Clinical Gastroenterology and Hepatology 2026;■:■–■

Hepatic Steatosis Is Associated With Increased Cardiovascular Risk Through Adverse Coronary Plaque Composition

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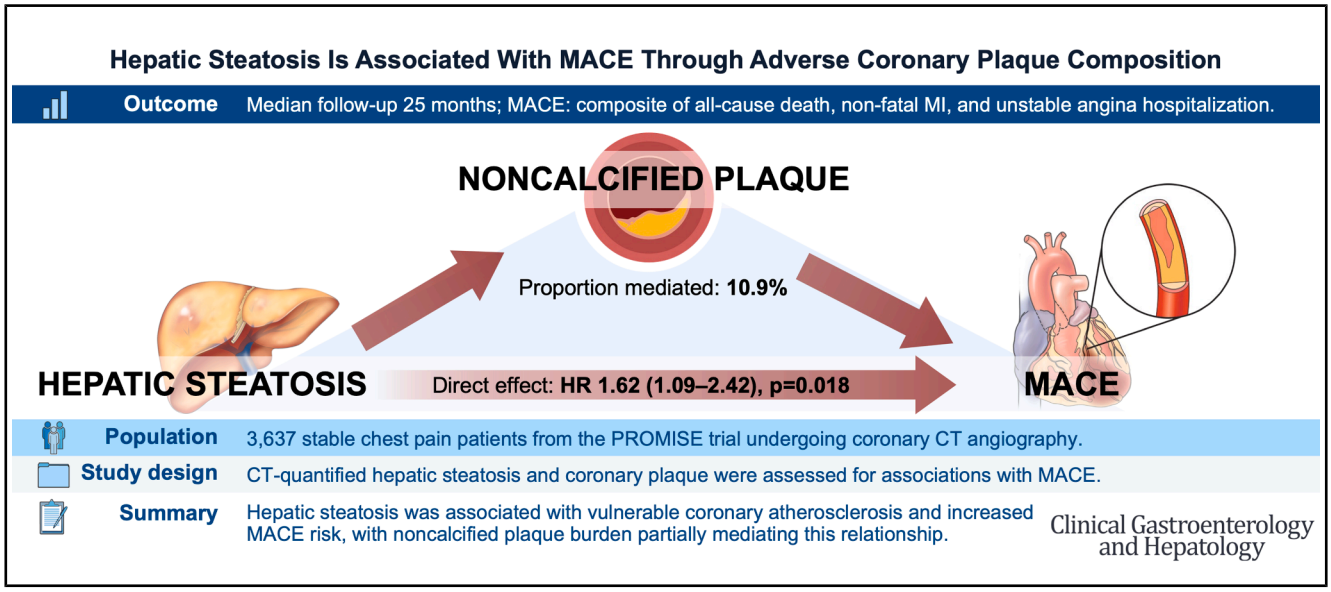

Abbreviations used in this paper: ASCVD, atherosclerotic cardiovascular disease; CCTA, coronary computed tomography angiography; CI, confidence interval; CPB, calcified plaque burden; CT, computed tomography; HR, hazard ratio; HU, Hounsfield unit; IQR, interquartile range; LAPB, low-attenuation plaque burden; MACE, major adverse cardiovascular events; NCPB, noncalcified plaque burden; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; TPB, total plaque burden.

1542-3565
https://doi.org/10.1016/j.cgh.2026.04.022

BACKGROUND & AIMS: **Hepatic steatosis has been associated with major adverse cardiovascular events independently of other cardiovascular risk factors and the severity of coronary artery disease. Nevertheless, the relationship between hepatic steatosis, coronary plaque composition, and major adverse cardiovascular events remains unclear.**

METHODS: **A central core laboratory analyzed Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) participants randomized to the computed tomography arm. Hepatic steatosis was assessed on noncontrast computed tomography using standard hepatic and splenic attenuation methods. Coronary computed tomography angiography was used to quantify total, calcified, noncalcified, and low-attenuation plaque volume and burden (% vessel volume). Multivariable regression and mediation analyses assessed relationships between hepatic steatosis, plaque components, and major adverse cardiovascular events (death, myocardial infarction, unstable angina hospitalization). The median follow-up was 25 months (interquartile range, 18–33 months).**

RESULTS: **Among 3637 patients (age, 60.6 ± 8.2 years; 51.4% female), 25.5% had hepatic steatosis and were slightly younger, more often male, had more cardiovascular risk factors, and had a higher rate of major adverse cardiovascular events (4.1% vs 2.5%) (all $P < .05$). After adjustment for clinical risk factors, hepatic steatosis was associated with greater noncalcified plaque burden (β, 0.15%; 95% confidence interval, 0.04–0.27; $P = .008$). Hepatic steatosis was associated with increased risk of major adverse cardiovascular events independent of atherosclerotic cardiovascular disease risk score, obesity, obstructive stenosis, and noncalcified plaque burden (adjusted hazard ratio, 1.69; 95% confidence interval, 1.12–2.54; $P = .012$), whereas noncalcified plaque burden mediated 11% of the association between hepatic steatosis and major adverse cardiovascular events.**

CONCLUSIONS: **Hepatic steatosis was associated with greater noncalcified plaque burden and increased risk of major adverse cardiovascular events, with noncalcified plaque burden accounting for a portion of this association, suggesting a link between hepatic steatosis and vulnerable coronary atherosclerosis. These findings support integrated cardiometabolic risk assessment in patients undergoing coronary computed tomography angiography.**
ClinicalTrials.gov number, NCT01174550.

Keywords: Coronary Computed Tomography Angiography; Hepatic Steatosis; Major Adverse Cardiovascular Events; Outcomes; Risk Stratification.

Steatotic liver disease affects approximately 30% to 40% of the United States population, with its prevalence continuing to rise.[1] The accumulation of fat within the liver, termed hepatic steatosis, has consequences that extend beyond hepatic complications, is associated with obesity, type 2 diabetes mellitus, hypertension, and dyslipidemia, and is increasingly recognized for its systemic implications, particularly adverse cardiovascular outcomes.[2] Cardiovascular disease is the leading cause of death among individuals with hepatic steatosis,[3] and hepatic steatosis has been linked to both the development of cardiovascular disease and a higher risk of major adverse cardiovascular events (MACE), independent of other cardiovascular risk factors and the extent of coronary artery disease.[4–9] However, the biological pathways through which hepatic steatosis may contribute to excess MACE risk remain incompletely understood.

