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Coronary artery calcium scores indicating secondary prevention level risk: Findings from the CAC consortium and FOURIER trial

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ABSTRACT

Background and aims: Coronary artery calcium (CAC) burden displays a stepwise association with atherosclerotic cardiovascular disease (ASCVD) risk. Among primary prevention patients, we sought to determine the CAC scores equivalent to ASCVD mortality rates observed in the FOURIER trial, a modern secondary prevention cohort.
Methods and Results: For the main analysis, we included participants from the CAC Consortium ≥50 years old with a 10-year ASCVD risk ≥7.5% (n = 20,207). Poisson regression was used to define the relationship between CAC and annual ASCVD mortality. Equations generated from the regression models were then used to derive CAC scores associated with equivalent annual ASCVD mortality as observed in FOURIER placebo participants from the overall trial and in key trial subgroups. The CAC Consortium participants had a similar age (65.5 *versus* 62.5 years) and sex (22% *versus* 24% female) distribution as FOURIER. The annualized ASCVD mortality rate in FOURIER participants (0.766 per 100 person-years) corresponded to a CAC score of 781 (418–1467). A CAC score of 255 (162–394) corresponded to an ASCVD mortality rate equivalent to the lowest risk FOURIER subgroup (presence of myocardial infarction >2 years prior to trial enrollment). No CAC score produced a risk equivalent to high-risk FOURIER subgroups, particularly those with symptomatic peripheral arterial disease and/or multivessel coronary heart disease.
Conclusions: Primary prevention individuals with increased CAC burden may have annualized ASCVD mortality rates equivalent to persons with stable secondary prevention-level risk. These findings argue for a risk continuum between higher risk primary prevention and stable secondary prevention patients, as their ASCVD risks may overlap.

1. Introduction

Current European Society of Cardiology (ESC) guidelines recommend coronary artery calcium (CAC) on non-contrast computed tomography (CT) as the best-established imaging modality to assess atherosclerotic cardiovascular disease (ASCVD) risk [1]. Similarly, American College of Cardiology (ACC)/American Heart Association (AHA) guidelines assign a IIa recommendation for the selective use of CAC scoring among persons at borderline or intermediate 10-year ASCVD risk (5–20%) to help guide the initiation of statin pharmacotherapy [2]. Individuals with higher CAC burden are thought to derive a larger benefit from primary prevention pharmacotherapies [3], as the number needed to treat with statins to prevent one primary ASCVD event is up to 23-fold lower in persons with CAC ≥100 compared to CAC = 0 [4]. Among primary prevention patients already on high-intensity statin therapy, novel lipid lowering agents may be important for

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residual risk reduction [5]; however, there is currently a dearth of information regarding the potential utility of CAC scoring to guide such clinical decision making beyond the initiation of statin therapy.

Prior data has suggested a risk spectrum across a range of commonly encountered CAC scores [6]. For example, there appears to be a graded, stepwise association between CAC burden and ASCVD risk independent of coronary stenosis [7], such that individuals with very high CAC (≥1000) who have not experienced an event have a similar ASCVD event rate and all-cause mortality compared to a stable, treated secondary prevention population [8]. Thus, understanding the CAC scores that are associated with ASCVD mortality rates equivalent to stable secondary prevention populations may be important for guiding the intensity of preventive approaches more broadly, such as the magnitude of low-density lipoprotein-cholesterol (LDL-C) lowering or the use of novel lipid-lowering therapies [5].

In 2017, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial randomized individuals with clinical ASCVD (81% myocardial infarction (MI), 20% stroke, and 14% peripheral arterial disease) on moderate or high-intensity statin therapy, with or without ezetimibe, to PCSK9 inhibition *versus* placebo and evaluated major ASCVD events, including death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization [9]. Over a median follow-up of 26 months, individuals randomized to PCSK9 inhibitor evolocumab had a 59% average reduction in LDL-C and a 1.5% absolute risk reduction of major ASCVD events, which corresponded to a number needed to treat of 74, for populations of similar risk. Results from FOURIER have influenced modern lipid-lowering guidelines [1,2], including the definition of high risk vs very high risk secondary prevention, as well as target LDL-C levels and use of add-on non-statin therapies.

Because FOURIER represents a modern, stable ASCVD prevention population who are on guideline-directed statin therapy, we sought to compare annualized ASCVD mortality rates observed in the placebo group of the FOURIER trial to primary prevention individuals from the CAC Consortium, the largest multicenter cohort study to perform CAC scanning among persons without clinical ASCVD who are enriched in risk factors.

