ORIGINAL RESEARCH

High-Sensitivity Troponin I Levels and Coronary Artery Disease Severity, Progression, and Long-Term Outcomes

Ayman Samman Tahhan, MD; Pratik Sandesara, MD; Salim S. Hayek, MD; Muhammad Hammadah, MD; Ayman Alkhoder, MD; Heval M. Kelli, MD; Matthew Topel, MD; Wesley T. O'Neal, MD; Nima Ghasemzadeh, MD; Yi-An Ko, PhD; Mohamad Mazen Gafeer, MD; Naser Abdelhadi, MD; Fahad Choudhary, MD; Keyur Patel, MD; Agim Beshiri, MD; Gillian Murtagh, MD; Jonathan Kim, MD; Peter Wilson, MD; Leslee Shaw, PhD; Viola Vaccarino, MD, PhD; Stephen E. Epstein, MD; Laurence Sperling, MD; Arshed A. Quyyumi, MD

***Background*—**The associations between high-sensitivity troponin I (hsTnI) levels and coronary artery disease (CAD) severity and progression remain unclear. We investigated whether there is an association between hsTnI and angiographic severity and progression of CAD and whether the predictive value of hsTnI level for incident cardiovascular outcomes is independent of CAD severity.

***Methods and Results*—**In 3087 patients (aged 63±12 years, 64% men) undergoing cardiac catheterization without evidence of acute myocardial infarction, the severity of CAD was calculated by the number of major coronary arteries with ≥50% stenosis and the Gensini score. CAD progression was assessed in a subset of 717 patients who had undergone ≥2 coronary angiograms >3 months before enrollment. Patients were followed up for incident all-cause mortality and incident cardiovascular events. Of the total population, 11% had normal angiograms, 23% had nonobstructive CAD, 20% had 1-vessel CAD, 20% had 2-vessel CAD, and 26% had 3-vessel CAD. After adjusting for age, sex, race, body mass index, smoking, hypertension, diabetes mellitus history, and renal function, hsTnI levels were independently associated with the severity of CAD measured by the Gensini score (log 2 ß=0.31; 95% confidence interval, 0.18–0.44; $P<0.001$) and with CAD progression (log 2 ß=0.36; 95% confidence interval, 0.14–0.58; $P=0.001$). hsTnI level was also a significant predictor of incident death, cardiovascular death, myocardial infarction, revascularization, and cardiac hospitalizations, independent of the aforementioned covariates and CAD severity.

***Conclusions*—**Higher hsTnI levels are associated with the underlying burden of coronary atherosclerosis, more rapid progression of CAD, and higher risk of all-cause mortality and incident cardiovascular events. Whether more aggressive treatment aimed at reducing hsTnI levels can modulate disease progression requires further investigation. **(*J Am Heart Assoc*. 2018;7:e007914. DOI: 10.1161/JAHA.117.007914.)**

Key Words: atherosclerosis • coronary angiography • coronary artery disease • troponin

Although coronary artery disease (CAD) may be present early in life, its progression over time is highly unpredictable. Coronary atherosclerosis can progress at variable rates, ranging from a gradual increase in luminal narrowing to an abrupt progression to total luminal occlusion, the latter often as a result of disruption of a vulnerable nonstenotic plaque attributable to rupture or erosion and subsequent thrombosis.[1] Thus, CAD progression may be silent and gradual or sudden and catastrophic, leading to acute coronary syndrome or death.[2] However, it appears that rapid CAD progression, whether "silent" or associated with clinical manifestations, is an independent predictor of adverse events.[3]

Availability of the new generation of high-sensitivity assays enables detection of low concentrations of circulating cardiac troponins. In contrast to the conventional troponin assays, the high-sensitivity troponin I (hsTnI) assay detects circulating troponin I in most patients with stable CAD in the absence of myocardial necrosis. High levels of circulating hsTnI or high-sensitivity troponin T have been associated with prevalent obstructive coronary atherosclerosis and with adverse

From the Division of Cardiology, Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine, Atlanta, GA (A.S.T., P.S., S.S.H., M.H., A.A., H.M.K., M.T., W.T.O'., N.G., M.M.G., N.A., F.C., K.P., J.K., P.W., L. Shaw, V.V., L. Sperling, A.A.Q.); Departments of Biostatistics and Bioinformatics (Y.-A.K.) and Epidemiology and Rollins School of Public Health (V.V.), Emory University, Atlanta, GA; Diagnostics Division, Abbott Laboratories, North Chicago, IL (A.B., G.M.); and MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, Washington, DC (S.E.E.).

Correspondence to: Arshed A. Quyyumi, MD, Division of Cardiology, Department of Medicine, Emory University School of Medicine, 1462 Clifton Rd NE, Ste 507, Atlanta, GA 30322. E-mail: aquyyum@emory.edu

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Clinical Perspective

What Is New?

- High levels of high-sensitivity cardiac troponin I are associated with more severe coronary artery disease and its accelerated angiographic progression.
- In patients with coronary artery disease, high-sensitivity cardiac troponin I levels can be used to risk stratify and predict future cardiovascular outcomes.

What Are the Clinical Implications?

- High-sensitivity cardiac troponin I is potentially a surrogate biomarker to monitor therapeutic responses in patients with coronary artery disease.
- Whether interventions aimed at reducing its levels are associated with improved outcomes requires further investigations.

incident cardiovascular events in patients with stable CAD or the general and elderly population.[4–9] hsTnI levels have been shown to be associated with CAD severity quantified by angiograms and atherosclerotic plaque burden using computed tomographic angiography in relatively small studies.[9–12] However, the relationship between hsTnI levels and CAD progression has not been studied to date. Moreover, whether the predictive value of hsTnI for cardiovascular outcomes is independent of CAD severity remains unknown.

