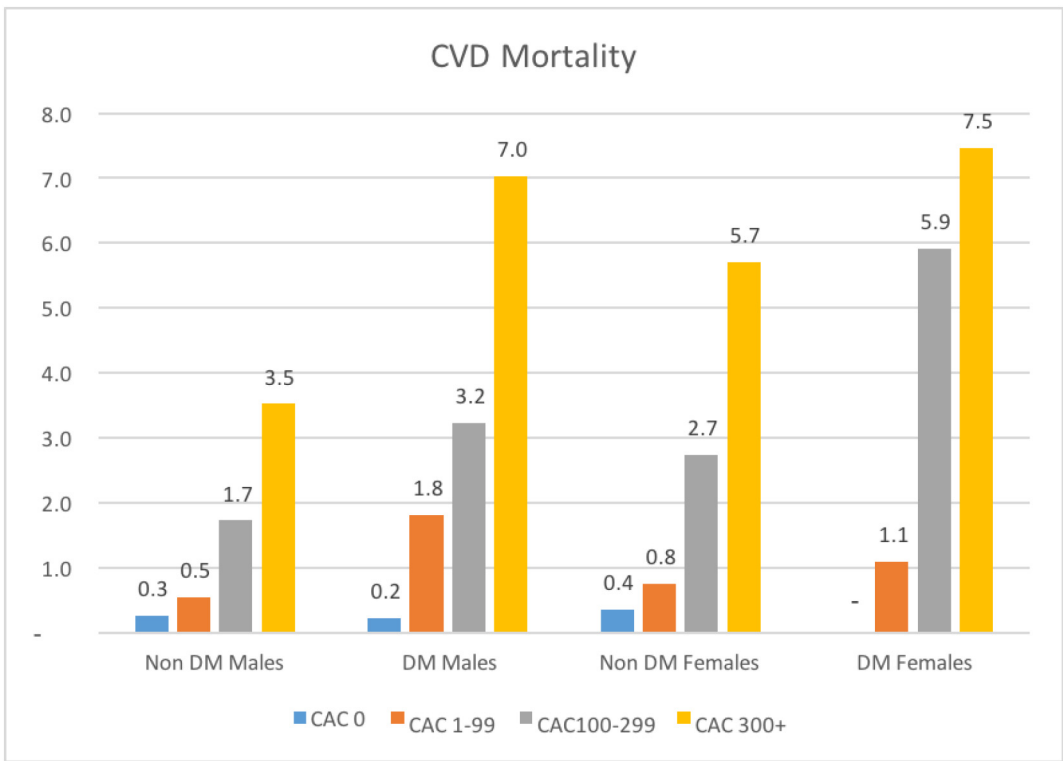

Fig. 5. Annualized cardiovascular disease mortality per 1000 person-years.

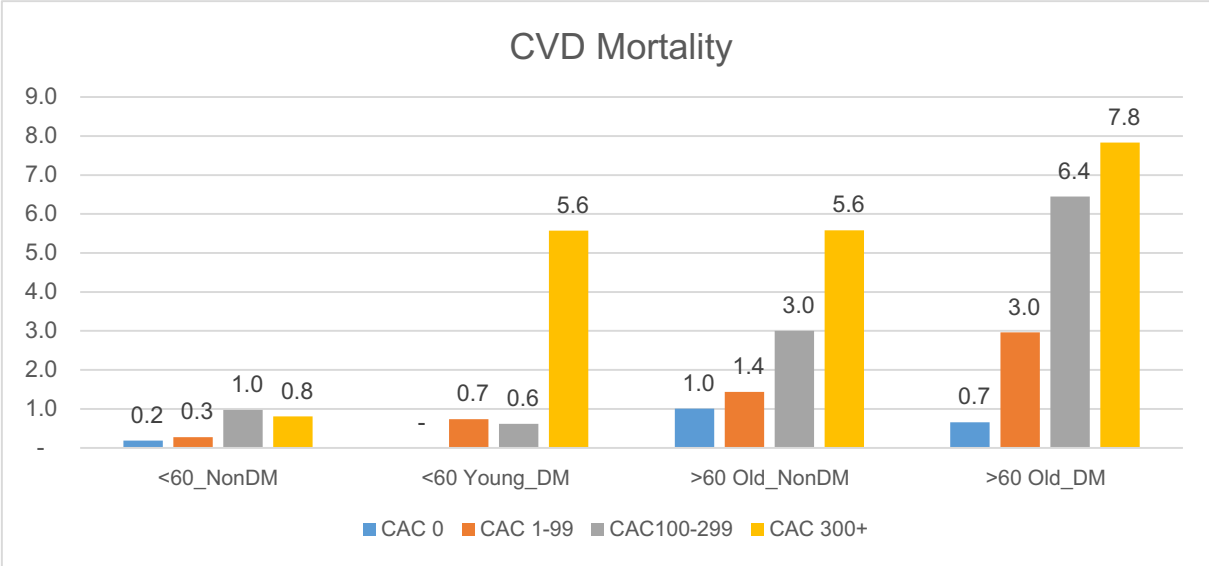

Fig. 6. Annualized cardiovascular disease mortality per 1000 person-years stratified by age cutoff of 60 years.

0.50 to 0.53 in participants with diabetes with follow-up of up to 15 years. Our data are consistent with other population-based studies including MESA; there was significant reclassification in all groups except non-diabetic females.

