Radiology

ORIGINAL RESEARCH • CARDIAC IMAGING

Coronary Artery Calcium Score Predicts Major Adverse Cardiovascular Events in Stable Chest Pain

The DISCHARGE Trial Group[1]

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Conflicts of interest are listed at the end of this article.

See also the editorial by Hanneman and Gulsin in this issue.

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Background: Coronary artery calcium (CAC) has prognostic value for major adverse cardiovascular events (MACE) in asymptomatic individuals, whereas its role in symptomatic patients is less clear.

Purpose: To assess the prognostic value of CAC scoring for MACE in participants with stable chest pain initially referred for invasive coronary angiography (ICA).

Materials and Methods: This prespecified subgroup analysis from the Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) trial, conducted between October 2015 and April 2019 across 26 centers in 16 countries, focused on adult patients with stable chest pain referred for ICA. Participants were randomly assigned to undergo either ICA or coronary CT. CAC scores from noncontrast CT scans were categorized into low, intermediate, and high groups based on scores of 0, 1–399, and 400 or higher, respectively. The end point of the study was the occurrence of MACE (myocardial infarction, stroke, and cardiovascular death) over a median 3.5-year follow-up, analyzed using Cox proportional hazard regression tests.

Results: The study involved 1749 participants (mean age, 60 years ± 10 [SD]; 992 female). The prevalence of obstructive coronary artery disease (CAD) at CT angiography rose from 4.1% (95% CI: 2.8, 5.8) in the CAC score 0 group to 76.1% (95% CI: 70.3, 81.2) in the CAC score 400 or higher group. Revascularization rates increased from 1.7% to 46.2% across the same groups ($P < .001$). The CAC score 0 group had a lower MACE risk (0.5%; HR, 0.08 [95% CI: 0.02, 0.30]; $P < .001$), as did the 1–399 CAC score group (1.9%; HR, 0.27 [95% CI: 0.13, 0.59]; $P = .001$), compared with the 400 or higher CAC score group (6.8%). No significant difference in MACE between sexes was observed ($P = .68$).

Conclusion: In participants with stable chest pain initially referred for ICA, a CAC score of 0 showed very low risk of MACE, and higher CAC scores showed increasing risk of obstructive CAD, revascularization, and MACE at follow-up.

Clinical trial registration no. NCT02400229

Supplemental material is available for this article.

Coronary artery calcium (CAC) scoring has emerged as a valuable tool in cardiovascular risk assessment beyond traditional risk factors, providing important prognostic information regarding the likelihood of major adverse cardiovascular events (MACE) (1,2). In particular, a CAC score of 0 has consistently demonstrated favorable outcomes and low rates of MACE in various studies (3,4).

Several landmark studies have highlighted the significance of a 0 CAC score in different clinical scenarios. The Multi-Ethnic Study of Atherosclerosis, or MESA, revealed that among asymptomatic individuals, those with a CAC score of 0 had the highest net reclassification index for risk compared with other negative risk markers, indicating potential for risk stratification with a 0 CAC score (5). In individuals with stable chest pain or dyspnea and a low to intermediate pretest probability of coronary artery disease (CAD) referred for functional testing, the Prospective Multicenter Imaging Study for Evaluation of Chest Pain, or PROMISE trial, demonstrated a remarkably low rate of cardiovascular death or myocardial infarction among those with a CAC score of 0 (6). These findings were further supported by the Scottish Computed Tomography of the Heart, or SCOT-HEART, trial, which investigated the use of CT in patients with either chest pain or history of CAD (7). In this trial, a CAC score of 0 was associated with a low rate of fatal or nonfatal myocardial infarction during median 4.8 years of follow-up (8).

Based on such accumulating evidence, the 2021 American Heart Association/American College of Cardiology guidelines recognized the clinical utility of a 0

Abbreviations

CAC = coronary artery calcium, CAD = coronary artery disease, DISCHARGE = Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease, HR = hazard ratio, ICA = invasive coronary angiography, MACE = major adverse cardiovascular events

Summary

In participants with stable chest pain referred for invasive coronary angiography, those with a coronary artery calcium score of 0 at CT had very low, while higher scores had increasing occurrence of major adverse cardiovascular events.

Key Results

- In a prospective study of 1749 participants with stable chest pain followed up for 3.5 years, those with a coronary artery calcium (CAC) score of 0 at CT had a lower prevalence of obstructive coronary artery disease (4.1%) than participants with a CAC score of 400 or higher (76.1%; $P < .001$).
- The major adverse cardiovascular events rate was lower in participants with a CAC score of 0 (0.5%; hazard ratio [HR], 0.08) than a CAC score of 400 or higher (6.8%; HR, 1 [reference]; $P < .001$).

CAC score in identifying patients presenting with stable chest pain, low pretest probability of obstructive CAD, and low risk of future cardiovascular events (9). However, despite the growing body of evidence, a paucity of knowledge remains regarding the prognostic implications of CAC scoring in individuals with stable chest pain who are clinically referred for invasive coronary angiography (ICA).

To address this research gap, a prespecified CT group analysis was conducted within the Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) trial, a pragmatic, multicenter, randomized trial evaluating the comparative effectiveness of CT versus ICA in individuals with stable chest pain and a clinical indication for ICA (10). The hypothesis was that incidence of MACE would be significantly lower in individuals with a CAC score of 0 compared with those with a CAC score of 1–399 or 400 or higher. In this analysis, the primary objective was to assess the prognostic value of CAC scoring in predicting MACE in participants with stable chest pain referred for ICA during a median follow-up of 3.5 years.

