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ORIGINAL RESEARCH

When Does a Calcium Score Equate to Secondary Prevention?

Insights From the Multinational CONFIRM Registry

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ABSTRACT

BACKGROUND Elevated coronary artery calcium (CAC) scores in subjects without prior atherosclerotic cardiovascular disease (ASCVD) have been shown to be associated with increased cardiovascular risk.

OBJECTIVES The authors sought to determine at what level individuals with elevated CAC scores who have not had an ASCVD event should be treated as aggressively for cardiovascular risk factors as patients who have already survived an ASCVD event.

METHODS The authors performed a cohort study comparing event rates of patients with established ASVCD to event rates in persons with no history of ASCVD and known calcium scores to ascertain at what level elevated CAC scores equate to risk associated with existing ASCVD. In the multinational CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry, the authors compared ASCVD event rates in persons without a history of myocardial infarction (MI) or revascularization (as categorized on CAC scores) to event rates in those with established ASCVD. They identified 4,511 individuals without known coronary artery disease (CAC) who were compared to 438 individuals with established ASCVD. CAC was categorized as 0, 1 to 100, 101 to 300, and >300. Cumulative major adverse cardiovascular events (MACE), MACE plus late revascularization, MI, and all-cause mortality incidence was assessed using the Kaplan-Meier method for persons with no ASCVD history by CAC level and persons with established ASCVD. Cox proportional hazards regression analysis was used to calculate HRs with 95% CIs, which were adjusted for traditional cardiovascular risk factors.

RESULTS The mean age was 57.6 ± 12.4 years (56% male). In total, 442 of 4,949 (9%) patients experienced MACEs over a median follow-up of 4 years (IQR: 1.7-5.7 years). Incident MACEs increased with higher CAC scores, with the highest rates observed with CAC score >300 and in those with prior ASCVD. All-cause mortality, MACEs, MACE + late revascularization, and MI event rates were not statistically significantly different in those with CAC >300 compared with established ASCVD (all $P > 0.05$). Persons with a CAC score <300 had substantially lower event rates.

CONCLUSIONS Patients with CAC scores >300 are at an equivalent risk of MACE and its components as those treated for established ASCVD. This observation, that those with CAC >300 have event rates comparable to those with established ASCVD, supplies important background for further study related to secondary prevention treatment targets in subjects without prior ASCVD with elevated CAC. Understanding the CAC scores that are associated with ASCVD risk equivalent to stable secondary prevention populations may be important for guiding the intensity of preventive approaches more broadly. (J Am Coll Cardiol Img 2023;16:1181-1189) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcification

CAD = coronary artery disease

CTA = computed tomography angiography

MACE = major adverse cardiovascular event

MI = myocardial infarction

Coronary artery calcification (CAC) has strong predictive power for future cardiovascular events.[1] Multiple studies have demonstrated that CAC scores >100 are associated with an up to 10-fold increased risk of atherosclerotic cardiovascular disease (ASCVD). The 2018 American College of Cardiology/American Heart Association cholesterol guidelines now advocate for calcium scoring for primary prevention in the decision to withhold, postpone, or initiate therapy if the decision about statin use remains uncertain.[2] These cholesterol guidelines for primary prevention state "if CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy." However, the guidelines advocate for even more aggressive therapy for patients with ASCVD,[3,4] and a high CAC may allow for more refined medical therapy even in those who have not yet experienced an ASCVD event. Thus, understanding a calcium score threshold at which patients are at similar risk to existing ASCVD would allow the identification of individuals who would benefit from more aggressive medical management. Thus, we evaluated in a multinational observational registry of patients undergoing CAC whether there was a threshold of CAC that was associated with an ASCVD event rate similar to patients who had already experienced ASCVD events.[5]