In this study, we investigated the association between plasma hsTnI levels and the following: (1) the angiographic severity of CAD, (2) the progression of CAD, and (3) whether the predictive value of hsTnI levels for incident cardiovascular events is independent of CAD severity.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Population

We studied 3087 adults ≥18 years from the Emory Cardiovascular Biobank, a prospective cohort of patients undergoing left-sided heart catheterization for suspected or confirmed CAD at 3 Emory healthcare sites in Atlanta, GA, between 2003 and 2015. Subjects with congenital heart disease, heart transplantation, severe anemia, and cancer were excluded. Participants were interviewed to collect demographic characteristics, medical history, medication use, and behavioral habits, as previously described.[13] Risk factor prevalence was determined by physician diagnosis and/or treatment for hypertension, hyperlipidemia, and diabetes mellitus. Blood pressure, heart rate, weight, and height were measured. Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2 (estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation) or urine albumin/creatinine ratio >30 mg/g. Medical records and *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnostic codes were reviewed to confirm self-reported medical history. The study complies with the Declaration of Helsinki and was approved by the institutional review board at Emory University (Atlanta, GA). All subjects provided written informed consent at enrollment.

Identification of CAD and Severity Scoring

All coronary angiograms were scored for luminal narrowing using a modified American Heart Association/American College of Cardiology classification.[14] Patients were designated as having no CAD, nonobstructive CAD (visible plaque resulting in <50% luminal stenosis), or significant CAD (at least 1 major epicardial vessel with ≥50% stenosis). The severity of their CAD was calculated on the basis of angiographic disease of their native vessels before revascularization. Those with a history of coronary artery bypass grafting or percutaneous coronary intervention were all labeled as having significant CAD. Quantitative angiographic scoring was performed using the Gensini score, which quantifies CAD severity by a nonlinear point system for degree of luminal narrowing, along with a multiplier for specific coronary tree locations. For example, 1 point is equivalent to a 25% lesion in the right coronary artery. The score has prognostic significance.[15] Severity of CAD was also quantified by number of major epicardial coronary arteries with ≥50% stenosis.

CAD Progression

A subset of 717 patients who had undergone ≥2 coronary angiograms at least 3 months before enrollment were identified, and the 2 angiograms furthest apart in time were quantified using the Gensini score. The net change in angiographic score was divided by number of years between the angiograms to calculate the Gensini progression rate/year. For example, development of a new 75% stenosis in the right coronary artery in an angiogram performed after 1 year will be associated with a Gensini change of 4 points.

Sample Collection and Measurement of hsTnI Level

Fasting arterial blood samples were collected at cardiac catheterization and stored at −80°C. High-sensitivity troponin I (hsTnI) was measured using the Abbott ARCHITECT analyzer

(Abbott Laboratories, North Chicago, IL), which has a limit of detection of 1.2 pg/mL and an interassay coefficient of variation of <10% at 4.7 pg/mL. The upper reference limit (99th centile) ranges between 24 and 30 pg/mL in healthy populations, with a sex-specific upper reference range of 36 pg/mL for men and 15 pg/mL for women.[16–20] Samples were centrifuged twice before analysis and according to manufacturer's instructions. Serum high-sensitivity C-reactive protein (hs-CRP) levels were determined in 2127 patients using a particle-enhanced immunoturbidimetry assay (First-Mark, a division of GenWay Biotech) that has a lower limit of detection of 0.03 mg/L.[21]

Follow-Up and Outcomes

We conducted follow-up, as previously described, to identify prespecified incident adverse cardiovascular outcomes, including death, cardiovascular death, myocardial infarction (MI), coronary revascularizations, hospitalizations attributable to cardiac causes, and combined major adverse cardiovascular events, which include all-cause mortality, MI, and coronary revascularization.[13] Follow-up was conducted by telephone, electronic medical record review, social security death index, and state records, and adjudication was conducted by personnel blinded to the hsTnI data.

Statistical Analysis

Subject characteristics were reported as descriptive statistics, with means, medians, SDs, and ranges. Differences between groups were assessed using the *t* test for continuous variables and χ^2 for categorical variables, where appropriate. Two-tailed $P \leq 0.05$ was considered statistically significant. For nonnormally distributed variables, such as hsTnI and CRP levels, comparisons between 2 groups were performed with the Mann-Whitney *U* test. Differences between ≥3 groups were assessed using Kruskal-Wallis tests in unadjusted analyses. For multivariable analyses, hsTnI levels were

Table 1. Baseline Characteristics

Characteristics	Normal Angiogram (n=345)	Nonobstructive CAD (n=720)	1-Vessel CAD (n=611)	2-Vessel CAD (n=615)	3-Vessel CAD (n=796)	*P* Value*
Age, mean (SD), y	56.9 (11.5)	61.1 (12.1)	64.3 (11.5)	65.5 (10.2)	66.4 (10.3)	<0.001
Male sex, n (%)	152 (44.1)	379 (52.6)	401 (65.6)	435 (70.7)	622 (78.1)	<0.001
Black race, n (%)	79 (22.9)	172 (23.9)	94 (15.4)	88 (14.3)	103 (12.9)	<0.001
Body mass index, mean (SD), kg/m^2	30.7 (7.4)	30.1 (6.9)	29.6 (5.6)	29.3 (6)	29.3 (5.7)	0.181
Estimated GFR, mean (SD), mL/min per 1.73 m^2	82.2 (19.9)	78.3 (20.8)	73.6 (21.5)	71.9 (21.8)	70.7 (21)	<0.001
Smoking, n (%)	195 (56.5)	453 (62.9)	441 (72.2)	424 (68.9)	553 (69.5)	<0.001
Diabetes mellitus, n (%)	62 (18)	196 (27.6)	215 (35.7)	199 (32.4)	333 (42.2)	<0.001
Hypertension, n (%)	222 (64.5)	487 (67.9)	488 (80)	496 (80.7)	639 (80.6)	<0.001
Hyperlipidemia, n (%)	178 (51.7)	426 (59.4)	473 (77.5)	467 (76.4)	658 (82.9)	<0.001
History of stroke, n (%)	11 (3.2)	56 (7.8)	58 (9.6)	60 (9.8)	90 (11.5)	0.001
History of heart failure, n (%)	40 (11.6)	157 (21.8)	165 (27)	143 (23.3)	228 (28.6)	<0.001
Ejection fraction, mean (SD), %	58 (9.2)	56.2 (10.5)	55 (11)	55 (10)	52 (12)	<0.001
History of myocardial infarction, n (%)	5 (1.5)	44 (6.3)	136 (22.7)	162 (27)	293 (37.7)	<0.001
History of PCI, n (%)	6 (1.7)	60 (8.3)	336 (55)	407 (66.2)	545 (68.5)	<0.001
History of CABG, n (%)	2 (0.6)	26 (3.6)	77 (12.6)	163 (26.5)	481 (60.4)	<0.001
ACE/ARB use, n (%)	131 (38)	332 (46.1)	360 (58.9)	390 (63.4)	528 (66.3)	<0.001
Aspirin use, n (%)	167 (48.4)	425 (59)	494 (80.9)	535 (87)	671 (84.3)	<0.001
Clopidogrel use, n (%)	9 (2.6)	75 (10.4)	325 (53.2)	415 (67.5)	485 (60.9)	<0.001
Statin use, n (%)	134 (38.8)	383 (53.2)	464 (75.9)	522 (84.9)	671 (84.3)	<0.001
β-Blocker use, n (%)	148 (42.9)	362 (50.3)	409 (66.9)	459 (74.6)	594 (74.6)	<0.001
hs-CRP, median (IQR), mg/dL	2.55 (1–5.3)	3.2 (1.3–6.33)	2.4 (1–6.2)	2.4 (1–5.4)	2.3 (1–6)	0.006
hsTnI, median (IQR), pg/mL	2.9 (1.8–4.3)	3.6 (2.2–6)	4.3 (2.7–7.7)	5.1 (3–8.6)	5.7 (3.4–9.8)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; GFR, glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; hsTnI, high-sensitivity troponin I; IQR, interquartile range; and PCI, percutaneous coronary intervention.
**P* value compares patients with CAD.