2. Patients and methods

2.1. Study population

The CAC Consortium is a multicenter cohort study that includes four high-volume centers in the United States, Cedars-Sinai Medical Center (Los Angeles, CA), PrevaHealth Wellness Diagnostic Center (Columbus, OH), Harbor-UCLA Medical Center (Torrance, CA), and Minneapolis Heart Institute (Minneapolis, MN). The multicenter retrospective cohort study aimed to assess the association between CAC and long-term, disease-specific mortality, and the study design and methods have been previously described in detail elsewhere [10]. In brief, investigators included individuals 18 years of age or older who were free of clinical ASCVD or had no cardiovascular symptoms at the time of CAC scanning. All participants in the CAC Consortium were clinically referred by a physician to undergo CAC scanning (1991–2010) due to uncertainty in risk assessment in the presence of underlying ASCVD risk factor(s).

We used ACC/AHA guidelines to define primary prevention groups for the current study. To simulate the primary guideline-based indication for CAC scoring [2,11], we included participants who were aged ≥50 years old with at least intermediate 10-year ASCVD risk ≥7.5% (n = 20,207) for our main study sample. To approximate the expanded indications for CAC scoring [12,13], we defined and included several additional subgroups. These subgroups included a low-risk population including persons aged ≥50 years old with at least borderline 10-year ASCVD risk and at least one risk factor (n = 22,612), and a high-risk population including persons aged ≥50 years old who had diabetes with at least intermediate 10-year ASCVD risk (n = 2277). Given the relevance to the VESALIUS-CV trial that will assess the effect of evolocumab in patients with high ASCVD risk (including diabetes) who have not had a previous MI (https://www.clinicaltrials.gov/ct2/show/NCT03872401), we included participants aged ≥40 years old with diabetes alone (n = 3281) in an additional analysis. Written informed consent for participation in research was collected at the centers at the time of CAC scanning at baseline.

2.2. Measurement of coronary artery calcium

A standard protocol was used to quantify CAC using non-contrast, ECG-gated cardiac CT at all participating medical centers [10]. Electron beam and multi-detector CT were used for imaging protocols, and earlier assessments have demonstrated that there are no clinically significant differences in CAC quantification between the two different scanning methods. Calcium scores were computed using the Agatston method.

2.3. Outcome ascertainment

Mortality due to ASCVD in the CAC Consortium was assessed by linking patient records with the Social Security Administration Death Master File using a previously validated algorithm. Death certificates were obtained from the National Death Index, and underlying cause of death was categorized into common causes of death using *International Classification of Diseases* (ICD), 9^{th} and 10^{th} *Revision* codes as described previously [14]. In the FOURIER trial, mortality attributable to ASCVD was defined as death due to MI, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, and/or other cardiovascular causes [9].

2.4. Evaluation of ASCVD risk factors

Assessment of ASCVD risk factors occurred contemporaneously with CAC testing. Diabetes and hypertension were defined by a previous clinical diagnosis or reported antihypertensive or glucose-lowering medication utilization. There was no information regarding the differentiation between type 1 *versus* type 2 diabetes. Dyslipidemia (LDL-C ≥160 mg/dL), hypertriglyceridemia (triglycerides ≥150 mg/dL), and low high-density lipoprotein-cholesterol (<40 mg/dL in men, <50 mg/dL in women) were defined by a previous clinical diagnosis or utilization of lipid-lowering therapy. Information on cigarette smoking and family history of coronary heart disease (CHD) (first-degree relative with history of CHD at any age) were obtained through self-report data. The 10-year risk for ASCVD was calculated using the pooled-cohort equations (PCE) [15], including using the raw equations to extrapolate risk for those less than 40 years of age. Multiple imputation was performed in the case of limited missing supportive binary risk factor data (28% of participants in the overall CAC Consortium cohort), by utilizing logistic regression and non-missing data on age, sex, race, other ASCVD risk factors, and CAC data. Of those participants with missing data, the majority (>72%) were lacking information for only one demographic or risk factor variable. The correlation coefficient for ASCVD scores calculated using partial imputation and directly calculated ASCVD scores was 0.95, indicative of robust agreement, and integrity of the multiple imputation process.