METHODS

The CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) study was established as a large, prospective, multinational dynamic observational cohort study of patients undergoing 64-slice coronary computed tomography angiography (CTA).[6,7] The CONFIRM registry is composed of 2 phases. Phase 1 CONFIRM is a derivation cohort that details demographic, clinical, and computed tomography findings for 27,125 consecutive patients (≥18 years of age) who were enrolled at 12 sites in 6 countries (the United States, Canada, Germany, Switzerland, Italy, and South Korea) between 2005 and 2009. These patients were followed for 3 to 5 years for a primary endpoint of all-cause death.[5] Phase 2 CONFIRM is a distinct nonoverlapping validation cohort, detailing identical elements to phase 1 and with event follow-up for 15,187 patients at 6 sites in 4 countries (the United States, Canada, Austria, and South Korea).[8] The CONFIRM sites were chosen on the basis of adequate volume, proficiency at performing and interpreting coronary CTA, diverse patient populations, and a mix of private and academic facilities in order to ensure a broad-based sample of patients. The CONFIRM cohorts we studied evaluated symptomatic subjects with known coronary artery disease (CAD) and subjects without prior ASCVD. The patients were followed up after coronary CTA to identify adverse CAD events including all-cause death, myocardial infarction (MI), unstable angina, target vessel revascularization, and CAD-related hospitalization.

We included 2 cohorts of those with complete follow-up for events, a cohort without known CAD and those with established ASCVD, for a total of 4,949 participants. Established ASCVD included

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participants with a documented history of MI, stroke, or peripheral arterial disease. All patients were assessed at the time of coronary CTA examination. Baseline demographics and traditional cardiovascular risk factors including age, sex, hypertension, diabetes, dyslipidemia, and current smoking status as well as symptoms related to heart disease and past medical history were collected for all patients. All testing, data acquisition and image postprocessing, and data interpretation for coronary CTA and CAC score in CONFIRM were performed according to the Society of Cardiovascular Computed Tomography guidelines.[9] Multidetector row computed tomography scanners consisting of 64 rows or greater acquired the CAC score as well as coronary CTA. Strategies for radiation dose reduction, which included prospective electrocardiographic-gated axial acquisition or electrocardiographic-gated tube current modulation and tube voltage reduction, were used.

The CAC score was calculated in accordance with the methods described previously by Agatston et al.[10] The CAC score was then categorized into the following 4 groups: 0 (very low), 1 to 99 (mild), 100 to 299 (moderate), and >300 (severe), respectively.

The primary study endpoint was a composite of major adverse cardiovascular events (MACEs), which included all-cause mortality, nonfatal MI, and hospitalization for unstable angina, and a separate analysis evaluated late target vessel revascularization (>90 days). Specific causes of death were not recorded in the CONFIRM registry. Patient follow-up was performed by each local institution by a dedicated physician and/or research nurse. The acquisition of follow-up data was approved by all study centers' Institutional Review Boards. Trained personnel from each site adjudicated all-cause mortality by a direct interview with physicians and/or witnesses, a review of hospital records, or querying national medical databases. Other nonfatal events such as MI as defined by the universal definition of MI,[11] unstable angina, and late target revascularization were collected via a combination of direct questioning of patients using a scripted interview and examination of the patients' medical records as previously described.[5-8] Unstable angina was defined as hospitalization for signs or symptoms of unstable angina defined as: 1) rest angina (ie, pain of characteristic nature and location occurring at rest and for prolonged periods [>20 minutes]; 2) new-onset angina (ie, recent [2 months] onset of moderate to severe angina [Canadian Cardiovascular Society grade II or III]); or 3) crescendo angina (ie, previous angina, which progressively increases in severity and intensity and at a lower threshold over a short period of time). Patients hospitalized for unstable angina were considered as having experienced CAD-related hospitalization whether target vessel revascularization was performed or not. Late coronary revascularization was defined as revascularization occurring ≥90 days after the index diagnostic test. We excluded short-term revascularization to avoid any treatment bias induced by visualization of stenosis on CTA leading to immediate revascularization.

From this prospective longitudinal registry, individuals undergoing CAC assessment with long-term follow-up and a detailed ASCVD history were compared. There were 3,050 subjects from the phase 1 CONFIRM registry with 5 years of follow-up, 805 with 3 years of follow-up, and 1,094 from the phase 2 part of the registry with 2 years of follow-up for a target population of 4,949 subjects (**Figure 1**). Follow-up for each endpoint was done at 1 time point in each subgroup, so follow-up times in **Figure 1** are similar for the 4 different endpoints.