Recent advances in coronary computed tomography angiography (CCTA) enable detailed quantification of total plaque burden and its noncalcified and calcified components.[10–14] These compositional measures may provide mechanistic insights, as noncalcified plaque and its low-attenuation plaque subcomponent mark vulnerable plaques prone to rupture and strongly predict acute coronary events.[15–18] Prior data from SCOT-HEART demonstrated that patients with hepatic steatosis have greater low-attenuation plaque burden[19]; however, this association was not independent of standard cardiovascular risk scores. Thus, it remains unclear whether hepatic steatosis relates to high-risk plaque phenotypes beyond traditional cardiometabolic risk factors, and whether these phenotypes contribute to the excess MACE risk observed in individuals with hepatic steatosis. Clarifying this relationship is clinically important, as it may refine cardiovascular risk stratification in this growing at-risk population. It may also inform preventive strategies targeting both metabolic and atherosclerotic pathways, particularly given that noncalcified plaque is modifiable.[20]

Accordingly, we utilized the coronary computed tomography (CT) arm of the Prospective Multicenter

Imaging Study for Evaluation of Chest Pain (PROMISE) to evaluate the relationships among hepatic steatosis, quantitative coronary plaque composition, and MACE. Specifically, we aimed to determine whether hepatic steatosis is associated with MACE independent of advanced quantitative plaque composition metrics, whether hepatic steatosis relates to specific plaque components, and whether those plaque components mediate the association between hepatic steatosis and adverse cardiovascular outcomes.

What You Need to Know

Background

Hepatic steatosis is common and associated with increased cardiovascular risk, but the mechanisms linking it to adverse outcomes remain incompletely understood.

Findings

In the PROMISE trial, patients with hepatic steatosis undergoing coronary computed tomography angiography had significantly greater noncalcified coronary plaque burden and higher major adverse cardiovascular event risk. Noncalcified plaque burden partially mediated this association, suggesting a potential liver–coronary axis.

Implications for patient care

Hepatic steatosis, incidentally detectable on routine computed tomography imaging, may identify patients with vulnerable coronary atherosclerosis and elevated cardiovascular risk. These findings support its consideration in integrated cardiometabolic risk assessment.

Methods

Study Design and Population

The PROMISE trial (ClinicalTrials.gov, Number: NCT01174550) was a randomized, comparative effectiveness study that enrolled 10,003 stable outpatients presenting with chest pain and no prior history of coronary artery disease across 193 North American sites.[21] In brief, participants were randomized 1:1 to receive either CCTA or functional testing as the first diagnostic approach.[22] For the present analysis, we included individuals randomized to the CCTA arm with available, diagnostic-quality, contrast-enhanced CCTA and noncontrast CT datasets. Exclusion criteria were noncontrast CT only, unavailable or nondiagnostic CCTA data, or absence of both liver and spleen on noncontrast CT (Supplementary Figure 1). All participants provided written informed consent, and the trial was approved by local or central institutional review boards.

Computed Tomography Image Analysis

Noncontrast images were analyzed in a blinded central core laboratory by experienced readers. Hepatic and splenic attenuation were measured using 3 circular regions of interest ($\geq$2 cm^2) placed on 3 separate axial levels of each organ, avoiding vascular and biliary structures.[23,24] Hepatic steatosis was defined as the presence of at least 1 of the following: (1) mean hepatic attenuation $\leq$40 Hounsfield units (HU); (2) hepatic attenuation minus splenic attenuation of $<$1 HU; or (3) liver-to-spleen attenuation ratio $<$1.[23,25,26] Coronary artery calcium was measured using the Agatston score.[27]

All contrast-enhanced CCTA images were acquired using standardized protocols and transferred to the core laboratory for blinded analysis by level III–certified readers,[16,28,29] In brief, each coronary segment was assessed for the presence of plaque, degree of stenosis, and high-risk plaque features (including napkin-ring sign, low-attenuation $<$30 HU, and positive remodeling[16]) (Supplementary Material). Quantitative plaque analysis was performed using dedicated semiautomated software (QAngioCT; Medis Medical Imaging Systems).[14] Following automated detection of the lumen and vessel wall, proximal and distal reference sites were defined, and manual adjustments were made if necessary. Voxels between the vessel wall and lumen were classified as plaque, and total plaque volume was quantified along with its components based on attenuation thresholds: calcified plaque ($\geq$350 HU), noncalcified plaque ($<$350 HU), and low-attenuation plaque ($<$30 HU). Plaque burden was calculated as plaque volume divided by vessel volume of analyzed segments.[15,30,31]

Study Endpoints

The primary endpoint was MACE, defined as a composite of all-cause death, nonfatal myocardial infarction, or hospitalization for unstable angina (Supplementary Material). Events were prospectively collected and adjudicated by an independent clinical events committee using predefined criteria.[21,22] The median follow-up duration was 25 months (interquartile range [IQR], 18–33 months).