Materials and Methods

Study Participants

The DISCHARGE trial (ClinicalTrials.gov identifier NCT02400229) was a prospective, pragmatic, multicenter, randomized study conducted at 26 centers across 16 European countries (10,11). The trial sought to address critical questions regarding the comparative effectiveness and safety of coronary CT angiography and ICA for individuals with stable chest pain and a low to intermediate pretest probability (10%–60%) of obstructive CAD.

A total of 3561 participants were enrolled in the trial after providing written informed consent. The study protocol underwent ethical review by the ethics committee of the coordinating site, the German Federal Office for Radiation Protection, and the local or national authorities at each trial site (11). This prespecified subgroup analysis

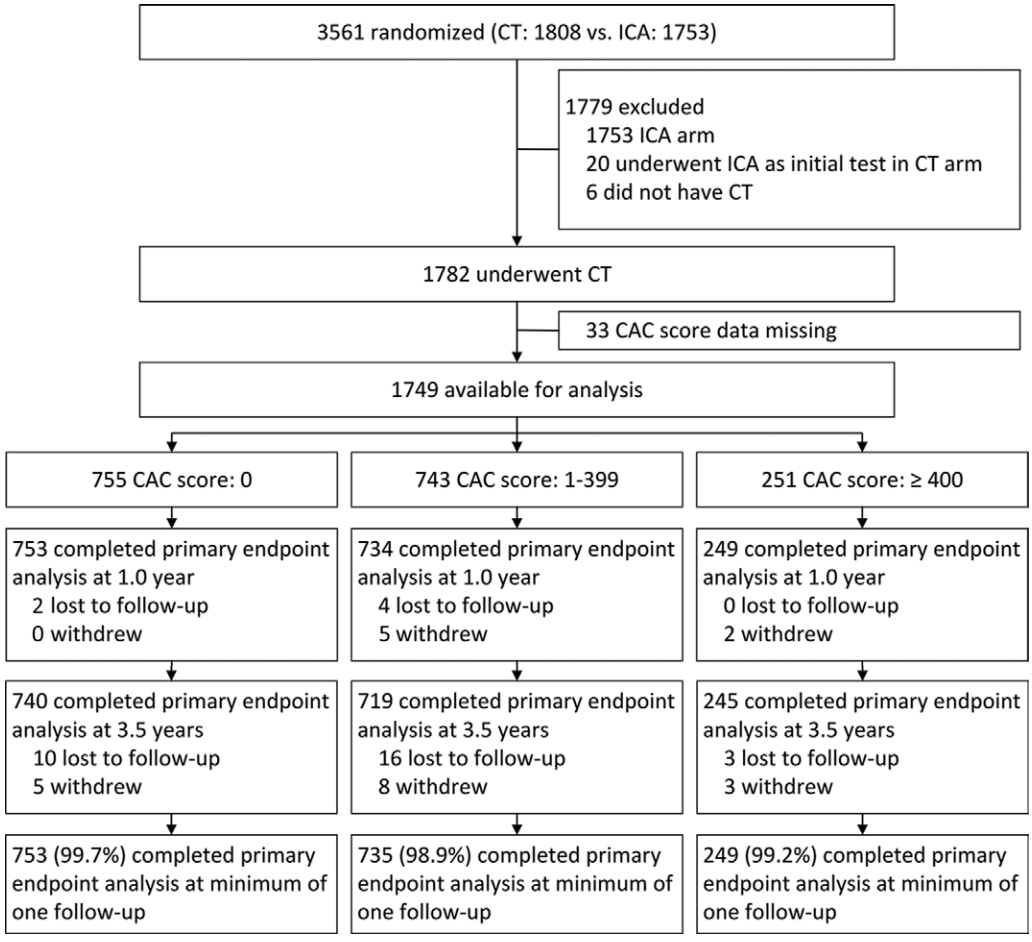

Figure 1: Flowchart of patient selection. CAC = coronary artery calcium, ICA = invasive coronary angiography.

(DISCHARGE Statistical Analysis Plan, Tables 14 #65,73, and 19 #98) (10) focused on the 1808 participants who were randomized to the initial CT arm of the study between October 2015 and April 2019. Data from these participants have previously been reported (10). The prior article dealt with the main outcomes of the trial during 3.5 years of follow-up, whereas this article reports the prespecified CAC subgroup analysis results. Among the 1808 participants, those who underwent CT as the initial test, had CAC score data available for analysis, and completed primary end point analysis at a minimum of one follow-up visit were included.

CT Protocol and CAC Calculation

The CT imaging protocol included the acquisition of electrocardiogram-gated non–contrast-enhanced CT scans for CAC scoring using 13 different scanners from four major vendors: Canon, General Electric, Philips, and Siemens. The scanners used had a minimum of 64 rows as listed in the main trial results (10,11). CAC scans were acquired using 120 kV and reconstructed using filtered back projection with a small field of view and a section thickness and increment of 3.0 mm. For scanners that did not support 3.0 mm reconstruction, alternate section thicknesses were used (2.4 mm for General Electric scanners and 2.5 mm for Philips scanners).

CAC scoring was performed by experienced radiologists, certified at least at level II. The Agatston method was used for CAC scoring (12), involving the identification and manual labeling of calcified plaques with an attenuation above 130 HU and an area of at least 1 mm^2. The plaque area per section was multiplied by an attenuation weight factor based on the peak attenuation of the plaque within predefined ranges (130–199 HU = weight factor of 1; 200–299 HU = 2; 300–399 HU = 3; and ≥400 HU = 4). The resulting scores from all sections were summed to obtain the total CAC score for each participant. Participants were then categorized into three risk groups based on their CAC scores: low (CAC score of 0), intermediate (CAC score of 1–399), and high risk (CAC score ≥400). The basis for these CAC score ranges was the CT-based management from the trial (10). A CAC score of 0 in addition to a negative CT angiogram was used to exclude CAD, while a CAC score of 400 or higher was used to guide treatment recommendations per European guidelines in effect at the time of the study (13).