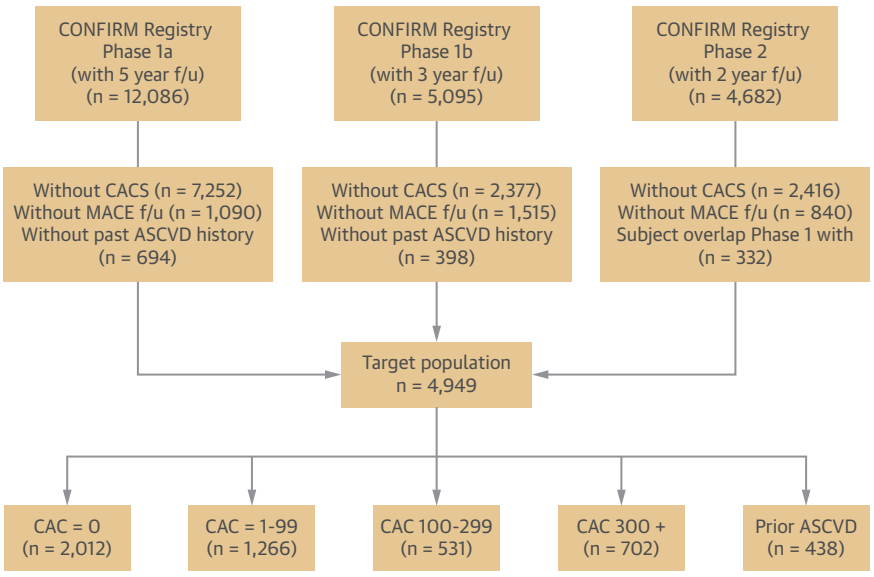
STATISTICAL METHODS. Continuous variables are expressed as mean ± SD or median (IQR) as appropriate. Categoric variables are reported as counts with proportions. Cumulative MACE, MACE + late revascularization, MI, and all-cause mortality incidence was assessed using the Kaplan-Meier method and compared with the log-rank test between persons with no ASCVD history by CAC level and persons with established ASCVD. Cox proportional hazards regression analysis was used to calculate HR with 95% CI. Multivariable analysis was adjusted for traditional cardiovascular risk factors such as age, sex, hypertension, diabetes, dyslipidemia, and current smoking. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc), and a value of $P < 0.05$ was considered statistically significant.

RESULTS

Of the 4,949 patients included, the mean age was 57.6 ± 12.4 years (56% male). The majority of the subjects were hypertensive (60%), whereas 56% had elevated cholesterol levels. Only 16% had diabetes mellitus, whereas 22% were past smokers. Patients were followed for a median of 4.7 years (IQR: 1.7-5.7 years). There were 254 (5%) deaths, 229 (5%) MI events, 442 (9%) MACEs, and 583 (12%) MACE plus late revascularization events (**Table 1**).

There were 4,511 subjects with no prior history of ASCVD, 438 subjects with prior ASCVD, and 299 who had prior MI specifically.[11] In those with no prior ASCVD event, age and cardiovascular risk factor incidence increased as the CAC score increased. The

FIGURE 1 Flowchart for All 3 Phases of CONFIRM Registry



This figure shows how the target population was derived from the overall cohort and the distribution by coronary artery calcium (CAC) scores and established atherosclerotic cardiovascular disease (ASCVD). CACS = coronary artery calcium score; CONFIRM = Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter; f/u = follow-up; MACE = major adverse cardiovascular events.