Statistical Analysis

Baseline clinical and imaging characteristics were summarized using means with standard deviations (SDs) or medians with IQRs for continuous variables, and counts with percentages for categorical variables; characteristics were stratified by the presence of hepatic steatosis and compared using independent 2-sample *t* tests, Wilcoxon rank-sum tests, or Fisher's exact tests, as appropriate. Associations between hepatic steatosis and quantitative plaque measures were evaluated using

linear regression models with log-transformed dependent variables (log[1+x]) and robust standard errors, adjusted for atherosclerotic cardiovascular disease (ASCVD) risk score and obesity. Associations between hepatic steatosis and MACE were assessed using Cox proportional hazards models, adjusting for ASCVD risk score (2013 pooled cohort equations), obesity (body mass index $\geq$30 kg/m^2), obstructive coronary stenosis ($\geq$50% diameter), and noncalcified plaque burden (NCPB). No violation of the proportional hazards assumption was observed based on Schoenfeld residuals. Sensitivity analyses were performed among participants with cardiometabolic risk factors, defined using available markers of insulin resistance.[1,32] These included body mass index $\geq$25 kg/m^2, diabetes, elevated blood pressure ($\geq$130/85 mm Hg) or antihypertensive therapy, triglycerides $\geq$150 mg/dL or lipid-lowering therapy, and reduced high-density lipoprotein cholesterol ($\leq$40 mg/dL in men, $\leq$50 mg/dL in women). Mediation analyses were performed to estimate the proportion of the association between hepatic steatosis and MACE explained by individual plaque components (Supplementary Material). Causal interpretation assumes no unmeasured confounding of the exposure–outcome, mediator–outcome, or exposure–mediator relationships, and no exposure-induced mediator–outcome confounding. As these assumptions cannot be verified in an observational setting, mediation results are presented as illustrative of potential pathways and should not be interpreted as definitive causal estimates. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported, and cumulative event rates were estimated using the Kaplan–Meier method and compared with log-rank tests. Given the exploratory nature of the study, all inferences were based on a 2-sided alpha level of .05 without adjustment for multiple comparisons. Statistical analyses were performed using Stata 18.0 (StataCorp LP) and R (version 4.5.1; R Foundation for Statistical Computing).

Results

Study Population

Of 10,003 patients randomized in PROMISE, 3637 (mean age, 60.6 $\pm$ 8.2 years; 51.4% female) were included in the present analysis (Supplementary Figure 1). Among them, 929 (25.5%) had hepatic steatosis. Compared with patients without steatosis, those with steatosis were slightly younger (59.4 $\pm$ 7.8 vs 60.9 $\pm$ 8.3 years; $P < .001$), more often male (55.2% vs 46.3%; $P < .001$), had a higher prevalence of diabetes (30.6% vs 16.1%) and metabolic syndrome (53.3% vs 29.9%; both $P < .001$), and had higher estimated 10-year ASCVD risk scores (median, 12.3% [IQR, 7.4%–20.0%] vs 10.6% [IQR, 5.8%–18.7%]; $P < .001$) (Supplementary Table 1). Laboratory differences included higher triglycerides (188.3 $\pm$ 136.2 vs 135.8 $\pm$ 86.6 mg/dL) and lower high-density lipoprotein cholesterol (46.8 $\pm$ 12.9 vs 52.9 $\pm$ 15.6 mg/dL), as well as higher high-sensitivity C-reactive protein (3.0 [IQR, 1.7–5.4] vs 2.1 [IQR, 1.1–4.3] mg/L) and interleukin-6 (2.0 [IQR, 1.3–3.0] vs 1.7 [IQR, 1.1–2.6]) (all $P < .001$).

Among patients with hepatic steatosis, those with NCPB equal to or above the median were more often male, smokers, and had a higher ASCVD risk score (14.0% [IQR, 8.5%–22.0%] vs 10.6% [IQR, 6.0%–18.0%]; all $P < .001$ compared with those with NCPB below the median) (Table 1). Aspirin use was modestly higher (51.6% vs 42.9%; $P = .011$), whereas statin use did not differ significantly. Lipid levels, high-sensitivity C-reactive protein, and interleukin-6 were similar between groups. MACE rate was higher for the composite of all-cause death, myocardial infarction, or unstable angina pectoris hospitalization (5.8% vs 2.4%; $P = .010$).

Patient characteristics stratified by the extent of total (TPB), calcified (CPB), and low-attenuation (LAPB) plaque burden and characteristics of excluded patients are presented in Supplementary Tables 2–5.

Hepatic Steatosis and Coronary Plaque Composition

Quantitative plaque analysis showed greater total plaque volume in patients with hepatic steatosis (median, 57.2 [IQR, 0.0–184] vs 36.9 [IQR, 0.0–166] mm^3; $P = .001$), particularly greater noncalcified (median, 34.3 [IQR, 0.0–112] vs 20.3 [IQR, 0.0–99.1] mm^3; $P < .001$) and low-attenuation plaque volume (median, 0.16 [IQR, 0.00–3.00] vs 0.03 [IQR, 0.00–1.84] mm^3; $P < .001$), whereas calcified plaque volume was only modestly higher (median, 9.7 [IQR, 0.0–53.8] vs 6.8 [IQR, 0.0–50.5] mm^3; $P = .025$) (Table 2). Similarly, NCPB (median, 16.7% vs 13.5%; $P = .005$) and LAPB (0.08% vs 0.01%; $P < .001$) were greater in patients with hepatic steatosis, whereas TPB and CPB did not differ significantly. Overall, patients with hepatic steatosis were more likely to have any detectable plaque (69.8% vs 64.0%; $P = .010$), whereas the prevalence of obstructive stenosis was similar to those without hepatic steatosis (15.5% vs 13.4%; $P = .112$).

In semilog univariable regression analyses, hepatic steatosis was associated with greater total, noncalcified, and low-attenuation plaque volume corresponding to relative increases of 33%, 33%, and 16%, respectively (all $P < .001$), whereas the association with calcified plaque volume was more modest (17%; $P = .026$) (Table 3). Similarly, hepatic steatosis was associated with higher TPB (19%; $P = .003$), NCPB (20%, $P = .001$), and LAPB (8%, $P < .001$), but not CPB.