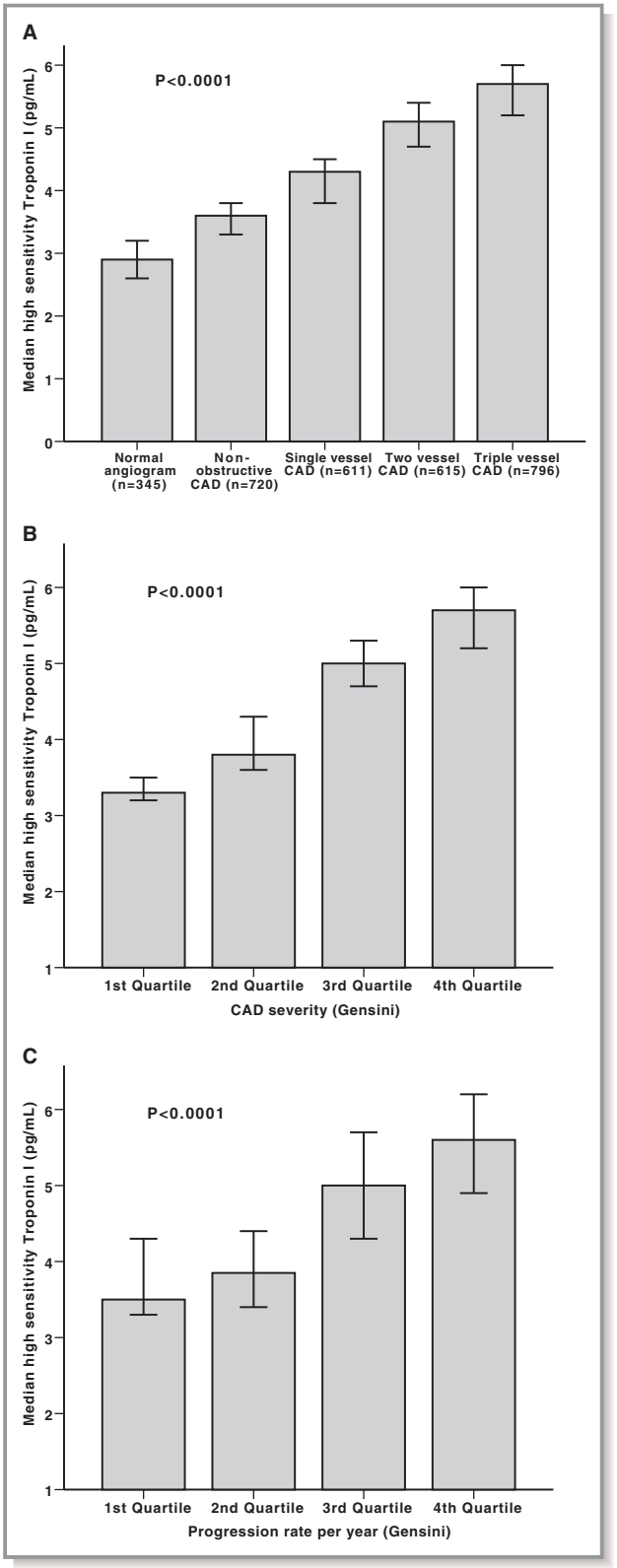

Figure 1. Boxplots demonstrating the correlation between high-sensitivity troponin I levels and prevalent coronary artery disease (CAD) severity measured as number of obstructed vessels (A), prevalent CAD severity measured by Gensini score quartiles (B), and CAD progression scores measured as quartiles of Gensini progression rate (C). *P* values for trend.

Table 2. Bivariate Correlations Between Continuous Variables and CAD Severity (Gensini Score) and Progression Rate (Gensini Progression Rate per Year)

	CAD Severity		CAD Progression Rate	
Variable	ρ	*P* Value	ρ	*P* Value
Age	0.23	<0.0001	0.06	0.104
Body mass index	−0.04	0.061	−0.09	0.018
High-density lipoprotein	−0.18	<0.0001	−0.05	0.201
Low-density lipoprotein	−0.16	<0.0001	−0.03	0.47
Estimated GFR	−0.17	<0.0001	−0.05	0.197
hs-CRP level	−0.06	0.003	−0.04	0.276
hsTnI level	0.26	<0.0001	0.20	<0.0001

CAD indicates coronary artery disease; GFR, glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; and hsTnI, high-sensitivity troponin I.

examined as both categorical variables stratified by quartiles (ranges: quartile 1, 0–2.7; quartile 2, 2.8–4.4; quartile 3, 4.5–7.8; and quartile 4, 7.9–35) and continuous variables. Characteristics incorporated in multivariable analyses included age, sex, race, body mass index, smoking history, hypertension, diabetes mellitus, estimated glomerular filtration rate, statin use, antiplatelet therapy, angiotensin pathway antagonist use, β-blocker therapy, and hs-CRP levels, when available. Spearman correlation coefficients were used to assess the relationship between hsTnI levels and angiographic CAD severity. A linear regression model was used for independent predictors of CAD severity and progression quantified by the Gensini rate. Regression coefficients are presented as point estimates with 95% confidence intervals (CIs). The Kaplan-Meier curves as well as the Cox proportional-hazards regression model were used to examine the association between hsTnI and all-cause death, cardiovascular death, MI, revascularization, hospitalizations, and major adverse cardiovascular events. Analysis was conducted using available data (9% with missing data) under the assumption of missing completely at random. Analyses were performed using IBM SPSS Statistics Version 22 (IBM, Armonk, NY) and R 3.2.2 (R Core Team, Vienna, Austria). Last, we examined the incremental value of adding hsTnI levels to a clinical model for predicting death. The C-statistic, continuous net reclassification improvement, and integrated discrimination improvement were calculated to evaluate the improvement in predictive ability of the models with and without hsTnI using the R packages survC1 and survIDINRI.