2.5. Statistical analysis

Study population characteristics were presented according to the main sample population (10-year ASCVD risk ≥7.5%), and also according to subgroups (10-year risk ≥5% with at least 1 risk factor, diabetes and 10-year risk ≥7.5%, and diabetes alone). Continuous variables were presented as means and standard deviations, while percentages are used for categorical variables. Due to a non-normal distribution of CAC, the median was used to represent the central

tendency of CAC scores. The Student's t-test and Wilcoxon signed-rank test were used to assess differences in normally and non-normally distributed continuous variables, respectively. Differences between categorical variables were evaluated through the Chi-square test.

We used Poisson regression within the CAC Consortium to derive annualized ASCVD mortality rates as a function of log CAC+1 [8]. These CAC-specific rates were then graphed as a function of the untransformed continuous CAC score, which produced very good to excellent fit to the raw data ($R^2 > 0.88$–0.99). No alternative approaches produced a superior fit for the data. We have presented a best line of fit in the form "y = X(ln CAC + 1) – b" to enhance interpretability for the reader. To maximize power, we included all CAC Consortium follow-up which occurred over a median follow-up period of 11 years.

ASCVD mortality rates from FOURIER were drawn from the placebo group. Attention was placed on specific FOURIER subgroups/characteristics as defined by Sabatine et al. [16]:timing of previous MI (<2 *versus* ≥2 years prior), number of previous MIs, and the presence/absence of residual multivessel obstructive CHD (≥40% stenosis in ≥2 large vessels). Based on this FOURIER subgroup analysis, high-risk features in the current study were defined as MI within the last 2 years, multiple prior MIs, and/or the presence of residual multivessel obstructive CHD [16]. Low risk was considered to be no residual obstructive coronary disease as defined by Sabatine et al. after the qualifying MI/revascularization [16].

Using equations derived from the logistic regression model, we calculated the CAC score that is associated with the same annual ASCVD mortality rate as observed in FOURIER. Similar to previous studies, confidence intervals for CAC equivalence estimates were calculated by performing calculations corresponding to ± 15% risk [17]. This range is drawn from the published confidence range of mortality ascertainment from the CAC Consortium [10].

3. Results

Primary prevention patients with at least an intermediate 10-year ASCVD risk were on average 65 years old, 22% were women and 12% were of non-white ethnicity (Table 1). These CAC Consortium participants had a similar age/sex distribution as FOURIER. A total of 32% and 51% of individuals with an ASCVD risk ≥7.5% had CAC 1–100 and CAC >100, respectively. Approximately half of participants with a 10-year ASCVD risk ≥7.5% or risk ≥5% with at least one major risk factor had CAC ≥100 (48.7%). Regardless of primary prevention group studied, at least 78% of persons had prevalent CAC within each primary prevention subgroup. The median CAC score for persons with a 10-year ASCVD risk ≥7.5% was 107 (9–441), and ranged from 91 (6–399) for individuals who had an ASCVD risk ≥5% with at least one risk factor to 175 (22–654) among those with diabetes and an ASCVD risk ≥7.5%.

The prevalence of risk factors, including dyslipidemia, current smoking, and a family history of CHD, were similar among all four primary prevention groups in the CAC Consortium. More than one-half of primary prevention patients who were at least an intermediate ASCVD risk had hypertension (55%) and dyslipidemia (66%), whereas 43% had a family history of CHD (43%). There was an overall similar prevalence (14%) for current cigarette smoking and diabetes in the main study sample.

The relationship between CAC burden and annualized ASCVD mortality was logarithmic. For a given CAC score, high-risk primary prevention subpopulations had a higher estimated annualized ASCVD mortality compared to low-risk primary prevention subgroups (Fig. 1 and Fig. 2). While all four primary prevention patient subgroups experienced similar logarithmic increases in ASCVD mortality risk for higher CAC burden, this association was strongest among persons with diabetes (Fig. 2B). Equations for the association between CAC burden and annualized ASCVD mortality are presented for primary prevention subgroups with each corresponding logarithmic graph. After adjusting for sex and age, higher CAC burden conferred a similar increased risk for ASCVD mortality across all primary prevention groups (Supplemental Table 1).

Among the main sample of primary prevention patients with at least an intermediate 10-year ASCVD risk, a CAC score of 781 corresponded to an annualized ASCVD mortality rate (0.766 per 100 person-years) equivalent to that observed in the FOURIER trial (Table 2 and Fig. 1A). However, lower CAC scores were equivalent to the lower risk FOURIER secondary prevention subsets including participants who suffered an MI > 2 years prior to study enrollment (255), those with only one previous MI (317), and those without residual obstructive

Table 1
Baseline characteristics of patients from the CAC Consortium.