After adjustment for ASCVD risk score and obesity, hepatic steatosis remained associated with greater total plaque volume (24%; $P = .007$), noncalcified plaque volume (24%; $P = .004$), and low-attenuation plaque

Table 1. Patient Characteristics Stratified by the Presence of Hepatic Steatosis and Extent of NCPB

	Hepatic steatosis (n = 929)			No hepatic steatosis (n = 2708)		
	NCPB ≥median (n = 464)	NCPB <median (n = 465)	*P*	NCPB ≥median (n = 1354)	NCPB <median (n = 1354)	*P*
Demographics						
Age, *y*	59.9 ± 7.8	59.0 ± 7.7	.063	61.9 ± 8.3	60.0 ± 8.2	**<.001**
Female	171 (36.9)	245 (52.7)	**<.001**	581 (42.9)	872 (64.4)	**<.001**
Race			.451			**.040**
White	396 (86.8)	389 (84.6)		1145 (85.5)	1121 (83.4)	
Black	33 (7.2)	45 (9.8)		117 (8.7)	158 (11.8)	
Asian	18 (4.0)	19 (4.1)		50 (3.7)	33 (2.5)	
Indian	5 (1.1)	3 (0.7)		5 (0.4)	10 (0.7)	
Hawaiian	0 (0.0)	2 (0.4)		4 (0.3)	3 (0.2)	
Other	4 (0.9)	2 (0.4)		19 (1.4)	19 (1.4)	
Ethnicity						
Hispanic or Latino	40 (8.8)	43 (9.4)	.818	77 (5.8)	103 (7.7)	.053
Primary presenting symptoms						
Chest pain	340 (73.3)	334 (71.8)	.659	983 (72.7)	1002 (74.1)	.409
Dyspnea	63 (13.6)	77 (16.6)	.233	183 (13.5)	195 (14.4)	.506
Other (fatigue, palpitations, other)	61 (13.1)	54 (11.6)	.487	187 (13.8)	155 (11.5)	.073
Cardiac risk factors						
Dyslipidemia	334 (72.0)	321 (69.0)	.350	929 (68.6)	869 (64.2)	**.016**
Hypertension	337 (72.6)	320 (68.8)	.220	847 (62.6)	816 (60.3)	.236
Current or past tobacco use	273 (58.8)	220 (47.3)	**<.001**	765 (56.5)	622 (46.0)	**<.001**
Diabetes	157 (33.8)	127 (27.3)	**.033**	247 (18.2)	190 (14.0)	**.003**
Metabolic syndrome	240 (51.7)	255 (54.8)	.358	443 (32.7)	366 (27.0)	**.001**
Sedentary lifestyle	229 (49.4)	248 (53.3)	.238	719 (53.3)	721 (53.4)	.969
Family history of premature CAD	168 (36.4)	158 (34.1)	.492	464 (34.4)	420 (31.1)	.071
BMI, kg/m^2 (mean ± SD)	31.4 ± 5.1	32.5 ± 6.0	**.006**	29.7 ± 5.4	29.5 ± 5.9	.070
Risk burden						
No risk factor	5 (1.1)	6 (1.3)	1.000	38 (2.8)	46 (3.4)	.438
ASCVD (2013) risk score, PCE (%)	14.0 (8.5–22.0)	10.6 (6.0–18.0)	**<.001**	12.9 (7.7–22.4)	8.3 (4.5–15.0)	**<.001**
Medication						
Aspirin	232 (51.6)	191 (42.9)	**.011**	626 (47.9)	522 (40.6)	**<.001**
Statin	219 (48.7)	195 (43.8)	.159	642 (49.1)	529 (41.2)	**<.001**
ACEi or ARB	225 (50.0)	215 (48.3)	.640	551 (42.2)	499 (38.9)	.093
Beta-blocker	119 (26.4)	129 (29.0)	.412	310 (23.7)	307 (23.9)	.927
Laboratory values						
Triglyceride, *mg/dL*	163 (115–233)	148 (107–212)	.108	120 (84–168)	114 (82–153)	**.048**
Total cholesterol, *mg/dL*	200 ± 52.3	197 ± 45.0	.426	195 ± 44.1	196 ± 40.3	.593
HDL, *mg/dL*	45.9 ± 12.5	47.8 ± 13.3	.082	50.5 ± 14.7	55.2 ± 16.1	**<.001**
LDL, *mg/dL*	116 ± 38.1	115 ± 36.5	.753	117 ± 37.9	115 ± 35.9	.588
hsCRP, *mg/L*	3.0 (1.7–5.5)	3.0 (1.6–5.3)	.772	2.2 (1.1–4.4)	2.1 (1.0–4.3)	.799
IL-6, *pg/mL*	1.7 (1.3–2.8)	2.2 (1.4–3.1)	.154	1.7 (1.1–2.7)	1.7 (1.1–2.6)	.249
MACE						
All-cause death, MI, or UAP hospitalization	27 (5.8)	11 (2.4)	**.010**	53 (3.9)	14 (1.0)	**<.001**
CV death or MI	11 (2.4)	5 (1.1)	.138	20 (1.5)	7 (0.5)	**.009**

NOTE. Data are resented as mean ± standard deviation, median (interquartile range), or number (%).

NOTE. Comparisons were performed between patients with NCPB ≥median and NCPB <median. Median NCPB in patients with hepatic steatosis: 16.7%, in patients without hepatic steatosis: 13.5%.

NOTE. Significant differences ($P < .05$) are highlighted in bold.

ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers, ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index, CAD, coronary artery disease, CV, cardiovascular, HDL, high-density lipoprotein, hsCRP, high-sensitivity C-reactive protein, IL-6, interleukin-6, LDL, low-density lipoprotein, MACE, major adverse cardiovascular events, MI, myocardial infarction, NCPB, noncalcified plaque burden, PCE, pooled cohort equations, UAP, unstable angina pectoris.