5. Limitations

Our study has several limitations including single center study design which limits generalizability. We did not have any data about

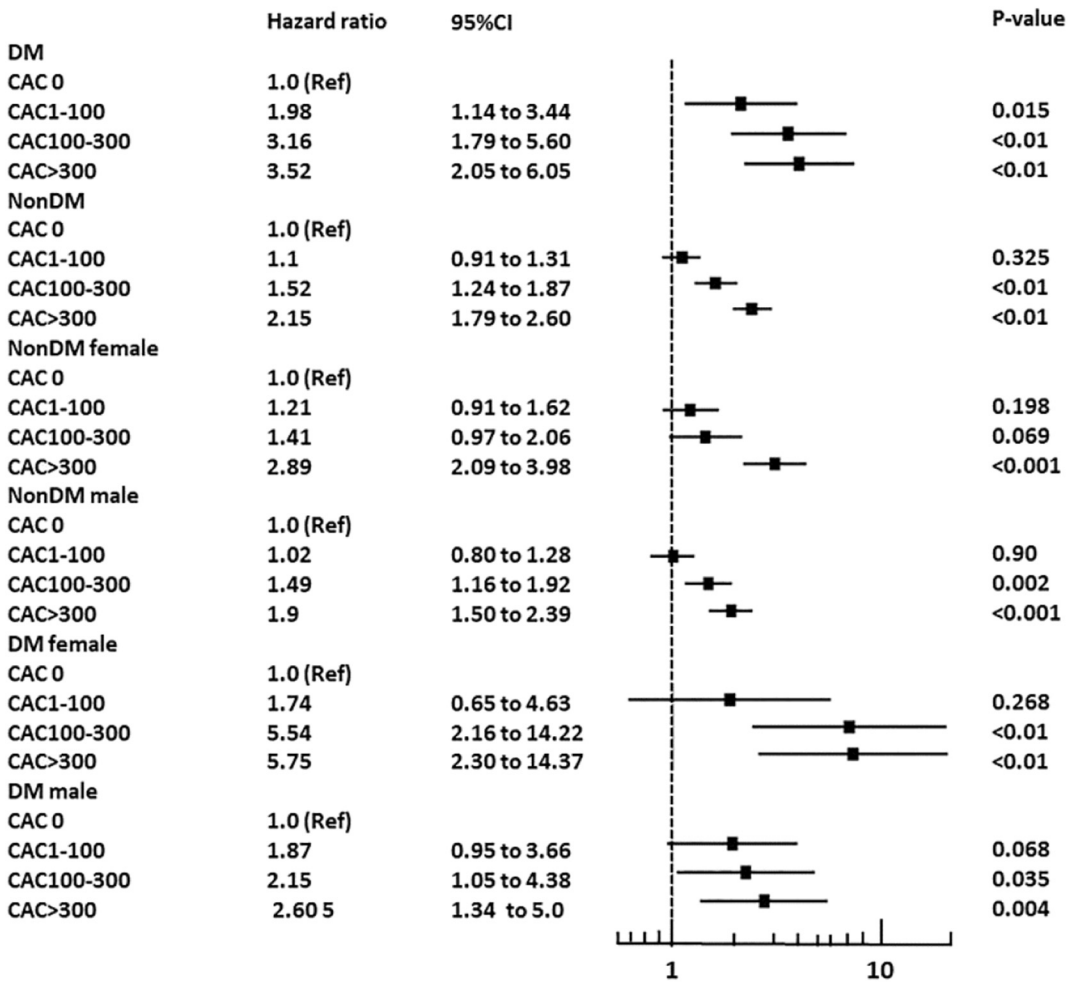

Fig. 7. Forest-Plot showing hazard ratios among males and females with and without diabetes stratified by CAC categories.

Table 2
Long term net reclassification improvement for all-cause mortality by coronary artery calcium among non-diabetic and diabetic males and females.

	NRI	NRI 95% CI	P value	% of events correctly classified	Events P value	% of nonevents correctly classified	Non-event P value
Non-diabetic female Model 2 (vs Model 1)	0.127	−0.12, 0.38	0.33	13%	0.3	1%	0.8
Non-diabetic male Model 2 (vs Model 1)	0.39	0.20, 0.57	≪0.0001	26%	0.006	13%	≪0.0001
Diabetic female Model 2 (vs Model 1)	0.73	0.09, 1.37	0.03	33%	0.3	40%	≪0.0001
Diabetic male Model 2 (vs Model 1)	0.44	0.06, 0.816	0.02	31%	0.09	13%	0.06

Model 1: age, hypertension, smoking, family history of premature coronary artery disease, dyslipidemia, and chest pain.
Model 2: age, hypertension, smoking, family history of premature coronary artery disease, dyslipidemia, and chest +logCAC.

lifestyle and medication changes post CAC scanning. Presence of CAC has been shown to improve the patient behavior and increased utilization of statins and aspirin. Nonetheless, a healthy lifestyle, more usage of aspirin and statins likely made our results more conservative. Furthermore, we cannot conclude how single CAC scanning would compare to CAC progression and changes/assessment in risk factors over time. Since, the use of categorical risk factors results in an underestimation in their predictive, there is a possibility that prognostic and reclassification value of CAC scoring was overinflated. Nonetheless, in current clinical practice physicians are often limited by availability of self-reported categorical data.

6. Conclusion

There was an incremental risk of CVD and all-cause mortality with increasing CAC across all groups. A significant percentage of individuals have no coronary calcification, specifically females. Coronary calcification seems to be associated with worse prognosis in females as compared to males. CAC carries a significant reclassification potential even in individuals with diabetes.

Declaration of Competing Interest

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