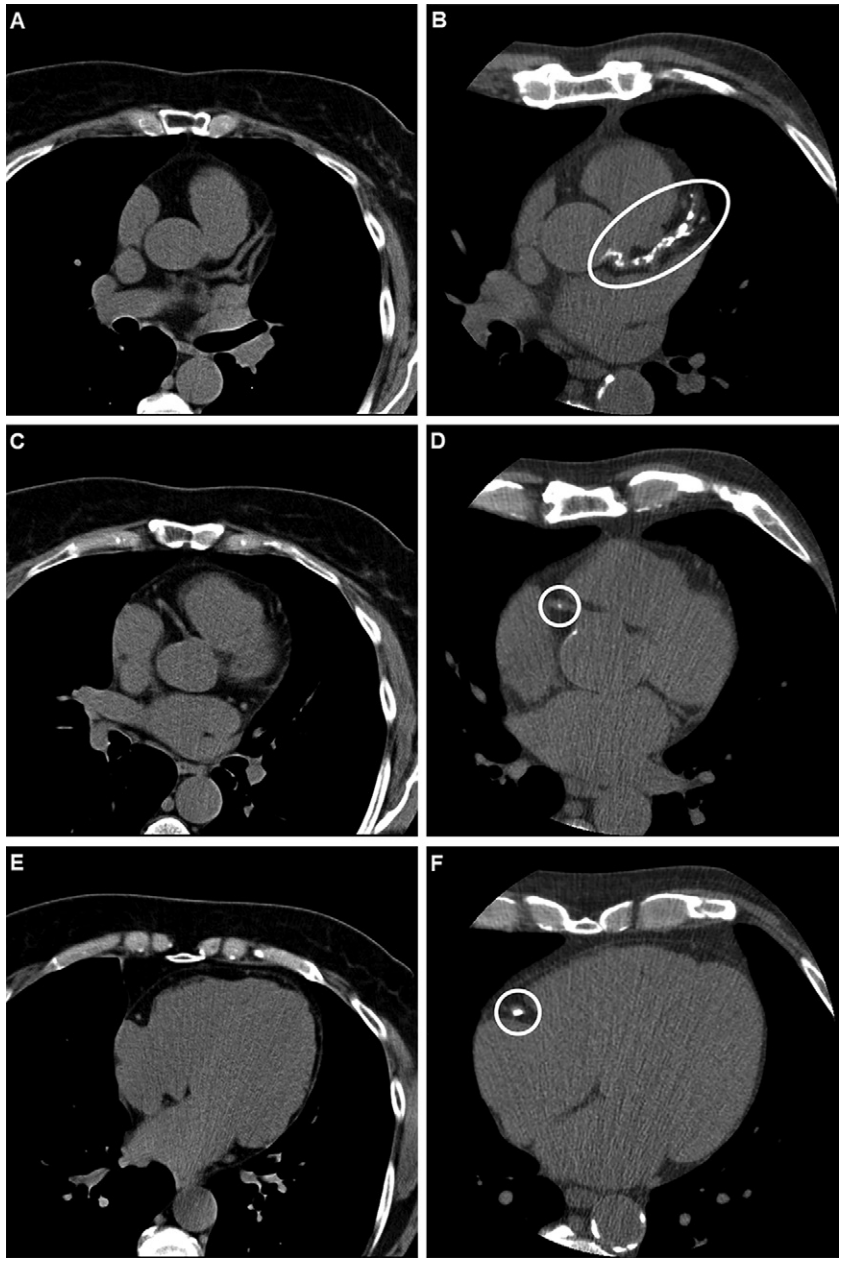

Figure 2: Example axial noncontrast CT scans in **(A, C, E)** a participant with a coronary artery calcium (CAC) score of 0, no signs of coronary artery disease at CT, and no major adverse cardiovascular events and **(B, D, F)** a participant who had a CAC score of 1013 (group with a CAC score of 400 or higher) and obstructive coronary artery disease at CT and required a revascularization procedure. With the scan on the left as reference, calcified plaques (ovals) can be seen on the right scan of the left main and left anterior descending arteries (proximal and mid segment, **B**) and the right coronary artery (proximal vessel segment, **D**; middle vessel segment, **F**).

Diagnostic Test Results

The rate of obstructive CAD, defined as a stenosis of at least 50% as determined at CT angiography, was recorded within the three predefined CAC score groups. Rates of percutaneous coronary intervention and coronary artery bypass grafting during initial management were also noted.