Table 2. Coronary Artery Disease Characteristics Stratified by the Presence of Hepatic Steatosis

	All patients (N = 3637)	Hepatic steatosis (n = 929)	No hepatic steatosis (n = 2708)	*P*
Quantitative plaque measures				
Plaque volume, mm^3				
Total	41.3 (0.0–172)	57.2 (0.0–184)	36.9 (0.0–166)	**.001**
Calcified	7.6 (0.0–51.2)	9.7 (0.0–53.8)	6.8 (0.0–50.5)	**.025**
Noncalcified	23.3 (0.0–103)	34.3 (0.0–112)	20.3 (0.0–99.1)	**<.001**
Low-attenuation	0.03 (0.00–2.06)	0.16 (0.00–3.00)	0.03 (0.00–1.84)	**<.001**
Plaque burden, %				
Total	27.5 (0.0–42.4)	29.1 (0.0–42.6)	26.9 (0.0–42.3)	.076
Calcified	4.9 (0.0–15.1)	5.1 (0.0–14.9)	4.7 (0.0–15.1)	.275
Noncalcified	14.3 (0.0–29.1)	16.7 (0.0–29.7)	13.5 (0.0–28.8)	**.005**
Low-attenuation	0.02 (0.00–0.53)	0.08 (0.00–0.79)	0.01 (0.00–0.46)	**<.001**
Traditional plaque measures				
CAC score, Agatston units	19 (0–157)	29 (0–167)	17 (0–152)	**.010**
Plaque present	2382 (65.5)	648 (69.8)	1734 (64.0)	**.002**
Obstructive stenosis (≥50%)	507 (13.9)	144 (15.5)	363 (13.4)	.112
Presence of HRP features	570 (15.7)	141 (15.2)	429 (15.8)	.676

NOTE. Data are presented as median (interquartile range), or number (%).
NOTE. Significant differences ($P < .05$) are highlighted in bold.
CAC, coronary artery calcium; HRP, high-risk plaque.

volume (11%; $P = .008$), whereas the association with calcified plaque volume was attenuated. For plaque burden, hepatic steatosis remained associated with higher TPB (15%; $P = .022$), NCPB (15%; $P = .008$), and LAPB (6%; $P = .006$), but not CPB. Findings were consistent in the subgroup of patients with

Table 3. Association of Hepatic Steatosis With Coronary Plaque Extent and Composition

All patients (N = 3637)	Univariable		Adjusted for ASCVD risk score and obesity	
Dependent variable	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
Plaque volume, mm^3				
Total	0.33[a] (0.15–0.51)	**<.001**	0.24 (0.07–0.41)	**.007**
Calcified	0.17 (0.02–0.32)	**.026**	0.11 (-0.03–0.25)	.134
Noncalcified	0.33 (0.16–0.49)	**<.001**	0.24 (0.08–0.41)	**.004**
Low-attenuation	0.16 (0.08–0.24)	**<.001**	0.11 (0.03–0.20)	**.008**
Plaque burden, %				
Total	0.19 (0.06–0.32)	**.003**	0.15 (0.02–0.27)	**.022**
Calcified	0.06 (−0.04 to 0.16)	.218	0.04 (−0.06 to 0.13)	.416
Noncalcified	0.20 (0.08–0.31)	**.001**	0.15 (0.04–0.27)	**.008**
Low-attenuation	0.08 (0.03–0.12)	**<.001**	0.06 (0.02–0.10)	**.006**
Patients with cardiometabolic risk factors (n = 3563)				
Plaque volume, mm^3				
Total	0.32 (0.13–0.50)	**.001**	0.21 (0.03–0.38)	**.019**
Calcified	0.16 (0.01–0.32)	**.034**	0.07 (−0.08 to 0.21)	.361
Noncalcified	0.31 (0.15–0.48)	**<.001**	0.22 (0.06–0.38)	**.008**
Low-attenuation	0.15 (0.07–0.24)	**<.001**	0.13 (0.04–0.21)	**.003**
Plaque burden, %				
Total	0.19 (0.06–0.31)	**.004**	0.12 (−0.01 to 0.24)	.061
Calcified	0.06 (−0.04 to 0.16)	.228	0.00 (−0.09 to 0.10)	.939
Noncalcified	0.19 (0.07–0.31)	**.001**	0.14 (0.02–0.25)	**.019**
Low-attenuation	0.07 (0.03–0.12)	**.001**	0.07 (0.02–0.11)	**.003**

NOTE. Semilog multivariable models (log-transformed dependent variable) were adjusted for ASCVD risk score and obesity and estimated with robust standard errors.
NOTE. Significant associations ($P < .05$) are highlighted in bold.
ASCVD, atherosclerotic cardiovascular disease risk; CI, confidence interval.
[a]Interpretation: Presence of hepatic steatosis is associated with an approximate 33% increase in plaque volume.

cardiometabolic risk factors, with hepatic steatosis independently associated with higher noncalcified plaque volume (22%; $P = .008$) and NCPB (14%; $P = .019$), as well as low-attenuation plaque volume (13%; $P = .003$) and LAPB (7%; $P = .003$), whereas associations with calcified plaque remained nonsignificant. For further data, refer to Supplementary Tables 6 and 7.

Interplay of Hepatic Steatosis, Noncalcified Plaque Burden, and Major Adverse Cardiovascular Events

Over a median follow-up of 25 months (IQR, 18–33 months), patients with hepatic steatosis experienced a nearly 2-fold higher incidence of MACE compared with those without hepatic steatosis (38 events [4.1%] vs 67 events [2.5%]; $P = .011$). Cumulative event rates were consistently higher among patients with hepatic steatosis across strata of plaque burden (Figure 1; Supplementary Figure 2).

In univariable Cox regression (Table 4), hepatic steatosis was associated with a higher risk of MACE (HR, 1.67; 95% CI, 1.12–2.48; $P = .012$). This relationship remained robust after adjustment for ASCVD risk score and obesity (adjusted HR, 1.80; 95% CI, 1.19–2.70; $P = .005$) and persisted when further accounting for obstructive stenosis and NCPB (adjusted HR, 1.69; 95% CI, 1.12–2.54; $P = .012$). Similar findings were observed in patients with cardiometabolic risk factors. Further sensitivity analyses are presented in Supplementary Tables 8–10.