prevalence of hyperlipidemia, hypertension, diabetes mellitus, and smoking was similar among those with CAC score >300 and those with established ASCVD (Table 2). Those with no prior ASCVD experienced 356 MACEs, and incident MACE increased with higher CAC scores, with the highest rate (20%) observed in individuals with CAC >300. Those with prior ASCVD experienced 86 (20%) MACEs, and those with prior MI experienced 68 (23%) MACE events. The same trend occurred when comparing event rates of those with no prior ASCVD but CAC score >300 vs those with prior ASCVD in MACEs and late revascularization (27% vs 27%), MI (10% vs 11%), and all-cause mortality (20% vs 20%) (Table 3). Examining patients with CAC score >300 and no prior ASCVD alone vs those with established ASCVD showed no difference in risk for MACEs (52.8 vs 53.6 events per 1,000 person-years; $P = 0.763$), MACE and late revascularization (73.9 vs 77.8 events per 1,000 person-years; $P = 0.855$), MI (26.9 vs 30.5 events per 1,000 person-years; $P = 0.672$), or all-cause mortality (29.0 vs 28.4 events per 1,000 person-years; $P = 0.690$). Patients with CAC >300 and no prior ASCVD vs those with prior MI also showed no difference in risk for MACEs ($P = 0.329$), MACE and late revascularization ($P = 0.439$), MI ($P = 0.365$), or all-cause mortality ($P = 0.602$) (Table 3, Central Illustration).

In Cox regression analysis, those with a CAC score of 0 (adjusted HR: 0.31 [95% CI: 0.22-0.45]; $P < 0.001$), a CAC score of 1 to 99 (adjusted HR: 0.41 [95% CI: 0.30-0.57]; $P < 0.001$), or a CAC score of 100 to 299 (adjusted HR: 0.59 [95% CI: 0.42-0.84]; $P = 0.003$)

TABLE 1 Characteristics of Patients Enrolled From the CONFIRM Registry

	Total Population (N = 4,949)	No Prior ASCVD (n = 4,511)	Prior ASCVD (n = 438)	*P* Value
Age, y	57.6 ± 12.4	57.0 ± 12.3	63.5 ± 11.5	<0.001[a]
BMI, kg/m^2	28.5 ± 5.5	28.5 ± 5.5	28.4 ± 5.6	0.813[a]
Male	2,781 (56)	2,473 (55)	308 (70)	<0.001[b]
Hypertension	2,971 (60)	2,651 (59)	320 (73)	<0.001[b]
High cholesterol	2,781 (56)	2,454 (55)	327 (75)	<0.001[b]
Current smoker	1,220 (25)	1,078 (24)	142 (33)	<0.001[b]
Diabetes	816 (16)	684 (15)	132 (30)	<0.001[b]
Family history of CAD	1,907 (39)	1,697 (38)	210 (48)	<0.001[b]
Aspirin	1,289 (26)	1,105 (24)	184 (42)	<0.001[b]
CAC score	8 (0-162)	4 (0-122)	278 (41-855)	<0.001[c]
All-cause mortality	254 (5)	205 (5)	49 (11)	
Myocardial infarction	229 (5)	180 (4)	49 (11)	
MACE	442 (9)	356 (8)	86 (20)	
MACE + late revascularization	583 (12)	466 (10)	117 (27)	

Values are mean ± SD, n (%), or median (IQR). [a]Analysis of variance. [b]Chi-square test. [c]Kruskall-Wallis test.

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAC = coronary artery calcium; CAD = coronary artery disease; CONFIRM = Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter; MACE = major adverse cardiovascular event.

TABLE 2 Risk Factors for Coronary Heart Disease in CONFIRM Subjects With No History of ASCVD Categorized by CAC Score and Persons With a History of ASCVD

	No Prior ASCVD				Prior ASCVD All CAC (n = 438)	Prior MI All CAC (n = 299)	*P* Value 1	*P* Value 2
	CAC 0 (n = 2,012)	CAC 1-99 (n = 1,266)	CAC 100-299 (n = 531)	CAC >300 (n = 702)				
Age, y	51.1 ± 11.9	58.7 ± 10.1	63.3 ± 10.0	66.1 ± 9.4	63.5 ± 11.5	63.3 ± 11.6	<0.001[a]	<0.001[a]
BMI, kg/m^2	28.5 ± 5.8	28.6 ± 5.4	28.3 ± 5.0	28.3 ± 5.4	28.4 ± 5.6	28.2 ± 5.8	0.743[a]	0.769[a]
Male	867 (43)	737 (61)	346 (65)	439 (63)	308 (70)	208 (70)	<0.001[b]	<0.001[b]
Hypertension	965 (48)	784 (60)	379 (71)	523 (75)	320 (73)	214 (72)	<0.001[b]	<0.001[b]
High cholesterol	864 (43)	747 (61)	357 (67)	486 (69)	327 (75)	221 (74)	<0.001[b]	<0.001[b]
Former smoker	321 (16)	268 (21)	130 (24)	198 (28)	148 (34)	109 (36)	<0.001[b]	<0.001[b]
Current smoker	390 (19)	325 (26)	141 (27)	222 (32)	142 (32)	107 (36)	<0.001[b]	<0.001[b]
Diabetes	200 (10)	197 (16)	109 (21)	178 (25)	132 (30)	87 (29)	<0.001[b]	<0.001[b]
Family history of CAD	787 (39)	469 (37)	202 (38)	239 (34)	210 (48)	142 (47)	0.001[b]	0.008[b]