Table 1: Baseline Participant Characteristics Stratified by CAC Score Group

Variable	CAC Score of 0 (*n* = 755)	CAC Score of 1–399 (*n* = 743)	CAC Score ≥400 (*n* = 251)	*P* Value
Age (y)*	56 ± 10 (30–84)	63 ± 9 (33–85)	66 ± 8 (44–84)	<.001
Sex				<.001
Female	492 (65.2)	410 (55.2)	90 (35.9)	
Male	263 (34.8)	333 (44.8)	161 (64.1)	
Pretest probability†	33.8 ± 10.3	39.0 ± 10.5	43.9 ± 9.6	<.001
Type of chest pain				<.001
Typical angina	122 (16.2)	94 (12.7)	14 (5.6)	
Atypical angina	360 (47.7)	324 (43.6)	128 (51.0)	
Nonanginal chest pain	255 (33.8)	302 (40.6)	99 (39.4)	
Other chest pain	18 (2.4)	23 (3.1)	10 (4.0)	
Cardiovascular risk factors				
Arterial hypertension	391 (51.8)	488 (65.7)	193 (76.9)	<.001
Diabetes mellitus	68 (9.0)	120 (16.2)	60 (23.9)	<.001
Hyperlipidemia	290 (38.4)	403 (54.2)	148 (59.0)	<.001
Peripheral artery disease	4 (0.5)	7 (0.9)	11 (4.4)	<.001
Valve disease	36 (4.8)	33 (4.4)	24 (9.6)	.005
Stroke	13 (1.7)	22 (3.0)	9 (3.6)	.16
Transient ischemic attack	10 (1.3)	15 (2.0)	6 (2.4)	.44
Prolonged ischemic neurologic deficit	1 (0.1)	1 (0.1)	0	
Carotid artery disease	2 (0.3)	19 (2.6)	14 (5.6)	<.001
Family history of premature CAD				
Female participants	155/489 (31.7)	125/407 (30.7)	30/90 (33.3)	
Male participants	75/262 (28.6)	79/333 (23.7)	31/161 (19.3)	
Missing	4 (0.5)	3 (0.4)	0	
Pulmonary risk factors				
Asthma	54 (7.2)	51 (6.9)	15 (6.0)	.81
Chronic obstructive pulmonary disease	19 (2.5)	41 (5.5)	10 (4.0)	.01
Cigarette smoking status				<.001
Currently smokes	146 (19.3)	141 (19.0)	42 (16.7)	
Formerly smoked	198 (26.2)	226 (30.4)	101 (40.2)	
Never smoked	388 (51.4)	354 (47.6)	98 (39.0)	
Missing	23 (3.0)	22 (3.0)	10 (4.0)	
Body mass index‡	28.8 ± 5.3	28.8 ± 4.81	28.9 ± 5.1	.99
Cardiovascular medications				
Statins	262 (34.7)	377 (50.7)	137 (54.6)	<.001
Antiplatelet agents	298 (39.5)	375 (50.5)	150 (59.8)	<.001
β-blockers	283 (37.5)	329 (44.3)	118 (47.0)	.006
Nitrates	65 (8.6)	87 (11.7)	37 (14.7)	.02
Calcium antagonists	123 (16.3)	162 (21.8)	69 (27.5)	<.001
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	286 (37.9)	397 (53.4)	164 (65.3)	<.001

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. Further baseline characteristics are provided in Table S1. CAC = coronary artery calcium, CAD = coronary artery disease.

* Data are means ± SDs, with ranges in parentheses.

† Data are means ± SDs. Pretest probability of CAD was calculated using an automated calculation tool (22) integrated into a web-based system of the electronic case report forms, which applied an updated model of the Diamond and Forrester method using participants' age, sex, and type of stable chest pain.

‡ Data are means ± SDs. Body mass index was calculated as participant weight in kilograms divided by participant height in meters squared.

Prognostic End Points

The primary prognostic end point included MACE, encompassing cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes included expanded MACE, which incorporated transient ischemic attacks and major procedure-related complications. Other secondary prognostic end points considered were composite outcomes, such as "vascular death or myocardial infarction," "cardiac death or

Table 2: Comparison of Diagnostic Strategies, Findings, and Invasive Management in Participants Stratified by CAC Score

Variable	CAC Score of 0 (n = 755)	CAC Score of 1–399 (n = 743)	CAC Score ≥400 (n = 251)	P Value
Time from enrollment to initial test (d)*	4 (0–14)	3 (0–15)	2 (0–14)	.66
Diagnostic findings				<.001
Obstructive CAD: ≥50% stenosis	31 (4.1)	221 (29.7)	191 (76.1)	
One vessel	17 (2.3)	90 (12.1)	39 (15.5)	
Two vessels	6 (0.8)	25 (3.4)	24 (9.6)	
High-risk anatomy†	8 (1.1)	106 (14.3)	128 (51.0)	
Nonobstructive CAD: 1%–49% stenosis	120 (15.9)	486 (65.4)	41 (16.3)	
No sign of CAD	557 (73.8)	0	0	
Nondiagnostic results‡	45 (6.0)	35 (4.7)	18 (7.2)	
Missing§	2 (0.3)	1 (0.1)	1 (0.4)	
ICA performed during initial management	28 (3.7)	170 (22.9)	171 (68.1)	<.001
ICA procedure access path				.07
Radial artery	20 (2.6)	139 (18.7)	151 (60.2)	
Femoral artery	8 (1.1)	29 (3.9)	17 (6.8)	
Other artery access‖	0	2 (0.3)	3 (1.2)	
PCI during initial management	13 (1.7)	87 (11.7)	85 (33.9)	<.001
CABG during initial management	0	6 (0.8)	31 (12.4)	<.001

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. CABG = coronary artery bypass grafting, CAC = coronary artery calcium, CAD = coronary artery disease, ICA = invasive coronary angiography, PCI = percutaneous coronary intervention.

* Data are medians, with IQRs in parentheses. Time to initial test results are cumulative incidence estimates.

† High-risk anatomy CAD was defined by the initial test as any three-vessel CAD or as left main coronary artery stenosis, proximal left anterior descending coronary artery stenosis, or the combination of these.

‡ Nondiagnostic test was defined as a relevant artifact at CT or poor opacification at CT or ICA that could conceal stenosis of 50% or more in a vessel with a reference diameter of 2 mm or larger without obstructive coronary artery stenosis elsewhere in the same participant. Participants were recommended to undergo further testing in cases of nondiagnostic initial tests.

§ Data missing: incomplete test (two in the group with a CAC score of 0, 0 in the group with a CAC score of 1–399, and one in the group with a CAC score ≥400) and test findings missing (0 in the group with a CAC score of 0, one in the group with a CAC score of 1–399, and 0 in the group with a CAC score ≥400).