	Main Sample	Low-Primary Prevention Risk	High-Primary Prevention Risk	
	ASCVD risk ≥7.5% (age >50)	ASCVD risk ≥7.5% or ASCVD risk≥ 5% with at least 1 risk factor (age >50)	Diabetes & ASCVD risk ≥7.5% (age >50)	Diabetes (age >40)[b]
N	20,207	22,612	2277	3281
Age, mean ± SD, years	65.4 ± 7.7	64.5 ± 7.9	63.8 ± 8.1	59.5 ± 9.7
Female, %	4376, 21.7%	5461, 24.2%	598, 26.3%	1084, 33.0%
Male, %	15,831, 78.3%	17,151, 75.9%	1679, 73.7%	2197, 67.0%
Race/Ethnicity, %				
White	11,680, 88.1%	13,290, 88.1%	1310, 74.9%	1867, 74.7%
Black	440, 3.3%	476, 3.2%	121, 6.9%	158, 6.33%
Hispanic	427, 3.2%	496, 3.3%	155, 8.9%	234, 9.37%
Asian	498, 3.8%	565, 3.75%	123, 7.0%	177, 7.1%
Other	218, 1.6%	252, 1.7%	40, 2.3%	62, 2.5%
CAC Prevalence, %				
CAC = 0	3396, 16.8%	4217, 18.7%	299, 13.1%	718, 21.9%
CAC 1-100	6474, 32.0%	7394, 32.7%	625, 27.5%	994, 30.3%
CAC >100	10,337, 51.2%	11,001, 48.7%	1353, 59.4%	1569, 47.8%
CAC Score[a], median (Q1, Q3), AU	107 (9, 441)	91 (6, 399)	175 (22.4, 653.8)	84 (2, 453)
Hypertension, %	10,610, 52.5%	12,414, 54.9%	1484, 65.2%	1956, 59.6%
Dyslipidemia, %	13,582, 67.2%	14,850, 65.7%	1569, 68.9%	2123, 64.7%
Diabetes, %	3001, 14.9%	3241, 14.3%	2277, 100%	3281, 100%
Current Smoking, %	2789, 14.9%	3336, 14.8%	286, 12.6%	370, 11.3%
Family History of CHD, %	8411, 41.6%	9583, 43.4%	974, 42.8%	1448, 44.1%

ASCVD = atherosclerotic cardiovascular disease CAC = coronary artery calcium; CHD = coronary heart disease.
[a] Among persons with CAC >0.
[b] All populations include age >50 years old except for diabetes which is age >40 years.