Values are mean ± SD or n (%), unless otherwise indicated. [a]Analysis of variance. [b]Chi-square test.

MI = myocardial infarction; *P* Value 1 = *P* for no prior ASCVD vs prior ASCVD; *P* Value 2 = *P* for no prior ASCVD vs prior MI; other abbreviations as in Table 1.

showed substantially lower risk of MACEs compared with those with prior ASCVD. A CAC level >300 was not statistically significantly lower compared with those with prior ASCVD (adjusted HR: 0.944 [95% CI: 0.717-1.244]; $P = 0.683$) for the prediction of MACEs. Secondary outcomes of MACE + late revascularization, MI, and all-cause mortality followed the same trend; CAC >300 was not a significant predictor compared with those with established ASCVD (Table 4).

DISCUSSION

Understanding when a subject without prior ASCVD is at the same risk as a patient with existing ASCVD is critical, especially when considering so many therapies are now advocated for known ASCVD.[12] There are limited data on what level of calcification (CAC score) is associated with similar risks as those who already suffered MI (secondary risk equivalent).[13] We analyzed event rates of patients with established ASVCD and compared them to the risk of individuals without prior ASCVD aggregated into groups with increasing calcium scores to determine which CAC scores afforded risk equivalent to a cohort with existing ASCVD.

To our knowledge, the present results represent the first study to demonstrate when a person with substantially elevated levels of atherosclerosis (CAC >300) is at similar ASCVD risk as a patient who has already suffered a cardiovascular event in the same cohort. Although this paper, given the limitations on