‖ Other access for ICA included radial and femoral artery access (0 in the group with a CAC score of 0, two in the group with a CAC score of 1–399, and two in the group with a CAC score ≥400) and brachial artery access (0 in the group with a CAC score of 0, 0 in the group with a CAC score of 1–399, and one in the group with a CAC score ≥400).

myocardial infarction," and "all-cause death, myocardial infarction, or stroke." For further details about reporting of events, see Appendix S1 and the DISCHARGE study protocol (10).

Statistical Analysis

Continuous variables are summarized as means ± SDs or medians with IQRs based on their distribution (normal vs nonnormal, respectively). Categorical variables are presented as frequencies with percentages. The χ^2 test (or Fisher exact test for small data sets) was used for categorical variables, an analysis of variance or independent-sample Student t test was used for normally distributed continuous variables, and the Kruskal-Wallis test (or Mann-Whitney U test) was used for nonnormally distributed variables. Ordinal variables were assessed using the linear-by-linear association test (14).

Cox proportional hazard regression tests were used on both the entire study sample and subsamples stratified by sex to assess the effect of CAC scores on the prognostic end point occurrence of MACE, accounting for competing risks and adjusting for age, and, if applicable, sex, diabetes, hypertension, hyperlipidemia, and family history of CAD (15). Hazard ratios (HRs) with corresponding 95% CIs and P values were estimated. The model assumption and accuracy was evaluated (Appendix S1). The Kaplan-Meier method was applied to generate survival curves for the three predefined CAC score groups.

The statistical analyses were performed and checked by two of the authors (L.M.S.H. and M. Mohamed) using SPSS for Windows (version 27, IBM) and R (version 4.1, The R Foundation). $P < .05$ was considered indicative of statistically significant difference.

A post hoc power calculation, based on a Cox proportional hazard regression accounting for competing risk, estimated the minimum MACE effect size across CAC score groups with a fixed sample of 1749 participants (Appendix S1). The calculation was performed using PASS software 2020 (NCSS).

Results

Participant Characteristics

A total of 3561 participants were recruited for the DISCHARGE trial, and 1808 were randomized to the CT

arm. Fifty-nine participants were excluded from this analysis: 33 with missing CAC score data, 20 who underwent ICA as the initial test in the CT arm, and six who did not undergo the scheduled CT examination. Thus, 1749 participants were available for CAC score analysis (mean age, 60 years ± 10 [SD]; 992 female). The distribution among the three CAC score risk categories was as follows: 755 had a CAC score of 0 (43.2%), 743 had a CAC score of 1–399 (42.5%), and 251 had a CAC score of 400 or higher (14.3%) (Fig 1). Example CAC scans in participants with a score of 400 or higher and a score of 0 are shown in Figure 2.

Baseline study participant characteristics in the three CAC score risk groups are presented in Tables 1 and S1. The results showed that CAC scores were higher with increasing mean age (group with CAC score of 0, 56 years ± 10; group with CAC score of 1–399, 63 years ± 9; and group with CAC score ≥400, 66 years ± 8; $P < .001$). Cardiovascular risk factors (arterial hypertension, diabetes mellitus, hyperlipidemia, peripheral artery disease) were more common in the groups with higher CAC score. The intake of cardiovascular medications increased steadily over the three CAC score risk categories, with a statistically significant difference in the highest CAC score (≥400) group (Tables 1, S1). Baseline characteristics of female and male participants are summarized in Tables S2 and S3, respectively.