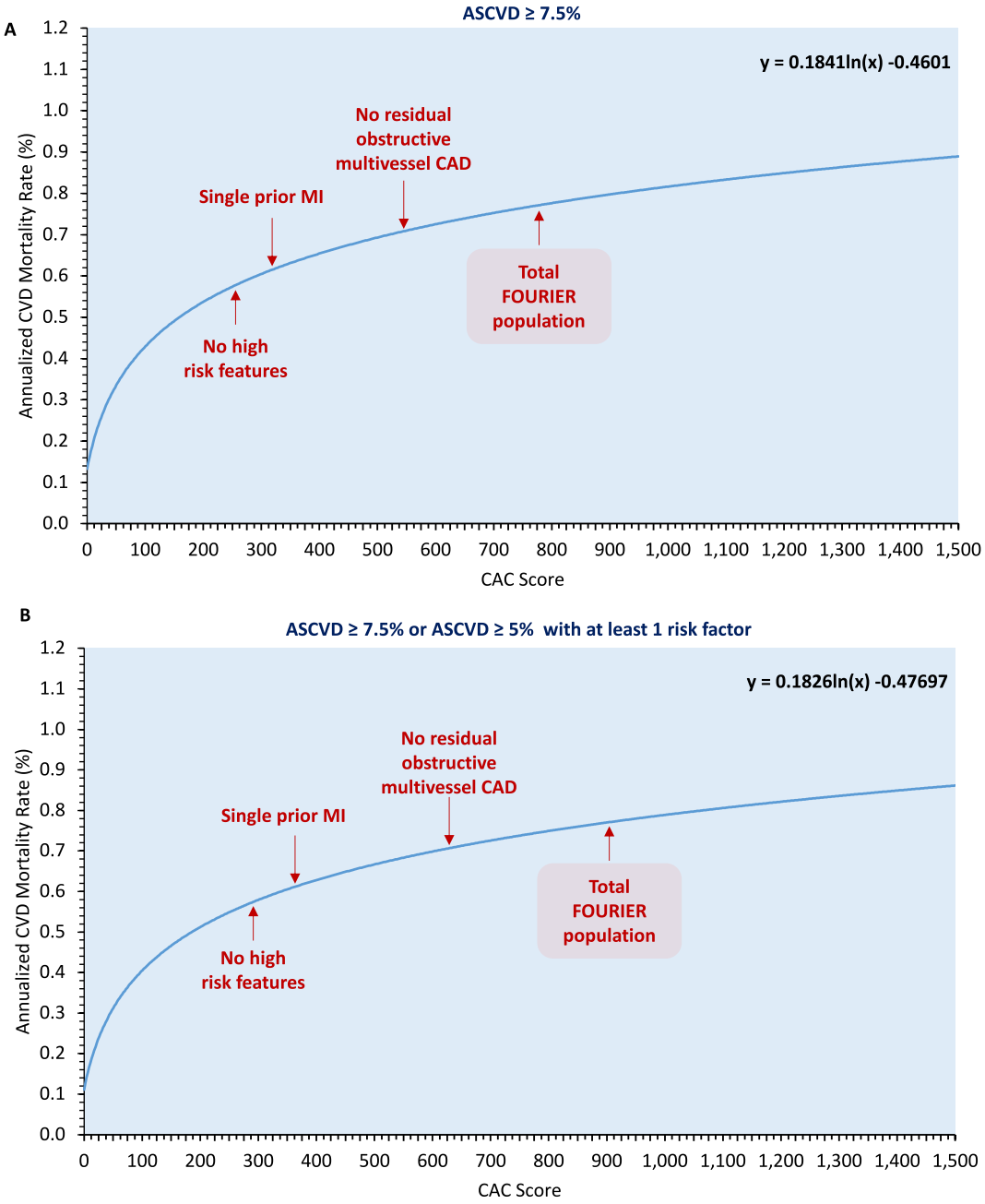

Fig. 1. Coronary artery calcium scores associated with secondary prevention ASCVD mortality risk in relevant ASCVD primary prevention subpopulations to lower-risk FOURIER subgroups.
**For a given CAC score, high-risk primary prevention patients defined by a 10-year risk ≥7.5% (A) had a higher estimated annualized ASCVD mortality compared to low-risk primary prevention patients (B), of whom additionally included persons with a 10-year risk ≥5% and at least one risk factor.

multivessel CHD after an index event/revascularization (545). After additionally considering primary prevention patients with an ASCVD risk ≥5% over the next 10 years, a CAC score of 904 corresponded to an annualized ASCVD mortality equivalent to FOURIER placebo group participants (Table 2 and Fig. 1A–B).

Considering patients from the CAC Consortium with diabetes, lower CAC scores corresponded to annualized ASCVD mortality rates observed in the overall FOURIER population and key FOURIER subgroups (Table 3, Fig. 2A–B). Among CAC consortium primary prevention individuals with diabetes, predicted CAC scores of 179, 206, and 294 corresponded to equivalent annualized ASCVD mortality rates to FOURIER participants with no high risk features, a single prior MI, and who did not have residual obstructive multivessel CHD, respectively.

In the CAC Consortium, there was no CAC score that produced a risk equivalent to the high-risk FOURIER subgroups. For example, the annualized ASCVD mortality rate of FOURIER patients with peripheral artery disease was nearly 1.1 per 100 person-years, which exceeded that of even patients with CAC = 1500 (0.89 per 100 patient-years) in our main study population from the CAC Consortium.

4. Discussion

Here, we demonstrate that a population of primary prevention individuals defined by CAC burden can have annualized ASCVD mortality rates equivalent to persons with stable secondary-prevention level risk. In particular, CAC scores ranging from 775 to 900 for a general at risk primary prevention population and CAC scores of 300–375 in persons with diabetes were associated with an ASCVD mortality risk equivalent