Results

Baseline characteristics of the 3087 patients, aged 63±12 years, by CAD severity are included in Table 1.

Relationship Between hsTnI Levels and Angiographic CAD Severity

hsTnI levels were detected in almost all patients (99.9%) and were lowest in subjects without significant native CAD (median, 3.3 pg/mL; interquartile range [IQR], 2.2–6 pg/mL) compared with those with 1-vessel CAD (median, 4.3 pg/mL; IQR, 2.7–7.7 pg/mL), 2-vessel CAD (median, 5.1 pg/mL; IQR, 3–8.6 pg/mL), or 3-vessel CAD (median, 5.7 pg/mL; IQR, 3.4–9.8 pg/mL) ($P<0.0001$) (Figure 1A). Similarly, hsTnI levels were associated with severity of CAD, measured by the Gensini score ($\rho=0.26$, $P<0.00001$) (Figure 1B). Thus, prevalence of 3-vessel CAD was greater in those with hsTnI in the highest versus lowest quartile (34.6% versus 13.2%; $P<0.001$). Bivariate correlations between continuous variables and CAD severity are demonstrated in Table 2. In multivariable analyses, independent predictors of worse CAD severity, measured by Gensini score, included age, sex, race, body mass index, diabetes mellitus, hypertension, hyperlipidemia, history of MI, antiplatelets, statin use, β-blocker use, and hsTnI levels (Table 3). For each doubling in hsTnI levels, there was a 35% increase (95% CI, 1.19–1.52; $P<0.0001$) in the risk of higher CAD severity. In contrast, hs-CRP was not independently associated with angiographic CAD severity ($P=0.56$). In subgroups analysis, high-density lipoprotein was negatively associated with more severe CAD ($\beta=-0.27$; 95% CI −0.37 to −0.17; $P<0.0001$), whereas low-density lipoprotein was not associated with CAD severity ($P=0.54$). hsTnI remained significantly associated with CAD severity, despite adjusting for low- and high-density lipoproteins ($P<0.0001$).

Relationship Between hsTnI Levels and Angiographic Progression of CAD

Of the 3087 patients enrolled, 717 had coronary angiography at least 3 months before enrollment. Patients who had prior angiograms were more likely to be older and male, have a higher prevalence of diabetes mellitus and hyperlipidemia, have worse renal function, and were more likely to have a history of coronary intervention (Table 4). hsTnI levels were not different between those with and without previous angiograms. The median length of time between angiograms was 3.8 years (IQR, 1.7–6.6 years). Bivariate correlations between CAD progression rate and continuous variables are shown in Table 2. There was a significant correlation between the hsTnI levels and the progression of CAD measured as Gensini rate/year ($\rho=0.2$, $P<0.0001$) (Figure 1C). Progression rate was 3.6-fold higher in those with hsTnI in the highest versus lowest quartile (1.5 versus 5.4; $P<0.001$). However, hs-CRP levels did not correlate with the Gensini rate of progression ($P=0.28$).

Furthermore, after adjustment for clinical variables (age, sex, race, body mass index, smoking, diabetes mellitus, hypertension, hyperlipidemia, heart failure, estimated

Table 3. Linear Regression Model for the Predictors of CAD Severity (Log 2 Gensini Score)

Variable	β	Lower CI	Upper CI	OR (95% CI)	*P* Value
Myocardial infarction history	2.34	2.04	2.65	10.4 (7.67–14.11)	<0.0001
Male sex	1.36	1.1	1.63	3.91 (3.01–5.08)	<0.0001
Antiplatelet therapy	1.09	0.76	1.42	2.98 (2.14–4.16)	<0.0001
Statin use	0.95	0.64	1.27	2.59 (1.89–3.55)	<0.0001
Hyperlipidemia	0.87	0.59	1.16	2.39 (1.8–3.18)	<0.0001
Diabetes mellitus	0.59	0.33	0.86	1.81 (1.38–2.36)	<0.0001
β-Blocker	0.58	0.3	0.86	1.79 (1.35–2.36)	<0.0001
Age (10-y increase)	0.40	0.03	0.05	1.49 (1.03–1.05)	<0.0001
hsTnI (log 2)	0.30	0.17	0.42	1.35 (1.19–1.52)	<0.0001
Hypertension	0.29	−0.02	0.59	1.33 (0.98–1.81)	0.063
Smoking history	0.17	−0.08	0.43	1.19 (0.92–1.54)	0.185
Angiotensin pathway antagonist	0.05	−0.22	0.32	1.05 (0.81–1.38)	0.7
GFR (10-U increase)	−0.05	−0.01	0.001	0.95 (0.99–1)	0.121
Heart failure history	−0.11	−0.4	0.19	0.9 (0.67–1.21)	0.47
BMI (5-U increase)	−0.12	−0.04	−0.003	0.89 (0.96–0.99)	0.02
Black race	−0.68	−1.01	−0.35	0.51 (0.36–0.71)	<0.0001

BMI indicates body mass index; CAD, coronary artery disease; CI, confidence interval; GFR, glomerular filtration rate; hsTnI, high-sensitivity troponin I; and OR, odds ratio.