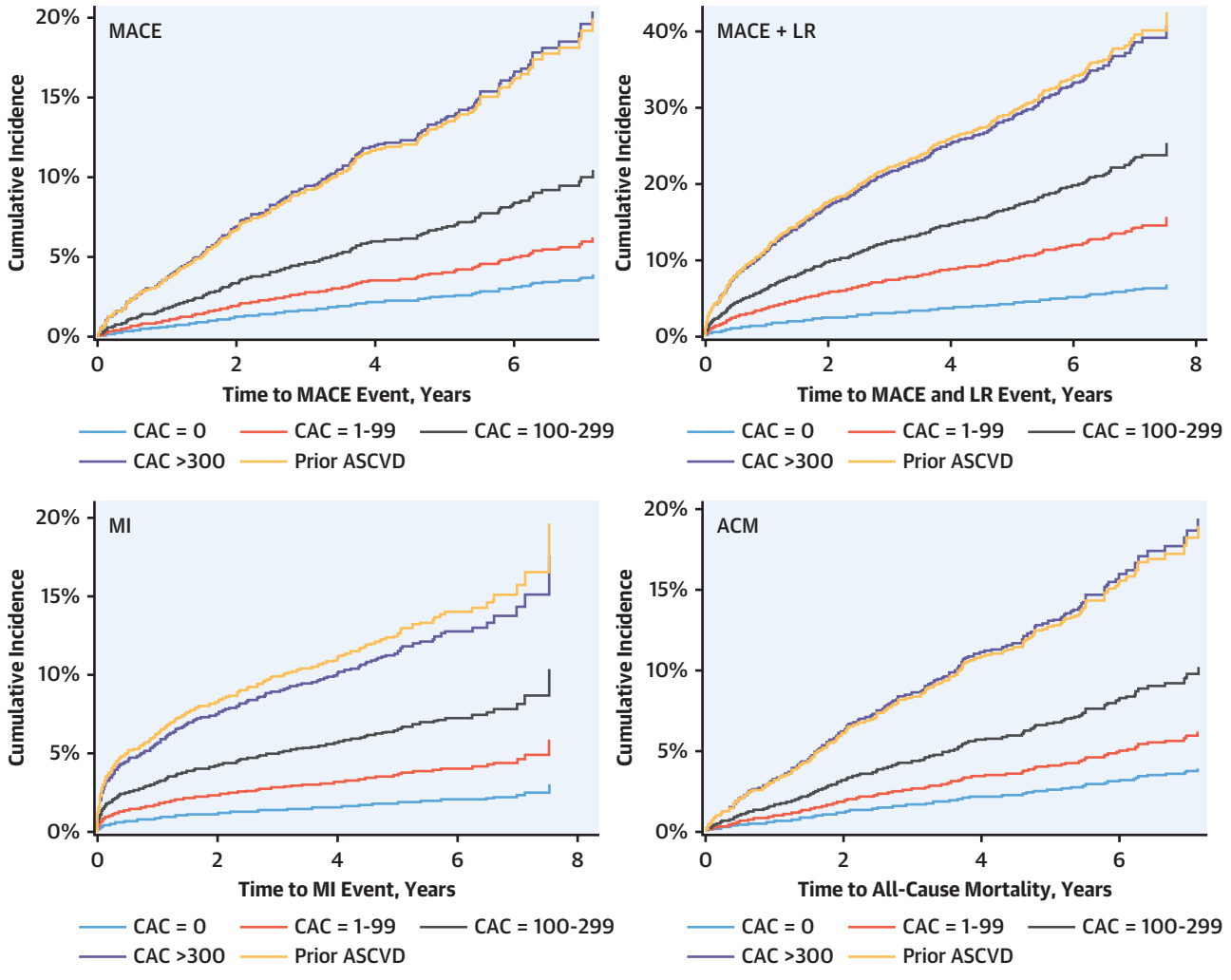
TABLE 3 Events in CONFIRM Subjects With No History of ASCVD Categorized by CAC Score and Persons With a History of ASCVD or a History of Prior MI

	No Prior ASCVD				Prior ASCVD All CAC	Prior MI All CAC	*P* Value 1	*P* Value 2
	CAC 0	CAC 1-99	CAC 100-299	CAC >300				
Incidence								
MACE	73 (4)	82 (6)	58 (11)	143 (20)	86 (20)	68 (23)	0.763	0.329
MACE + LR	78 (4)	116 (9)	81 (15)	191 (27)	117 (27)	88 (29)	0.855	0.439
MI	34 (2)	43 (3)	31 (6)	73 (10)	49 (11)	37 (12)	0.672	0.365
All-cause mortality	45 (4)	45 (6)	31 (11)	84 (20)	49 (20)	39 (23)	0.690	0.602
Rates per 1,000 PY								
MACE	8.8	15.9	28.0	52.8	53.6	63.6		
MACE + LR	9.4	22.9	40.3	73.9	77.8	87.3		
MI	4.1	8.3	45.0	26.9	30.5	34.6		
All-cause mortality	5.4	8.5	14.4	29.0	28.4	33.7		

Values are n (%) or n.

LR = late revascularization; *P* Value 1 = chi-square test for no prior ASCVD CAC score >300 vs prior ASCVD; *P* Value 2 = chi-square test for no prior ASCVD CAD score >300 vs prior MI; PY = person-years; other abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION Event Rates by CAC Score Categories for MACE Compared to Prior ASCVD Patients



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Event rates by coronary artery calcium (CAC) score distribution for major adverse cardiovascular events (MACE) **(upper left)**, MACE + late revascularization (LR) **(upper right)**, myocardial infarction (MI) **(lower left)**, and all-cause mortality (ACM) **(lower right)**. Follow-up was consistent for all endpoints, and each endpoint demonstrates that the event rates for CAC >300 are similar to those of patients who have established cardiovascular disease. ASCVD = atherosclerotic cardiovascular disease.