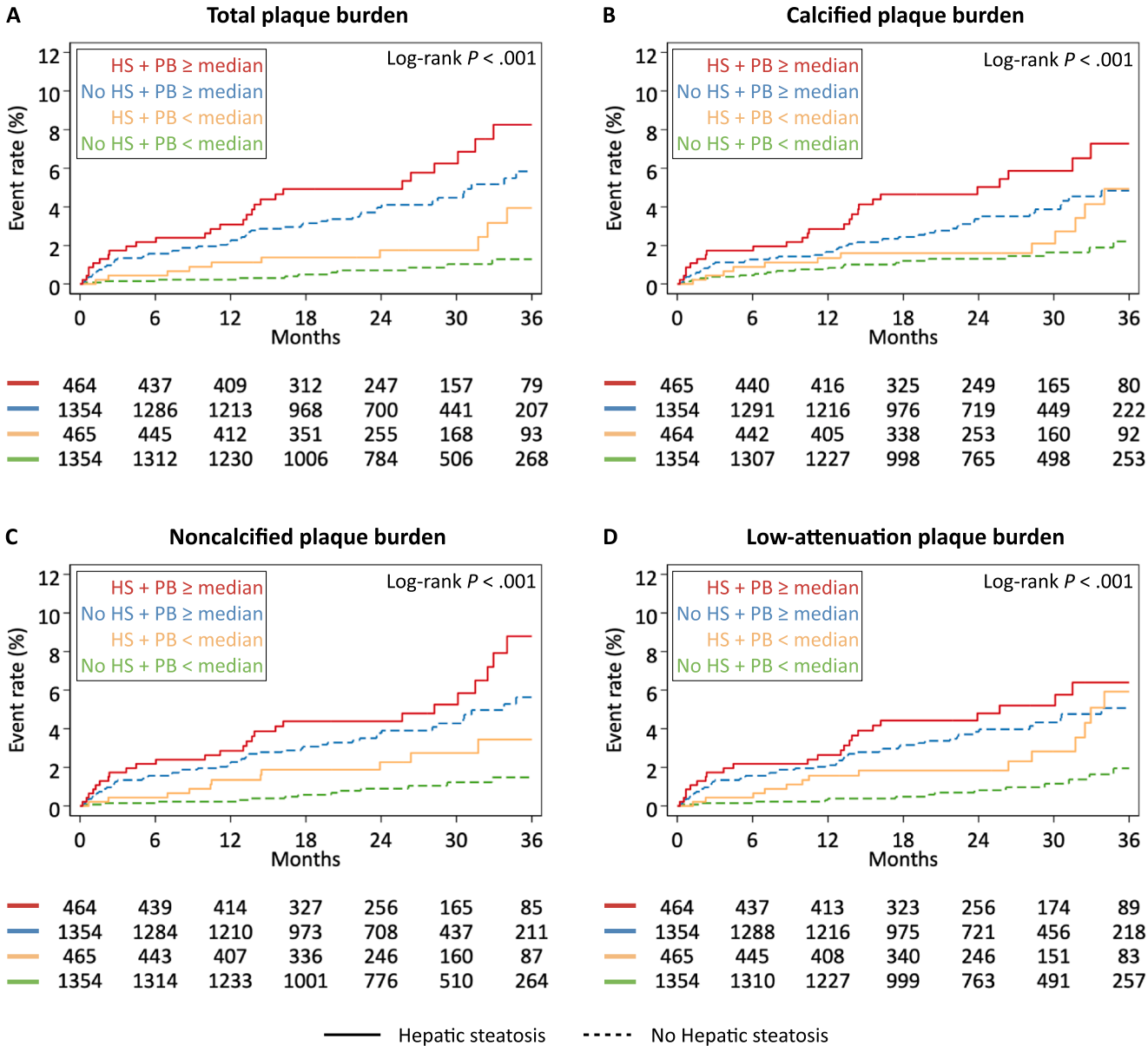

Figure 1. Association of hepatic steatosis and plaque burden with MACE. Kaplan–Meier curves display cumulative event rates stratified by the presence (*solid lines*) or absence (*dashed lines*) of hepatic steatosis, and the extent of coronary plaque burden (plaque burden below or above the median) for TPB (*A*), CPB (*B*), NCPB (*C*), and LAPB (*D*). HS, hepatic steatosis; PB, plaque burden.

Table 4. Associations of Hepatic Steatosis, Cardiometabolic Risk, and Plaque Burden With MACE

			Multivariable analysis			
	Univariable		Model 1		Model 2	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
All patients (N = 3637)						
Hepatic steatosis	1.67 (1.12–2.48)	**.012**	1.80 (1.19–2.70)	**.005**	1.69 (1.12–2.54)	**.012**
ASCVD risk score, per 1%	1.03 (1.02–1.05)	**<.001**	1.03 (1.02–1.05)	**<.001**	1.02 (1.01–1.04)	**.001**
Obesity[a]	0.72 (0.49–1.07)	.104	0.60 (0.40–0.91)	**.015**	0.62 (0.41–0.93)	**.020**
Stenosis ≥50%	4.74 (3.21–6.98)	**<.001**			2.71 (1.73–4.24)	**<.001**
NCPB	1.41 (1.27–1.56)	**<.001**			1.22 (1.08–1.38)	**.001**
Patients with cardiometabolic risk factors (n = 3563)						
Hepatic steatosis	1.59 (1.07–2.38)	**.023**	1.72 (1.14–2.60)	**.010**	1.62 (1.07–2.44)	**.022**
ASCVD risk score, per 1%	1.03 (1.02–1.05)	**<.001**	1.03 (1.02–1.05)	**<.001**	1.02 (1.01–1.04)	**.001**
Obesity	0.71 (0.48–1.05)	.085	0.60 (0.40–0.90)	**.015**	0.62 (0.41–0.93)	**.020**
Stenosis ≥50%	4.62 (3.13–6.83)	**<.001**			2.64 (1.69–4.15)	**<.001**
NCPB	1.41 (1.27–1.56)	**<.001**			1.23 (1.09–1.39)	**.001**

NOTE. HRs and 95% CIs are shown from Cox proportional hazards models. Univariable models included each variable separately. Model 1 was adjusted for atherosclerotic cardiovascular disease risk score and obesity. Model 2 was further adjusted for obstructive stenosis (≥50%) and NCPB (per 10%).
NOTE. Significant associations ($P < .05$) are highlighted in bold.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; NCPB, noncalcified plaque burden.
[a]In sensitivity analyses, higher body mass index was associated with a modest inverse association with MACE, which was attenuated after full adjustment, thus warranting cautious interpretation of obesity when defined using a dichotomous body mass index cutoff (≥30 kg/m^2).