glomerular filtration rate, statin use, antiplatelet therapy, angiotensin pathway antagonist use, β-blocker therapy, and CAD severity), the hsTnI level was independently associated with the progression rate (ß=0.36; 95% CI, 0.14–0.58; *P*=0.001). For each doubling in hsTnI levels, there was a 43% increase (95% CI, 1.15–1.78) in the risk of progression rate. Similar results were observed when CAD progression was defined as >4 Gensini points/year as a cutoff (correlates with new 75% stenosis in the right coronary artery); thus, for each 100% higher level of hsTnI, there was a 40% increase in the likelihood of progression (95% CI, 1.2–1.7; *P*=0.0001). Other predictors of CAD progression included male sex (hazard ratio [HR], 1.7; 95% CI, 1.1–2.6; *P*=0.012), baseline Gensini score (HR, 1.10; 95% CI, 1.05–1.16; *P*=0.0002), and β-blocker use (HR, 1.7; 95% CI, 1.1–2.7; *P*=0.015). Subjects with CAD progression (defined as Gensini progression rate

Table 4. Adjusted Cox Regression Model for the Association Between hsTnI Levels and Incident Events

Variable	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Death (n=431)				
hsTnI (100% increase)	1.68 (1.56–1.82)	<0.0001	1.53 (1.39–1.69)	<0.0001
Quartile 2 vs 1	1.57 (1.12–2.2)	0.009	1.21 (0.84–1.75)	0.304
Quartile 3 vs 1	2.87 (2.11–3.91)	<0.0001	1.99 (1.42–2.81)	<0.0001
Quartile 4 vs 1	5.02 (3.75–6.73)	<0.0001	3.35 (2.39–4.71)	<0.0001
Cardiovascular death (n=239)				
hsTnI (100% increase)	1.84 (1.66–2.05)	<0.0001	1.71 (1.5–1.95)	<0.0001
Quartile 2 vs 1	1.57 (0.96–2.56)	0.073	1.14 (0.67–1.95)	0.628
Quartile 3 vs 1	3.27 (2.11–5.07)	<0.0001	2.33 (1.44–3.77)	0.001
Quartile 4 vs 1	6.65 (4.4–10.06)	<0.0001	4.30 (2.68–6.9)	<0.0001
MI (n=99)				
hsTnI (100% increase)	1.6 (1.36–1.88)	<0.0001	1.37 (1.12–1.68)	0.002
Quartile 2 vs 1	2 (0.99–4.04)	0.053	1.47 (0.69–3.13)	0.313
Quartile 3 vs 1	3.15 (1.63–6.1)	0.001	2.01 (0.98–4.11)	0.057
Quartile 4 vs 1	4.76 (2.52–9.01)	<0.0001	2.5 (1.22–5.14)	0.012
Revascularization (n=680)				
hsTnI (100% increase)	1.26 (1.18–1.34)	<0.0001	1.1 (1.02–1.19)	0.018
Quartile 2 vs 1	1.38 (1.11–1.72)	0.003	1.18 (0.93–1.49)	0.170
Quartile 3 vs 1	1.46 (1.18–1.81)	0.001	1.11 (0.88–1.42)	0.383
Quartile 4 vs 1	2.02 (1.64–2.48)	<0.0001	1.34 (1.05–1.71)	0.019
Combined all-cause mortality, MI, or coronary revascularization (n=875)				
hsTnI (100% increase)	1.36 (1.29–1.44)	<0.0001	1.19 (1.11–1.28)	<0.0001
Quartile 2 vs 1	1.37 (1.12–1.67)	0.002	1.14 (0.92–1.41)	0.224
Quartile 3 vs 1	1.7 (1.4–2.06)	<0.0001	1.25 (1.01–1.55)	0.042
Quartile 4 vs 1	2.5 (2.08–3.01)	<0.0001	1.64 (1.32–2.03)	<0.0001
Cardiac hospitalizations (n=1022)				
hsTnI (100% increase)	1.35 (1.28–1.42)	<0.0001	1.24 (1.17–1.32)	<0.0001
Quartile 2 vs 1	1.28 (1.06–1.54)	0.009	1.13 (0.93–1.38)	0.214
Quartile 3 vs 1	1.67 (1.39–1.99)	<0.0001	1.35 (1.11–1.64)	0.003
Quartile 4 vs 1	2.5 (2.11–2.96)	<0.0001	1.90 (1.56–2.32)	<0.0001

Adjusted Cox regression model for age, sex, race, body mass index, smoking, diabetes mellitus, hypertension, hyperlipidemia, heart failure, estimated glomerular filtration rate, statin use, antiplatelet therapy, angiotensin pathway antagonist use, β-blocker therapy, and coronary artery disease severity (Gensini score). Quartiles ranges are as follows: quartile 1, 0 to 2.7 pg/mL; quartile 2, 2.8 to 4.4 pg/mL; quartile 3, 4.5 to 7.8 pg/mL; and quartile 4, 7.9 to 35 pg/mL. CI indicates confidence interval; HR, hazard ratio; hsTnI, high-sensitivity troponin I; and MI, myocardial infarction.

Table 5. Baseline Characteristics for Patients With and Without Previous Angiograms

Characteristics	Patients Without Previous Angiogram (n=2370)	Patients With Previous Angiogram (n=717)	*P* Value*
Age, mean (SD), y	63.1 (11.8)	64.7 (10.4)	<0.0001
Male sex, n (%)	1480 (62.4)	509 (71)	<0.0001
Black race, n (%)	447 (18.9)	89 (12.4)	<0.0001
Body mass index, mean (SD), kg/m^2	29.7 (6.2)	29.9 (6.4)	0.711
Estimated GFR, mean (SD), mL/min per 1.73 m^2	75.1 (21.7)	72.9 (20.5)	0.004
Smoking, n (%)	1587 (67)	479 (66.8)	0.938
Diabetes mellitus, n (%)	727 (31)	278 (38.8)	<0.0001
Hypertension, n (%)	1786 (75.6)	546 (76.2)	0.77
Hyperlipidemia, n (%)	1639 (69.5)	563 (78.5)	<0.0001
History of stroke, n (%)	206 (8.8)	69 (9.7)	0.469
History of heart failure, n (%)	555 (23.4)	178 (24.8)	0.438
Ejection fraction, mean (SD), %	55 (11)	54 (11)	<0.0001
History of myocardial infarction, n (%)	367 (15.9)	273 (38.1)	<0.0001
History of PCI, n (%)	824 (34.8)	530 (73.9)	<0.0001
History of CABG, n (%)	469 (19.8)	280 (39.1)	<0.0001
ACE/ARB use, n (%)	1249 (52.7)	492 (68.6)	<0.0001
Aspirin use, n (%)	1704 (71.9)	588 (82)	<0.0001
Clopidogrel use, n (%)	889 (37.5)	420 (58.6)	<0.0001
Statin use, n (%)	1594 (67.3)	580 (80.9)	<0.0001
β-Blocker use, n (%)	1452 (61.3)	520 (72.5)	<0.0001
hs-CRP, median (IQR), mg/dL	2.6 (1.1–6.4)	2.4 (1–5.7)	0.185
hsTnI, median (IQR), pg/mL	4.4 (2.6–7.9)	4.4 (2.8–7.5)	0.493

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; hsTnI, high-sensitivity troponin I; IQR, interquartile range; and PCI, percutaneous coronary intervention.
**P* value compares patients with and without previous angiogram.