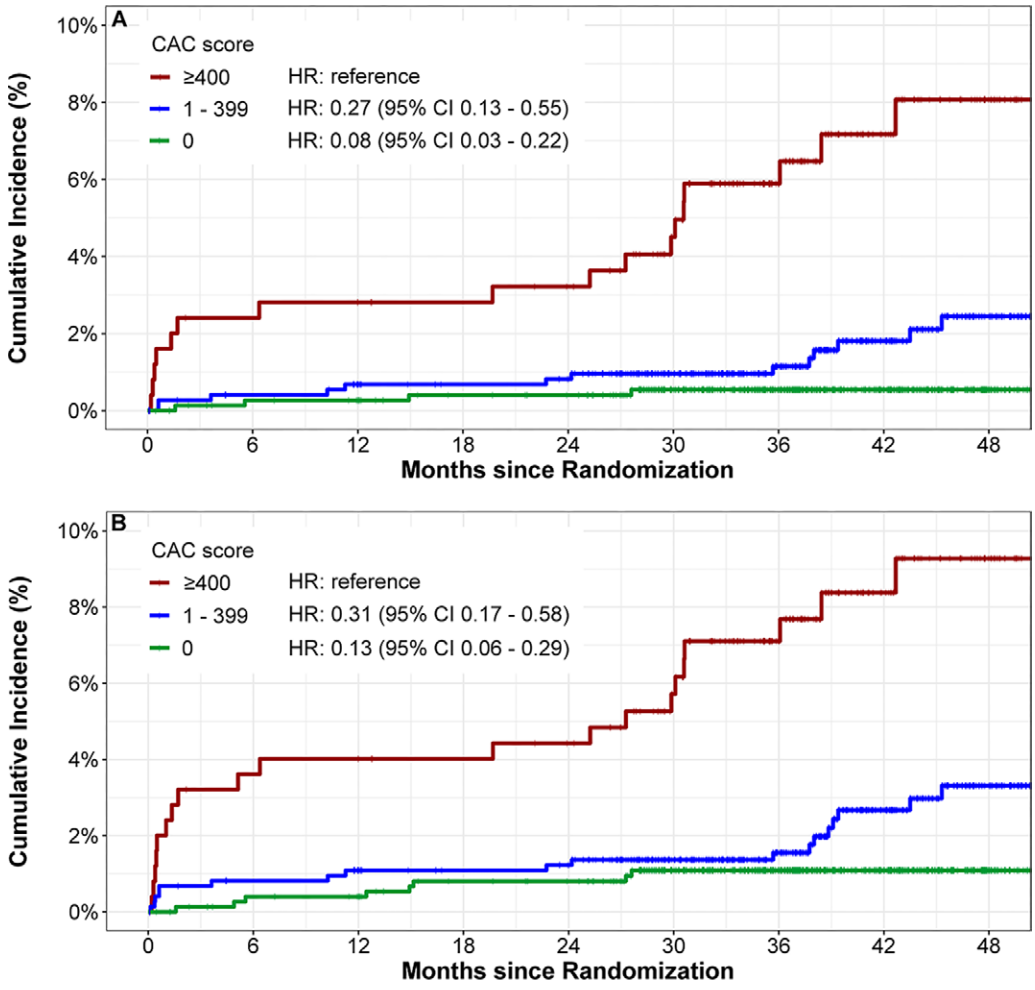

Figure 3: Time-to-event curves for **(A)** the primary prognostic end point major adverse cardiovascular events (MACE) and **(B)** secondary prognostic composite end point of expanded MACE (cardiovascular death, myocardial infarction, stroke, transient ischemic attack, or major procedure-related complications). The MACE rate was lower in patients with lower coronary artery calcium (CAC) scores (CAC score ≥400: 17 participants [6.8%] and hazard ratio [HR], 1 [reference]; CAC score of 1–399: 14 participants [1.9%] and HR, 0.27 [95% CI: 0.13, 0.55] [$P < .001$]; CAC score of 0: four participants [0.5%] and HR, 0.08 [95% CI: 0.03, 0.22] [$P < .001$]). The expanded MACE rate was lower in patients with lower CAC scores (CAC score ≥400: 20 participants [8.0%] and HR, 1 [reference]; CAC score of 1–399: 19 participants [2.6%] and HR, 0.31 [95% CI: 0.17, 0.58] [$P < .001$]; CAC score of 0: eight participants [1.1%] and HR, 0.13 [95% CI: 0.06, 0.29] [$P < .001$]). Results were not adjusted for cardiovascular risk factors.

Diagnostic Test Results

The proportion of participants with obstructive CAD at CT angiography increased from 31 of 755 (4.1% [95% CI: 2.8, 5.8]) in the group with a CAC score of 0 to 191 of 251 (76.1% [95% CI: 70.3, 81.2]) in the group with a CAC score of 400 or higher, as did the proportions of high-risk obstructive CAD (from 1.1% [95% CI: 0.5, 2.1] to 51.0% [95% CI: 44.6, 57.3]) ($P < .001$) (Table 2). The rate of percutaneous coronary intervention increased from 13 of 755 participants (1.7% [95% CI: 0.9, 2.9]) in the group with a CAC score of 0 to 85 of 251 participants (33.9% [95% CI: 28.0, 40.1]) in the group with a CAC score of 400 or higher ($P < .001$), and the rate of coronary artery bypass grafting during initial management increased from 0 of 755 participants in the group with a CAC score of 0 to six of 743 participants (0.8% [95% CI: 0.3, 1.7]) in the group with a CAC score of 1–399 to 31 of 251 participants (12.4% [95% CI: 8.5, 17.1]) in the group with a CAC score of 400 or higher ($P < .001$) (Table 2).

There was no evidence of a difference between male and female participants for obstructive CAD ($P = .11$; $P = .64$), percutaneous coronary intervention ($P = .25$; $P = .40$), or coronary artery bypass grafting (no cases; $P = .96$) during initial management in the groups with a CAC score of 0 and 400 or higher, respectively (Table S4). In the group with a score of

Table 3: Primary and Secondary Prognostic End Points in Participants Stratified by CAC Score and Adjusted for Cardiovascular Risk Factors

Variable	CAC Score of 0 (*n* = 755)	CAC Score of 1–399 (*n* = 743)	CAC Score ≥400 (*n* = 251)*	Harrell C Index	Brier Score
MACE				0.77	2.3
Event	4 (0.5)	14 (1.9)	17 (6.8)		
HR†	0.08 (0.02, 0.30)	0.27 (0.13, 0.59)	1 (reference)		
P value	<.001	.001			
Nonfatal myocardial infarction				0.83	0.9
Event	1 (0.1)	9 (1.2)	11 (4.4)		
HR	0.03 (0.004, 0.29)	0.27 (0.10, 0.74)	1 (reference)		
P value	.02	.01			
Nonfatal stroke				0.64	0.5
Event	3 (0.4)	3 (0.4)	3 (1.2)		
HR	0.27 (0.03, 2.66)	0.28 (0.04, 1.92)	1 (reference)		
P value	.26	.20			
Cardiovascular death					
Event	0	3 (0.4)	4 (1.6)		
HR‡	NA	NA	NA		
P value	NA	NA			
Expanded MACE composite§				0.74	2.7
Event	8 (1.1)	19 (2.6)	20 (8.0)		
HR	0.18 (0.07, 0.49)	0.35 (0.17, 0.70)	1 (reference)		
P value	.001	.003			
Vascular death or myocardial infarction				0.83	1.5
Event	1 (0.1)	10 (1.3)	12 (4.8)		
HR	0.03 (0.004, 0.30)	0.30 (0.12, 0.79)	1 (reference)		
P value	.002	.01			
Cardiac death or myocardial infarction				0.84	1.7
Event	1 (0.1)	11 (1.5)	13 (5.2)		
HR	0.03 (0.004, 0.26)	0.30 (0.12, 0.70)	1 (reference)		
P value	.001	.006			
All-cause death, myocardial infarction, or stroke				0.71	4.2
Event	11 (1.5)	31 (4.2)	23 (9.2)		
HR	0.27 (0.12, 0.64)	0.56 (0.31, 1.02)	1 (reference)		
P value	.003	.06			

Note.—Data for events are numbers of participants, with percentages in parentheses; data in parentheses for hazard ratios (HRs) are 95% CIs. CAC = coronary artery calcium, MACE = major adverse cardiovascular events, NA = not applicable.