information on treatment and other clinical indicators of risk, does not completely answer the question, it provides important background for further areas of study. We demonstrated that persons with the highest CAC score have risk similar to but no higher than persons who are treated for established CVD. This becomes important because in patients with known ASCVD, the 2018 Cholesterol Clinical Practice Guidelines recommend more intensive low-density lipoprotein cholesterol lowering with the addition of nonstatin therapy (ie, ezetimibe, bempedoic acid, and/or proprotein convertase subtilisin/kexin type 9 inhibitors) in individuals who are deemed high or very high risk.[1,14] In the current study, we demonstrate that primary prevention individuals with a CAC score ≥300 had an annualized rate for hard cardiovascular events similar to that of stable high-risk ASCVD patients (post-MI) in the CONFIRM registry. Our results suggest that there should be less distinction between primary and known ASCVD patients because we show that their risk for CVD events could overlap or the risk could be

TABLE 4 Cox Regression Analysis for the Prediction of MACE, MACE + LR, MI, and ACM According to CAC Score in Individuals With No History of ASCVD (by CAC Level) vs Patients With Established ASCVD

		Nonadjusted			Adjusted[a]		
Risk Category	Outcome	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Prior ASCVD	MACE	Ref.	NA	NA	Ref.	NA	NA
CAC = 0		0.17	0.12-0.23	<0.001	0.31	0.22-0.45	<0.001
CAC 1-99		0.31	0.23-0.42	<0.001	0.41	0.30-0.57	<0.001
CAC 100-299		0.53	0.38-0.74	0.002	0.59	0.42-0.84	0.003
CAC >300		1.00	0.77-1.31	0.997	0.94	0.72-1.24	0.683
Prior ASCVD	MACE + LR	Ref.	NA	NA	Ref.	NA	NA
CAC = 0		0.13	0.10-0.17	<0.001	0.22	0.16-0.31	<0.001
CAC 1-99		0.31	0.24-0.40	<0.001	0.41	0.31-0.53	<0.001
CAC 100-299		0.53	0.40-0.70	<0.001	0.59	0.44-0.78	0.003
CAC >300		0.97	0.77-1.22	0.790	0.94	0.74-1.19	0.614
Prior ASCVD	MI	Ref.	NA	NA	Ref.	NA	NA
CAC = 0		0.14	0.09-0.22	<0.001	0.19	0.11-0.31	<0.001
CAC 1-99		0.28	0.18-0.14	<0.001	0.33	0.22-0.52	<0.001
CAC 100-299		0.50	0.32-0.79	0.003	0.56	0.35-0.88	0.013
CAC >300		0.90	0.63-1.30	0.904	0.93	0.64-1.36	0.716
Prior ASCVD	ACM	Ref.	NA	NA	Ref.	NA	NA
CAC = 0		0.19	0.13-0.29	<0.001	0.49	0.31-0.77	0.002
CAC 1-99		0.31	0.20-0.46	<0.001	0.46	0.30-0.71	0.004
CAC 100-299		0.51	0.33-0.80	0.004	0.58	0.37-0.92	0.021
CAC >300		1.03	0.72-1.46	0.878	0.90	0.63-1.28	0.550

[a]Model adjusted for age, sex, diabetes mellitus, hyperlipidemia, hypertension, family history, and current smoking.
ACM = all-cause mortality; NA = not applicable; Ref. = Reference; other abbreviations as in Tables 1 to 3.

even higher in certain primary prevention populations. These findings are in agreement with a previous study of the CAC Consortium of primary prevention patients showing CVD mortality event rates equivalent to those in secondary prevention patients from the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study.[13] More specifically, the authors of the CAC Consortium found a cardiovascular mortality annualized event rate of 0.80% per year in their study population vs 0.77% per year in the FOURIER study.[13] This study demonstrated that CAC scores ranging from 255 to 781 for a general at-risk primary prevention population were associated with an ASCVD risk equivalent to secondary prevention.[15] However, MESA (Multi-Ethnic Study of Atherosclerosis) represents a very healthy population of subjects without prior ASCVD with 15 years of follow-up[16] compared with a FOURIER population with a 3-year follow-up derived from a very high-risk enriched for risk factor ASCVD population.