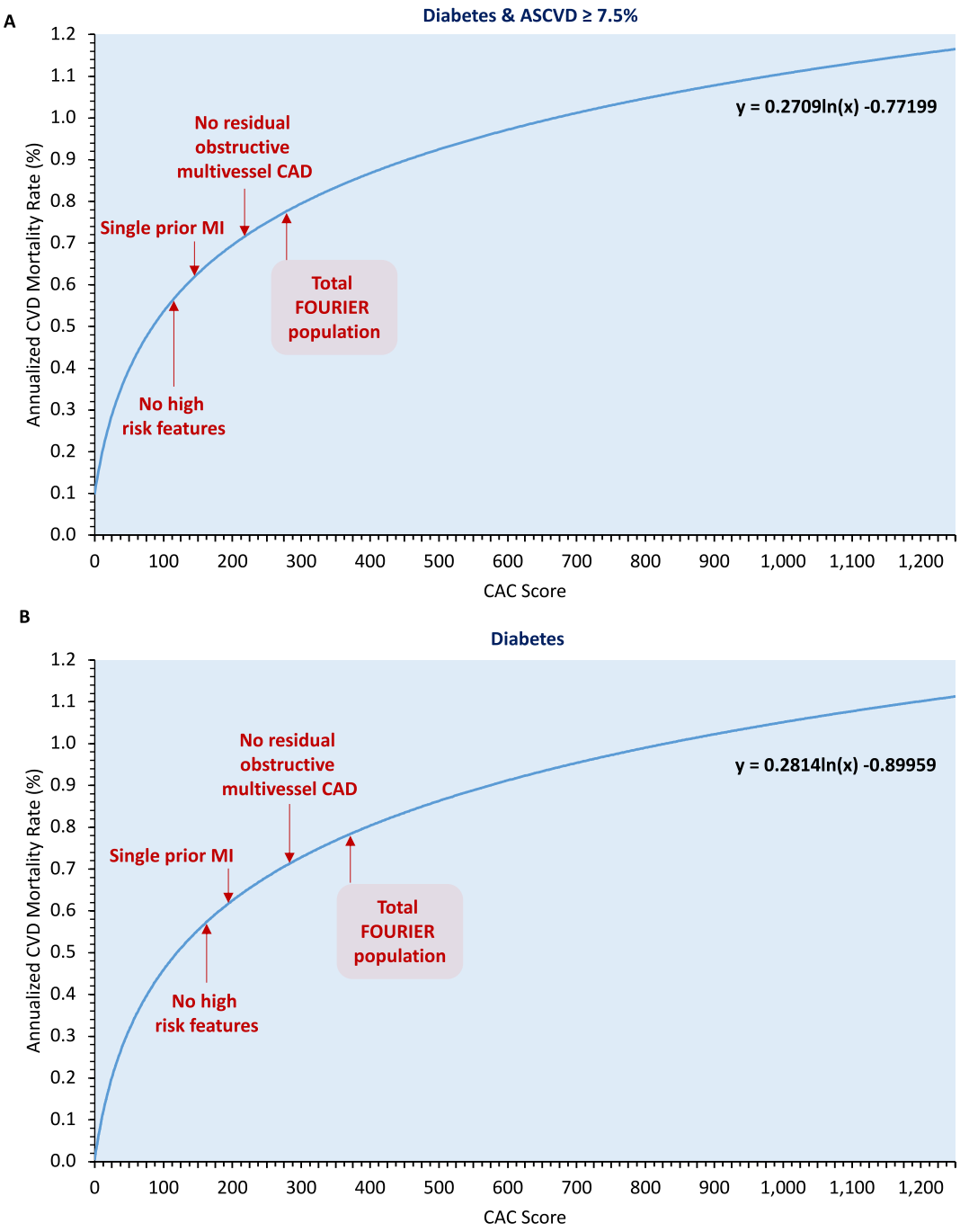

Fig. 2. Coronary artery calcium scores associated with secondary prevention ASCVD mortality risk in relevant diabetes primary prevention subpopulations to lower-risk FOURIER subgroups.
*While four primary prevention patient subgroups experienced similar logarithmic increases in ASCVD mortality risk for higher CAC burden, these associations were strongest when considering persons with diabetes and a 10-year risk ≥7.5% (A) and diabetes alone (B).

to the overall FOURIER trial population. These results also suggest that a CAC score >300 in a typical CAC scoring primary prevention population is of similar risk as a stable treated secondary prevention patient with a single previous MI event (one of the low risk subsets from FOURIER). Thus, our findings argue for a risk continuum between higher risk primary *versus* stable secondary prevention patients, as their risks may overlap [18].