* No *P* value is reported, as this is the reference group.

† The HR has been adjusted to account for the following cardiovascular risk factors: age, sex, diabetes mellitus, arterial hypertension, hyperlipidemia, and family history of coronary artery disease.

‡ No HR can be calculated due to the sample size being equal to 0 in the group with a CAC score of 0.

§ Cardiovascular death, myocardial infarction, stroke, transient ischemic attack, or major procedure-related complication.

1–399, male participants had higher rates of CAD and revascularizations than female participants (Table S4). Broken down by sex, the proportions of female and male participants with obstructive CAD increased from 16 of 492 (3.3%) and 15 of 263 (5.7%), respectively, in the group with a CAC score of 0 to 70 of 90 (77.8%) and 121 of 161 (75.2%), respectively, in the group with a score of 400 or higher, as did the proportions of high-risk obstructive CAD (from seven of 492 [1.4%] and one of 263 [0.4%], respectively, to 45 of 90 [50.0%] and 83 of 161 [51.6%], respectively) ($P < .001$ for the comparison between CAC score groups for both male and female participants) (Tables S5, S6).

Primary and Secondary Prognostic End Points

Median follow-up was 3.5 years (IQR, 2.9–4.2 years), during which 35 MACE occurred. The portion of participants lost to follow-up was two of 755 (0.3%) in the group with a CAC score of 0, eight of 743 (1.1%) in the 1–399 group, and two of 251

(0.8%) in the 400 or higher group. Analysis by CAC score group revealed a higher rate of MACE in participants with high CAC. Cumulative incidences of MACE and expanded MACE are summarized in Tables S7 and S8, respectively. The MACE rate was lowest within the group with a CAC score of 0, with only four of 755 participants experiencing MACE (three strokes and one myocardial infarction), and increased within the group with a CAC score of 1–399, with 14 of 743 participants experiencing MACE. In the group with the highest CAC scores (≥400), 17 of 251 participants experienced MACE (6.8%; HR of 1, reference) (Fig 3A, Table 3).

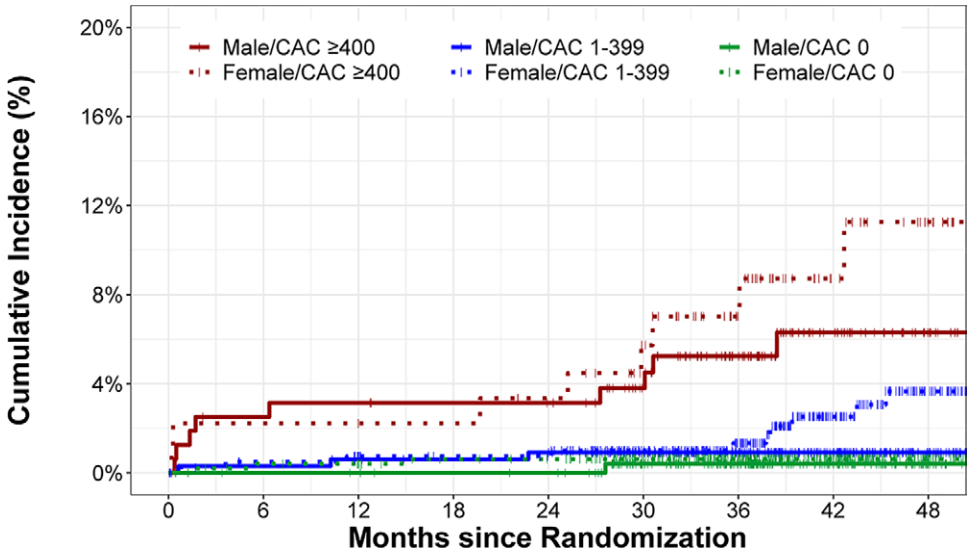

Figure 4: Time-to-event curves for the primary prognostic end point major adverse cardiovascular events (MACE) stratified by sex shows no evidence of a difference between female participants (dotted lines) and male participants (solid lines) (coronary artery calcium [CAC] score ≥400: 8.9% vs 5.6%, respectively, and hazard ratio [HR], 1.63 [95% CI: 0.63, 4.21] [P = .31]; CAC score of 1–399: 2.4% vs 1.2% and HR, 2.01 [95% CI: 0.62, 6.49] [P = .24]; CAC score of 0: 0.6% vs 0.4% and HR, 1.61 [95% CI: 0.17, 15.41] [P = .68]). Results were not adjusted for age.

Cox regression analysis adjusted for age, sex, diabetes, hypertension, hyperlipidemia, and family history of CAD showed an association between CAC scores and MACE. CAC scores of 0 and 1–399 were associated with a lower risk of MACE than CAC scores of 400 or higher (0 CAC score: HR, 0.08 [95% CI: 0.02, 0.30] [P < .001]; and CAC score of 1–399: HR, 0.27 [95% CI: 0.13, 0.59] [P = .001]). The results for the Harrell C index and Brier scores are presented in Table 3. All models (except nonfatal stroke) showed acceptable discrimination, with MACE, nonfatal myocardial infarction, and cardiovascular death yielding the highest C indexes. Results adjusted only by age and sex are summarized in Table S9.