>4) had an increased risk of mortality (HR, 1.64; 95% CI, 1.14–2.33; *P*=0.008), cardiovascular death/MI (HR, 1.92; 95% CI, 1.26–2.93; *P*=0.002), and major adverse cardiovascular events (HR, 2.01; 95% CI, 1.58–2.55; *P*<0.001).

Relationship Between hsTnI Levels and Incident Cardiovascular Events

After a mean follow-up of 5.2±3.1 years, there were 431 deaths (15.5%) from all causes, 239 deaths (8.6%) from cardiovascular causes, 99 incident MIs (3.6%), 680 coronary revascularization procedures (24.3%), and 1022 hospitalizations for cardiac causes (36.6%). In unadjusted analyses, increase in hsTnI level was associated with increased risk of all-cause death, cardiovascular death, MI, revascularization procedures, cardiac hospitalizations, and major adverse cardiovascular event rate (Table 5). Kaplan-Meier survival curves for association between hsTnI quartiles and clinical outcomes are shown in Figure 2.

After adjusting for demographic and clinical characteristics, as previously detailed, hsTnI levels, both as a continuous variable and in quartiles, remained an independent predictor of all the aforementioned clinical outcomes (Table 5). These results remained significant even after adjusting for high-density lipoproteins, low-density lipoproteins, and hs-CRP levels in a subset of 2127 patients. We also derived an optimal cutoff using Youden's index (sensitivity+specificity−1) for the outcome of cardiovascular death (5.15 pg/mL [57th percentile]), above which the risk of cardiovascular death is as follows: unadjusted HR, 3.9; 95% CI, 3.0 to 5.0 (*P*<0.0001); adjusted HR, 2.8; 95% CI, 2.1 to 3.8 (*P*<0.0001) (Table 6). We found no significant heterogeneity in the HR for mortality on the basis of age, sex, race, and presence of individual risk factors like smoking, diabetes mellitus, hypertension, or hyperlipidemia, heart failure, statin use, or conservative versus invasive management. However, we found a significant trend for hsTnI to have better predictive value in those with versus without chronic kidney disease (interaction *P*=0.03) (Figure 3).