It should be noted that a CAC score >300 has been advocated as high risk in guidelines going back to at least 2006.[17-20] However, these patients have never been advocated as risk equivalent to known ASCVD, allowing the use of nonstatin medication such as protein convertase subtilisin/kexin type 9 inhibitors, which are only advocated for patients with established ASCVD. Studies of persons with elevated CAC randomized to protein convertase subtilisin/kexin type 9 inhibitors for cardiovascular risk reduction are ongoing (VESALIUS-CV [Effect of EVolocumab on Major Cardiovascular Events in PatiEntS at High CArdiovascuLar RIsk WithoUt Prior Myocardial Infarction or Stroke; NCT03872401]).

Persons with diabetes for a long time were considered secondary risk equivalents, but this has been shown to be incorrect.[21] Diabetes increases risk similar to other risk factors but does not elevate a person to secondary prevention targets, and these patients do not qualify for therapies such as inclisiran, bempedoic acid, protein convertase subtilisin/kexin type 9 inhibitors, or other therapies relegated to those with established ASCVD. We performed a sensitivity analysis and demonstrated that eliminating persons with diabetes does not change the association (data not shown).

STUDY LIMITATIONS. ASCVD endpoints were site reported by clinicians at the individual sites. The

study sites of CONFIRM are all recognized experts in cardiac computed tomography with extensive experience with clinical trials and outcome studies.[22] Cohort studies in the United States using cardiac computed tomography, such as MESA, only enrolled subjects without prior ASCVD, so similar validation analysis cannot be done in these large epidemiologic studies. Furthermore, we focused solely on noncontrast CAC in this study. Recent data from the ICONIC (Incident Chronic Obstructive Pulmonary Disease Cohort Study), SCOT-HEART (Scottish Computed Tomography of the Heart), and PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trials have observed the relatively greater importance of noncalcified plaque,[23] and our group is currently evaluating the relative contribution of noncalcified plaque to risk stratification beyond CAC alone. It must be emphasized that as an observation, prospective study, we did not have complete information on treatment and other clinical indicators of risk, which limits the conclusions. Furthermore, because this was a referred population for coronary CTA across many indications, caution must be taken when generalizing to the general population. For example, renal dysfunction was rare in this cohort because all patients were undergoing coronary CTA, and abnormal renal function is a relative or absolute contraindication to scanning. Despite these limitations, the referrals for the cohort of subjects without prior ASCVD were specifically to evaluate atherosclerosis (and subsequent risk), which would be a similar utility to the advocated utility of CAC scanning in the target population.[14] It is possible that those with established ASCVD are more aggressively treated than those with high CAC, and this will reduce the rate of events in the ASCVD cohort.

CONCLUSIONS

Patients with CAC scores >300 are at an equivalent risk of major cardiovascular events as treated patients with established ASCVD in this cohort. This strongly supports the algorithms of the American College of Cardiology/American Heart Association calling for the use of high-dose statins in persons with CAC scores >300 and provides important background for studies of other therapies currently largely or solely relegated to established ASCVD (eg, protein convertase subtilisin/kexin type 9 inhibitors, icosapent ethyl, bempedoic acid, and so on).[15,24,25] These findings may contribute useful information when considering the intensification of medical therapy in patients who have not yet suffered an ASCVD event.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The implications of understanding that a CAC score >300 equates to secondary prevention risk will allow for more advanced therapies to be applied in these higher-risk individuals, matching the intensity of therapy with the intensity of risk. Awaiting myocardial infarction, stroke, or cardiovascular death to quality for advanced secondary prevention therapies is both unnecessary and Darwinian because some patients will die before qualifying for these advanced therapies.

TRANSLATIONAL OUTLOOK: Guidelines continue to evolve and will need to adapt this new information on secondary prevention targets with CAC. There are a host of secondary prevention therapies (antiplatelets, diabetes therapies, and advanced lipid therapies) that are currently approved for secondary prevention only. Understanding when a patient transitions from primary prevention risk to a higher level of risk before the event will continue to need more research and study.

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