The rate of secondary end point expanded MACE (additionally including transient ischemic attacks and major procedure-related complications) was also lower in participants with lower CAC scores (CAC score of 0: eight of 755 [1.1%] and HR, 0.18 [95% CI: 0.07, 0.49] [P = .001]; vs CAC score of 1–399: 19 of 743 [2.6%] and HR, 0.35 [95% CI: 0.17, 0.70] [P = .003]; vs CAC score of ≥400: 20 of 251 [8.0%] and HR of 1, reference) (Fig 3B, Table 3). The rate and risk of additional secondary outcomes were lower in participants with lower CAC scores (Table 3).

Primary Prognostic End Point by Sex

The results for the analysis of the primary prognostic end point by CAC score group and sex adjusted for age are summarized in Table S10. There was no evidence of a difference between male and female participants in MACE (0.4% vs 0.6%, respectively, in the group with a CAC score of 0 [P = .68], 1.2% vs 2.4% in the group with a CAC score of 1–399 [P = .24], and 5.6% vs 8.9% in the group with a CAC score of 400 or higher [P = .31]). When the outcome of MACE and its components were analyzed in CAC score subgroups, the P values for interaction for differences between male and female participants were nonsignificant (Table S10, Fig 4).

Comparison with other studies can be found in Table S11.

Discussion

In our prespecified analysis of the pragmatic, multicenter, randomized Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) trial, in individuals with stable chest pain and an intermediate probability of coronary artery disease (CAD) referred for invasive coronary angiography, a coronary artery calcium (CAC) score of 0 was associated with a lower prevalence of obstructive CAD (4.1%; P < .001) and, over a period of 3.5 years, with a low major adverse cardiovascular events (MACE) rate of 0.5% (P < .001), suggesting that CAC scoring showed excellent performance in ruling out MACE in symptomatic individuals with stable chest pain and an intermediate pretest probability of CAD.

Our findings align with the results from two other randomized controlled clinical trials, the PROMISE and SCOT-HEART trials, which also investigated the association between CAC scores and MACE in individuals with stable chest pain (6,8). In the PROMISE subanalysis of participants with an obstructive CAD prevalence of 11.5%, only 1.5% of participants with a CAC score of 0 had at least one 50% or higher stenosis at coronary CT angiography, indicating that a score of 0 correctly excluded obstructive CAD in 97.3% of participants (6). In contrast, the Collaborative Meta-analysis of Cardiac CT, or COME-CCT, Consortium, which included a high-pretest-probability diagnostic cohort, reported different results (16). Among participants with a CAC score of 0, the COME-CCT found an ICA rate of obstructive CAD of 17%, while the rates for participants with scores of 1–400 and higher than 400 were 44% and 74%,

respectively. However, despite the variations in these results, both studies showed that a CAC score of 0 was associated with lower risk of MACE compared with higher scores. The SCOT-HEART trial, which evaluated the impact of CT angiography on diagnosis and management of participants with suspected coronary heart disease, also found that a CAC score of 0 reliably ruled out obstructive CAD in 98% of individuals (8). Additionally, the rate of fatal and nonfatal myocardial infarctions for participants with a CAC score of 0 was 0.6%, compared with 6.3% for participants with a score of 400 or higher, indicating the strong ability of a CAC score of 0 to exclude MACE.

In addition to symptomatic individuals, several landmark studies have explored the relationship between CAC scores and MACE in asymptomatic individuals. MESA, a population-based prospective cohort study, investigated the prevalence, risk factors, and progression of subclinical cardiovascular disease in participants with no signs of cardiovascular disease at baseline (17). Over a mean follow-up of 10.3 years, MESA analyzed rates of MACE, defined as nonfatal myocardial infarction, death from coronary heart disease, or resuscitated cardiac arrest. Among all the groups analyzed, those with a CAC score of 0 had the lowest MACE rate at 1.7% (5). Thus, it has been consistently shown that a CAC score of 0 is highly accurate in minimizing the risk of MACE in both symptomatic and asymptomatic patients while also being associated with a low rate of obstructive CAD.

Our study corroborates these concepts and adds several notable findings. First, it specifically focused on CAC scoring in a group referred for ICA, which had not been extensively studied. By addressing this group, the trial fills an important research gap and provides valuable insights for patients initially being considered for ICA with stable chest pain and intermediate pretest probability of CAD.

Second, the inclusion of patients from 26 clinical centers in 16 European countries examined using 13 different CT scanners, representing all major vendors, is a major strength, as previous large trials included patients from North America (6) or Scotland (18). This diversity of centers and scanners suggests that the findings are applicable to a broader patient population. Moreover, previous studies have shown excellent agreement in CAC scoring within a given data set (19) and reasonably low interscanner variability (20,21). Therefore, the results from the pragmatic DISCHARGE trial may be confidently generalized to clinical practice.

A third strength of our study is the substantial representation of female patients, accounting for 57% of the participants compared with 51% (6) and 44% (8) in previous trials. Historically, cardiac trials have underrepresented female patients in research studies on CAD. By including a sizeable number of female participants, the DISCHARGE trial helps to address sex bias and provide more robust and reliable data regarding risk assessment and decision-making for both symptomatic male and female patients.

Despite these insights, we acknowledge several limitations. First, our study focused on the prognostic value of CAC scoring in patients with stable chest pain. The applicability of our findings to other patient populations, such as those with acute coronary syndrome or prior revascularization, remains uncertain. Second, our study focused on midterm follow-up (median, 3.5 years). The longer-term prognostic value of CAC scoring and its ability to predict cardiovascular events beyond this time frame are important to evaluate. Future studies with extended follow-up periods would be valuable in assessing the durability and long-term predictive accuracy of CAC scoring in symptomatic patient populations.

In conclusion, in participants with stable chest pain referred for invasive coronary angiography, a coronary artery calcium score of 0 showed very low risk of major adverse cardiovascular events (MACE) at follow-up, and increasing scores were associated with increasing rates of obstructive coronary artery disease, revascularization, and MACE.

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