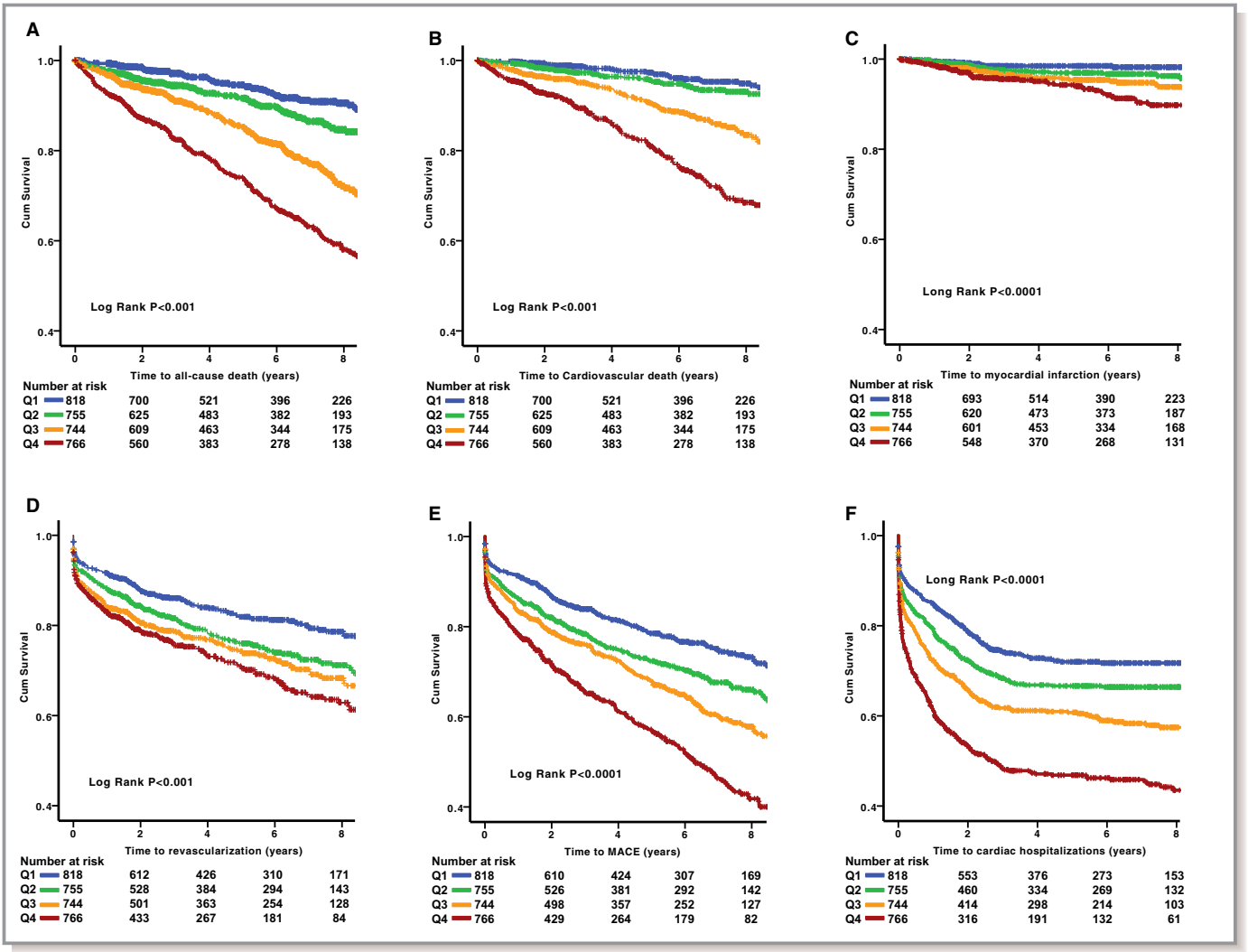

Figure 2. Kaplan-Meier curves for association between levels of high-sensitivity troponin I (hsTnI) by quartiles for the primary end point of all-cause death (A), cardiovascular death (B), incident myocardial infarction (C), revascularization (D) major adverse cardiovascular events (MACEs; E) and cardiac hospitalizations (F). Colored lines represent quartiles (Qs) of hsTnI levels (blue, lowest Q [0–2.7 pg/mL]; green, second Q [2.8–4.4 pg/mL]; orange, third Q [4.5–7.8 pg/mL]; red, highest Q [7.9–35 pg/mL]). Cum indicates cumulative.

CAD severity, measured by Gensini score, was an independent predictor of cardiovascular death/MI and additive to hsTnI. To assess the incremental prognostic value of hsTnI level in relation to established risk predictors and CAD severity, patients were stratified into groups according to combined strata of CAD severity and hsTnI quartiles (Figure 4). Compared with the group within the lowest hsTnI quartile and normal angiogram (reference group), patients within the highest hsTnI quartile and 3-vessel CAD had an HR of 11.1 (95% CI, 3.4–36.7) for cardiovascular death/MI (P<0.0001).

Risk Prediction Performance

We tested the incremental value of adding hsTnI level to a model with significant traditional risk factors and clinical characteristics (including age, sex, race, body mass index, smoking history, hypertension, diabetes mellitus, hyperlipidemia, estimated glomerular filtration rate, history of MI, history of heart failure, and CAD severity) in predicting incident cardiovascular death/MI events. Addition of hsTnI significantly improved the C-statistic (from 0.683 to 0.710; Δ=0.027 [95% CI, 0.008–0.044]), the continuous net reclassification improvement (0.250 [95% CI, 0.113–0.420]; P=0.02), and the integrated discrimination improvement (0.046 [95% CI, 0.020–0.087]; P=0.02).

Discussion

In this large cohort of patients with suspected or confirmed CAD, we demonstrate that elevated circulating levels of hsTnI are associated with the severity and progression of

Table 6. Adjusted Cox Regression Model for the Association Between hsTnI Levels (Using Cutoff of 5.15 pg/mL) and Incident Events

Variable	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Death (n=431)	2.93 (2.44–3.52)	<0.001	2.14 (1.73–2.65)	<0.001
Cardiovascular death (n=239)	3.86 (2.97–5)	<0.001	2.85 (2.11–3.86)	<0.001
MI (n=99)	2.73 (1.86–4.02)	<0.001	2.00 (1.27–3.10)	0.002
Revascularization (n=680)	1.5 (1.3–1.73)	<0.001	1.16 (0.98–1.37)	0.076
Combined all-cause mortality, MI, or coronary revascularization (n=875)	1.89 (1.68–2.13)	<0.001	1.40 (1.21–1.62)	<0.001
Cardiac hospitalizations (n=1022)	1.9 (1.69–2.14)	<0.001	1.57 (1.37–1.80)	<0.001

Adjusted Cox regression model for age, sex, race, body mass index, smoking, diabetes mellitus, hypertension, hyperlipidemia, heart failure, estimated glomerular filtration rate, statin use, antiplatelet therapy, angiotensin pathway antagonist use, β-blocker therapy, and coronary artery disease severity (Gensini score). CI indicates confidence interval; HR, hazard ratio; hsTnI, high-sensitivity troponin I; and MI, myocardial infarction.

angiographic CAD and its adverse outcomes. hsTnI levels are higher in those with greater severity of CAD, confirmed by the number of narrowed coronary arteries or angiographic atherosclerotic burden, independent of cardiovascular risk factors. Furthermore, for the first time, we found a robust association between hsTnI and CAD progression. More