In mediation analyses (Figure 2), NCPB was consistent with partial mediation of the association between hepatic steatosis and MACE, with an estimated proportion mediated of 10.9% (indirect effect HR, 1.05; 95% CI, 1.01–1.10, $P = .014$). TPB showed a similar pattern that did not reach statistical significance (proportion mediated, 11.7%; indirect effect HR, 1.05; 95% CI, 1.00–1.11, $P = .056$).

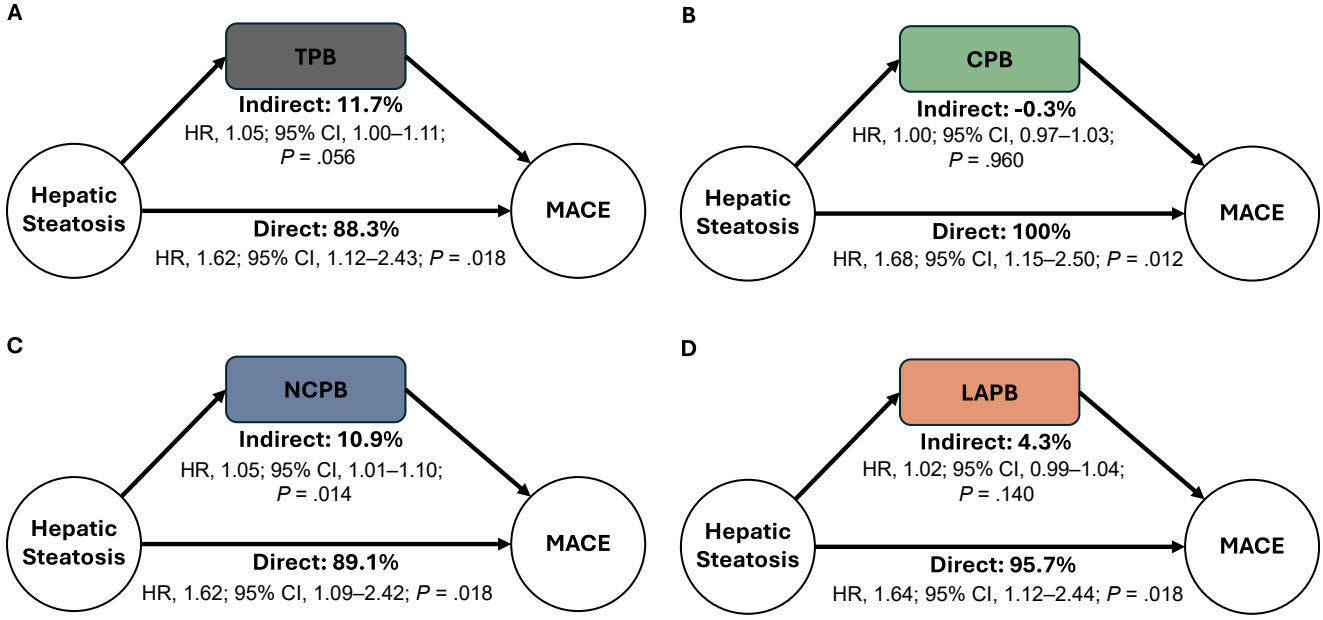

Figure 2. Mediation of the association between hepatic steatosis and MACE by coronary plaque burden. Mediation diagrams illustrate the direct and indirect effects of hepatic steatosis on MACE through TPB (*A*), CPB (*B*), NCPB (*C*), and LAPB (*D*). *Circles* represent exposure (hepatic steatosis) and outcome (MACE), and *colored rectangles* represent plaque burden subtypes as mediators. *Arrows* denote direct and indirect pathways with corresponding HRs (95% CIs) and *P* values. Percentages indicate the proportion of the total effect explained by each pathway. Notably, for NCPB (*C*), 10.9% of the total effect of hepatic steatosis on MACE was mediated through the indirect pathway.

Discussion

In this large, multicenter cohort of symptomatic outpatients undergoing CCTA, we found that hepatic steatosis was associated with a higher burden of noncalcified coronary plaque, an increased risk of MACE, and that NCPB accounted for a meaningful proportion of this excess risk. These findings provide novel mechanistic insight into the link between hepatic steatosis and adverse cardiovascular outcomes and extend prior work by demonstrating that the association between hepatic steatosis and vulnerable plaque phenotypes is independent of established clinical cardiovascular risk factors.

Three main observations emerge from our analysis. First, despite only modest differences in overall coronary plaque presence and stenosis severity, patients with hepatic steatosis exhibited a distinctly higher burden of noncalcified and low-attenuation plaque—features that are characteristic of vulnerable, rupture-prone lesions. Second, hepatic steatosis was associated with a 1.7-fold higher MACE risk, independent of ASCVD risk score, obesity, obstructive coronary stenosis, and quantitative plaque metrics. Third, mediation analyses identified NCPB as a partial contributor, explaining approximately 11% of the excess cardiovascular risk associated with hepatic steatosis. Together, these findings suggest that hepatic steatosis is associated with a subgroup of patients with more adverse coronary plaque biology and heightened clinical vulnerability, and with potentially modifiable coronary plaque features. This creates an opportunity to longitudinally study changes in noncalcified plaque in patients with hepatic steatosis and to explore therapies targeting plaque composition as a surrogate biomarker.

Our results expand upon a growing body of evidence linking hepatic steatosis with subclinical and clinical cardiovascular disease. Prior studies have reported associations between hepatic steatosis and coronary calcium progression, high-risk coronary artery plaques, and higher rates of clinical events.[4,8,33–36] However, few investigations have integrated advanced quantitative coronary plaque imaging with adjudicated outcome data. The SCOT-HEART trial previously demonstrated that patients with hepatic steatosis exhibit greater LAPB, a finding consistent with our results. Importantly, both SCOT-HEART and our data show that this association did not remain significant after adjustment for clinical risk.[19] In contrast, our data show that hepatic steatosis relates to NCPB independent of ASCVD risk score and obesity, underscoring a potential direct link between steatosis and adverse coronary plaque phenotypes. Differences in study populations, plaque quantification algorithms, or risk factor distributions may account for these divergent findings. Our results additionally extend beyond SCOT-HEART by directly testing whether plaque composition mediates the relationship between hepatic steatosis and incident cardiovascular events.