The main clinical implication of our findings is that CAC scores may potentially provide value for guiding the intensity of LDL-C lowering in high-risk primary prevention and stable secondary prevention patients, beyond the initial initiation of statin therapy. Our observations support a prior Multi-Ethnic Study of Atherosclerosis (MESA) analysis which showed that CAC scores of approximately 900 in participants with 10-year ASCVD risk >7.5% produce an equivalent a 3-point major adverse cardiovascular event (MACE) risk as in the overall FOURIER population [8]. MESA investigators also observed that CAC scores between 300 and 500 corresponded to equivalent MACE for lower-risk FOURIER subgroups, including persons with no multi-vessel disease, only 1 previous MI, and persons with no high-risk features. We expand on this concept by testing different primary prevention populations (including a separate analysis for diabetes) and examine additional FOURIER subgroups with application to a real-world setting of clinical

Table 2
Coronary artery calcium scores associated with secondary prevention ASCVD mortality risk in whole population to lower-risk FOURIER subgroups.

CAC Consortium population	No high risk features[a]	Single prior MI[b]	No residual obstructive multivessel CAD[c]	Total FOURIER population
ASCVD ≥7.5%	255 (162–394)	317 (194–517)	545 (308–965)	781 (418–1457)
ASCVD ≥7.5% or ASCVD ≥5% with at least 1 risk factor	292 (185–454)	364 (223–596)	630 (355–1120)	904 (482–1697)

ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcium, MI = myocardial infarction. Confidence range reflects the possible 15% underestimation of equivalent risk within the CAC Consortium.

[a] Timing of qualifying MI: high risk was considered within the preceding two years, low risk as >2 years before trial enrollment.

[b] Number of prior MIs: high risk was considered to be one or more additional prior MIs in addition to the index qualifying event, low risk was considered just one prior MI that was the qualifying event to be included in the trial.

[c] Presence of residual multi-vessel coronary artery disease: high risk was considered to be residual obstructive coronary artery disease (≥40% stenosis in ≥2 large vessels) after the qualifying MI and related revascularization, low risk was considered to be no residual obstructive coronary disease after the qualifying MI/revascularization.

Table 3
Coronary artery calcium scores associated with secondary prevention ASCVD mortality risk in diabetes population to lower-risk FOURIER subgroups.

CAC Consortium population	No high risk features[a]	Single prior MI[b]	No residual obstructive multivessel CAD[c]	Total FOURIER population
Diabetes & ASCVD ≥7.5%	137 (100–184)	158 (114–221)	229 (155–337)	292 (191–467)
Diabetes	179 (133–238)	206 (150–284)	294 (203–427)	372 (247–560)

ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcium, MI = myocardial infarction. Confidence range reflects the possible 15% underestimation of equivalent risk within the CAC Consortium.

[a] Timing of qualifying MI: high risk was considered within the preceding two years, low risk as >2 years before trial enrollment.

[b] Number of prior MIs: high risk was considered to be one or more additional prior MIs in addition to the index qualifying event, low risk was considered just one prior MI that was the qualifying event to be included in the trial.

[c] Presence of residual multi-vessel coronary artery disease: high risk was considered to be residual obstructive coronary artery disease (≥40% stenosis in ≥2 large vessels) after the qualifying MI and related revascularization, low risk was considered to be no residual obstructive coronary disease after the qualifying MI/revascularization.

CAC scoring. In particular, we found that a lower accumulated CAC burden was necessary to produce equivalent secondary prevention mortality risk in higher risk compared to lower risk primary prevention patients. For example, a CAC score of 372 produced equivalent secondary prevention mortality risk in persons with diabetes, whereas a much higher CAC burden (904) was necessary to achieve the same mortality event rate for those with at least borderline risk and one risk factor (lower risk).

Currently, CAC scoring is used in contemporary ASCVD risk stratification when there is uncertainty in risk to assess the utility of initiating statin pharmacotherapy. In particular, the absence of CAC confers a high number needed to treat and is strongly associated with a very low risk of an incident ASCVD event beyond 10 years, even among statin eligible candidates. While the power of zero concept attributable to CAC = 0 has been exceedingly useful to improve precision in the allocation of preventive therapies, very little information has been available on utilizing prevalent CAC scores to guide the intensity of treatment. To this end, our current study provides foundational evidence to leverage the spectrum of CAC scores to categorize risk among primary prevention patients with a 10-year risk ≥7.5%.

Based on clinical trial evidence, it has been shown that a large majority of individuals with a previous MI are eligible to receive novel secondary prevention therapies, including lipid-lowering therapies [19]. This evidence is important to consider given that we demonstrate how CAC scoring may help to identify equivalently high risk prior to an initial event, as elevated CAC burden even in the primary prevention setting is associated with annualized ASCVD event rates equivalent to secondary prevention risk. For example, we found that CAC approximately between 300 and 400 among primary prevention individuals with a 10-year ASCVD risk ≥5% with at least one risk factor or those with a 10-year risk ≥7.5% corresponded to an annual ASCVD event rate similar to that of FOURIER participants who had a single previous MI. Thus, it is possible that primary prevention individuals with CAC ≥300 who are already on high-intensity statin therapy may potentially benefit from novel add-on preventive therapies [20]. In addition, given the observed stepwise increases in ASCVD mortality for higher CAC scores, there may be utility in selective repeat CAC scores for advanced risk assessment via repeat non-contrast CT even after the initial initiation of CAC >0 and initial statin therapy [13].