The mechanisms linking hepatic steatosis to vulnerable coronary plaque are complex and multifactorial. Steatotic liver disease is characterized by systemic metabolic dysfunction, including insulin resistance, dyslipidemia, oxidative stress, and chronic low-grade inflammation,[37] a profile mirrored in our cohort by both higher triglyceride concentrations and elevated inflammatory biomarkers among individuals with hepatic steatosis. Together, these perturbations promote atherogenesis by driving proinflammatory, triglyceride-rich lipoprotein profiles, endothelial dysfunction, and macrophage activation within the arterial wall, thereby driving the development of lipid-rich, rupture-prone coronary plaque.[2] Our mediation analysis further suggests that NCPB may represent a pathway through which hepatic steatosis contributes to heightened cardiovascular risk. Although only a portion of the observed risk is explained by plaque composition, our findings support the biological plausibility of a liver–coronary axis whereby hepatic steatosis amplifies the development of vulnerable coronary atherosclerosis. Future studies incorporating CT-based assessment of regional adipose tissue compartments, particularly visceral adiposity, may further refine this liver–coronary paradigm and improve understanding of cardiometabolic risk heterogeneity in hepatic steatosis.

Clinical Implications

Beyond mechanistic insight, the predominance of noncalcified plaque among patients with hepatic steatosis has therapeutic relevance. Noncalcified plaque is a treatment-responsive component of coronary atherosclerosis. Multiple intravascular imaging trials, including the ASTEROID, SATURN, and REVERSAL studies,[38] as well as CCTA imaging studies,[39,40] have demonstrated that intensive lipid-lowering therapy can slow or even reverse noncalcified and fibrofatty plaque. Within this framework, our results suggest that patients with hepatic steatosis and elevated NCPB may particularly benefit from earlier or more intensive preventive therapies.

Looking ahead, whether targeted therapies, such as high-intensity statins, glucagon-like peptide-1 receptor agonists, or emerging metabolic agents, can preferentially slow progression of noncalcified plaque in hepatic steatosis requires a prospective study. Because standalone coronary artery calcium scoring may underestimate risk in steatosis-related coronary disease, quantitative CCTA with plaque imaging offers a more sensitive approach for identifying high-risk patients and monitoring response to therapy. Serial CCTA integrated with liver–coronary phenotyping may further refine risk stratification and guide personalized prevention. Ultimately, prospective trials combining metabolic and vascular interventions with longitudinal plaque imaging are needed to determine whether modifying noncalcified plaque reduces cardiovascular risk in hepatic steatosis.

Limitations

Several limitations merit consideration. First, hepatic steatosis was defined by CT rather than biopsy, which precludes histologic confirmation and characterization of steatohepatitis or fibrosis. Inclusion required diagnostic-quality CCTA, noncontrast CT, and adequate visualization of the liver and spleen, which may be influenced by factors such as body habitus and scanner field-of-view, potentially introducing selection bias. Further, CT has limited sensitivity for mild hepatic steatosis and cannot distinguish disease subtypes. However, CT-based assessment reflects how steatosis can be detected in routine CCTA practice and allows contemporaneous incorporation into cardiovascular risk assessment. Second, imaging and risk factors were assessed only at baseline, so we could not evaluate changes in steatosis, metabolic control, or plaque characteristics over time. Third, data on alcohol use and viral hepatitis were not available. As an observational analysis, residual confounding cannot be excluded, and mediation results should be interpreted as hypothesis-generating and supportive of, rather than definitive proof of, underlying biological pathways. Finally, although this cohort reflects a clinically relevant population of symptomatic chest pain patients undergoing cardiovascular risk evaluation, the findings may not be directly generalizable to asymptomatic or lower-risk populations.

Conclusions

Hepatic steatosis is associated with an increased burden of noncalcified plaque and with a higher risk of MACE, independent of other clinical and imaging-based risk factors. NCPB was consistent with partial mediation of the excess cardiovascular risk associated with hepatic steatosis, suggesting a potential pathway linking hepatic steatosis to vulnerable coronary atherosclerosis. These findings emphasize the need for integrated metabolic and atherosclerosis prevention strategies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2026.04.022.

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Conflicts of interest

These authors disclose the following: Jan M. Brendel is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) #540505270. Márton Kolossváry receives consultation fees from Elucid Bioimaging Inc; and was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences and by the 2025-2.1.1-EKÖP-2025-00019-FK-127 University Research Scholarship Program of the Ministry of Culture and Innovation from the National Research, Development, and Innovation Fund of Hungary, project number PD 147269 and Excellence 151118 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development, and Innovation Fund, financed under the PD_23 and Excellence_24 Funding scheme. Sara Ersözlü has received speaking and consultancy honoraria and research Funding from Amicus Therapeutics; and travel cost support from Alnylam Pharmaceuticals. Maros Ferencik reports consulting fees from Cleerly, HeartFlow, Elucid, and BioMarin; advisory board of Cleerly and Elucid; and stock options from Elucid. Michael T. Lu reports Funding to his institution from the American Heart Association, Amgen, AstraZeneca, Ionis, Johnson & Johnson Innovation, Kowa Pharmaceuticals America, MedImmune, National Academy of Medicine, National Heart, Lung, and Blood Institute, and Risk

Management Foundation of the Harvard Medical Institutions outside the submitted work. Udo Hoffmann is employed by Cleerly. Borek Foldyna reports institutional research support from National Institutes of Health/National Heart, Lung, and Blood Institute, AstraZeneca, MedImmune, Cleerly, and MedTrace, all outside the submitted work. The remaining authors disclose no conflicts.

Funding
This study was supported by National Institutes of Health/National Heart, Lung, and Blood Institute grants #R01HL098236, #R01HL098237, #R01HL098305, #R01HL170877, and #R01HL146145. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability
Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) data sets are available at https://biolincc.nhlbi.nih.gov/studies/promise. There are no commercial use data restrictions and no data restrictions based on area of research.