Our findings may also have relevance to ongoing clinical trials. VESALIUS (NCT03872401) is an ongoing double-blind, randomized placebo-controlled trial that is assessing whether PCSK9 inhibition via evolocumab reduces MACE among high-risk primary prevention patients, including a subset of patients with diabetes. Given that significant subclinical CHD is one major inclusion criteria for populations in VESALIUS, this trial may help to further answer whether CAC scoring can help guide the intensity of LDL-C lowering and/or eligibility for novel preventive therapies for residual ASCVD risk reduction in persons who have not yet had a primary event. Our results have implications for interpreting VESALIUS, including interpretation of the risk level of population enrolled as a result of subclinical atherosclerosis imaging vs. the risk level of the prior secondary prevention FOURIER trial population.

The major strengths of our study included the measurement of CAC via non-contrast CT among more than 25,000 individuals enriched in risk factors who had not yet experienced an ASCVD event, which is a guideline-directed imaging modality for primary prevention [10]. New clinical guidelines from the National Lipid Association [21] have begun to raise the question of whether CAC can guide non-statin therapy utilization in primary prevention patients, whereas ACC/AHA [2] and ESC/European Atherosclerosis Society (EAS) [11] guidelines do not provide precise recommendations for the utility of CAC beyond the initiation of statin therapy. Therefore, our study helps to fill such knowledge gaps and provides crucial information about the CAC scores equivalent of secondary prevention risk using robust logistic regression modeling. Along these lines, we leveraged results derived from the FOURIER trial, which resembles one of the most modern trials to assess secondary prevention outcomes in patients with clinical ASCVD.

Our study should be interpreted in the setting of certain limitations. First, ASCVD mortality was not the primary outcome of FOURIER [9], and the approach to defining ASCVD-related mortality between the CAC Consortium and FOURIER differed (death certificates *vs.* case adjudication). Second, consistent with the literature [22], we assumed a logarithmic relationship between CAC and ASCVD mortality; however,

alternative model fits (i.e. polynomial or power) - particularly those affecting the tail ends of the CAC distribution - may produce slightly different CAC score equivalents (up to 25%). Furthermore, we did not have information on medication utilization after individuals underwent CAC scanning, and it is likely that individuals with higher CAC scores were more aggressively treated with preventive therapies. The result of this limitation, however, would be a conservative bias, as the ASCVD mortality rate would be underestimated as a larger proportion of primary prevention patients with high CAC scores were on intensive preventive treatment regimens. Finally, as a clinical-referral population, the CAC Consortium is not designed to be fully representative of the general population. Accordingly, a large proportion of the CAC Consortium is of Caucasian ethnicity and future studies are undoubtedly required in population samples that include a larger proportion of minority ethnic groups.

To conclude, primary prevention individuals can be defined by CAC burden who have annualized ASCVD mortality rates equivalent to certain persons with stable secondary prevention risk. In particular, CAC scores ranging from 775 to 900 for a general at-risk primary prevention population and CAC scores of 300–375 in primary prevention patients with diabetes were associated with an ASCVD mortality risk equivalent to secondary prevention. These findings argue for a risk continuum between higher risk primary prevention *versus* low to average risk stable secondary prevention patients based on CAC burden, as their ASCVD risks may overlap.

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Author contributions

OD, ACR and MJB participated in the conception and design of the study, and drafted the manuscript. OD, ACR and ZAD conducted the statistical analyses and prepared the tables and figures together with MJB. ACR, EDM, MBM, KN, ADO, AWP, RB and JHP participated in the interpretation of the data, drafting of the manuscript, and revised subsequent drafts critically for important intellectual content. All authors approved the final version.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was funded in part by an investigator-initiated grant from Amgen. Dr. John Page is an employee of Amgen. Grants - NIH, FDA, AHA, Amgen, Aetna Foundation. Honoraria - Amgen, Sanofi, Regeneron, Novartis, Novo Nordisk, Bayer, Akcea, 89Bio, Zogenix, Tricida, Gilead.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.02.006.

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