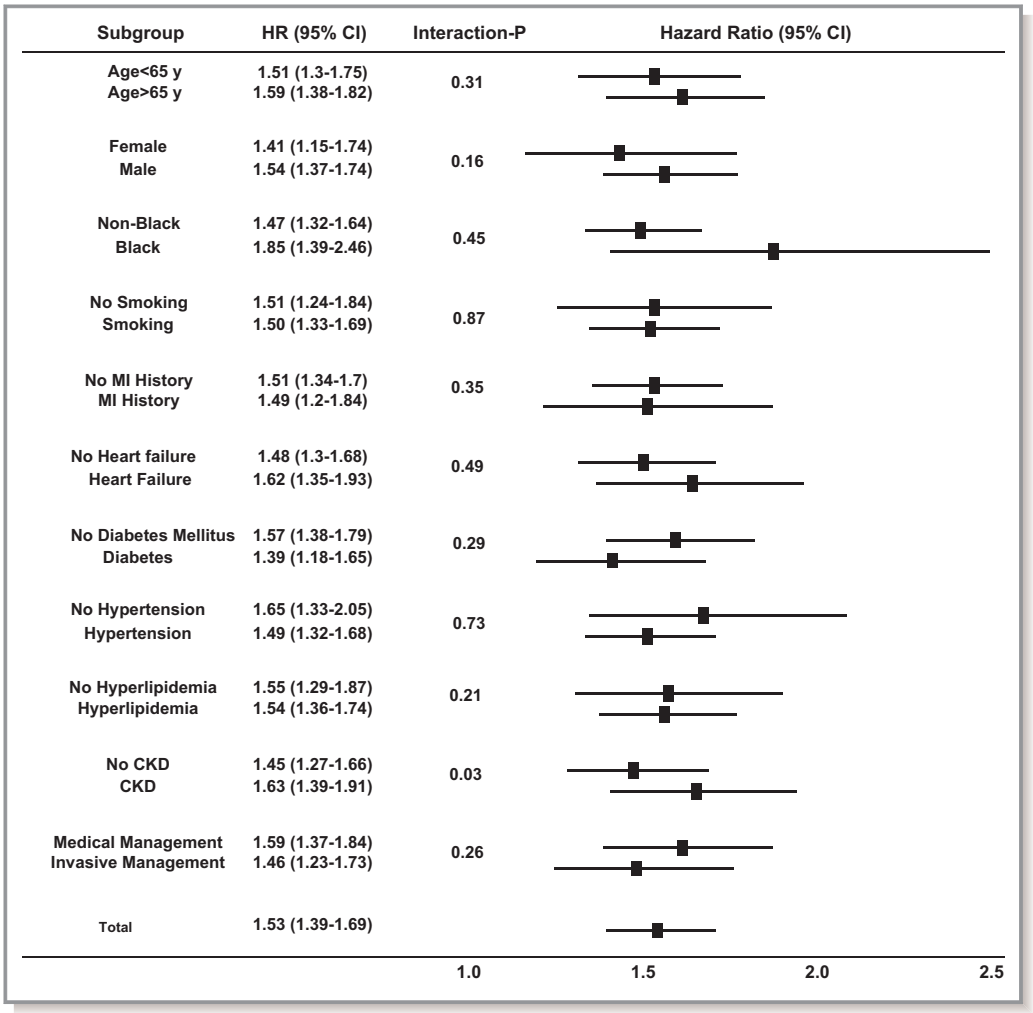

Figure 3. Forest plot interaction of high-sensitivity troponin I with clinical covariates for the outcomes of death. CI indicates confidence interval; CKD, chronic kidney disease; HR, hazard ratio; and MI, myocardial infarction.

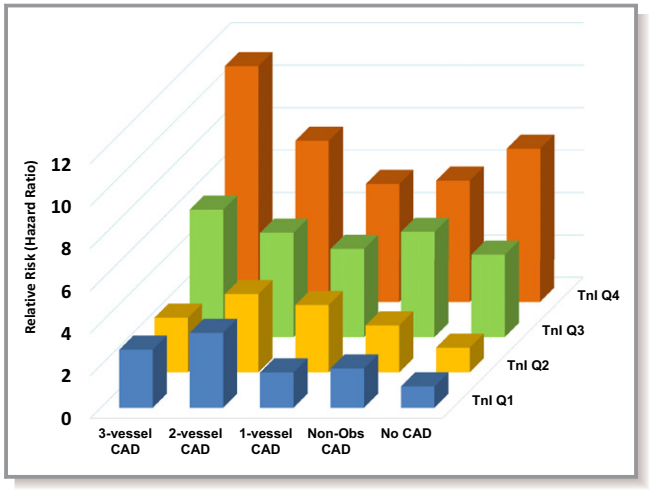

Figure 4. Relative risk (hazard ratio) of cardiovascular death/myocardial infarction in combined strata of coronary artery disease (CAD) severity and high-sensitivity troponin I quartiles. Non-Obs indicates nonobstructive; and TnI, troponin I.

important, our data showed that hsTnI is a strong predictor of incident mortality and morbidity, independent of and additive to CAD severity. Thus, compared with those in the lowest quartile, patients in the highest quartile of hsTnI levels had an adjusted >4-fold increased risk of cardiovascular death during follow-up. hsTnI significantly improved discrimination of future cardiovascular outcomes over a standard clinical model, as evidenced by improvement in the C-statistic, integrated discrimination improvement, and net reclassification improvement.

Although hsTnI has been extensively studied in populations with and without cardiovascular disease, its relationship to CAD severity has only been explored in few studies with limited numbers of patients. hsTnI was found to be associated with angiographic and computed tomographic CAD severity in few smaller studies.[9–12,22] We confirmed the association between hsTnI levels and comprehensively analyzed angiographic native CAD severity in a much larger population.

Elevated circulating levels of hsTnI do not necessarily implicate myocardial cell death.[23–27] Increased metabolic demand of the heart can lead to cleavage and release of cardiac hsTnI. In addition, microinjury caused by dislodgement of thrombi in small coronary vessels could be a potential cause for elevated levels of hsTnI and may explain the observation that more severe CAD was associated with higher hsTnI level.[12,28]

Another important finding is the association between the elevated hsTnI level and accelerated coronary atherosclerosis. Higher hsTnI levels were associated with progression in terms of both frequency and severity. Those in the highest quartile of hsTnI levels had >3-fold higher rate of CAD progression. As previously reported, CAD progression was not predicted by hs-CRP level,[29,30] a finding that may be explained by the fact that the gradual progression of CAD may not be associated with inflammation to the same extent as an abrupt progression of a vulnerable and inflamed plaque. Although previous studies showed the prognostic utility of hsTnI in CAD populations from large trials, including HOPE (Heart Outcomes Prevention Evaluation) and PEACE (Prevention of Events With Angiotensin Converting Enzyme Inhibition), none of them adjusted for the underlying severity of CAD.[31,32] In this cohort of >3000 patients who were carefully phenotyped for CAD severity, we demonstrate strong predictive value of hsTnI levels for all cardiovascular outcomes independent of and additive to CAD severity. Thus, in comparison to those without CAD with hsTnI levels in the lowest quartile, those with 3-vessel CAD and hsTnI levels in the highest quartile had >11-fold higher mortality.

Using receiver-operating curve analysis, we found 5.2 pg/mL to be the optimal cutoff in a population enriched for CAD. Interestingly, this corresponds to the same cutoff identified by a recent study of patients without established CAD.[33] hsTnI levels are modifiable by interventions such as statin use, and these changes are predictive of outcomes, as shown in previous studies.[4,33] Therefore, hsTnI could serve as a potential surrogate biomarker to monitor therapeutic responses in patients with CAD. This can be addressed in an adequately powered randomized clinical trial.

Our study has important strengths, including a large cohort size with detailed phenotyping of CAD burden, long-term follow-up with a large number of incident cardiovascular events, and exploration of the interaction of hsTnI levels with CAD severity. Although coronary angiography remains the gold standard for documenting the severity of CAD, the selection of patients for repeated angiography and its timing may have introduced bias because only subjects with symptoms were undergoing repeated angiography. This may have selected a cohort with more comorbidities and advanced CAD. As a consequence, we may have overestimated the true overall incidence of CAD progression. Nevertheless, 31% of those who had repeated angiograms had no significant CAD progression and served as a control group and those with retrospective progression had worse clinical outcomes during follow-up. Because this was a retrospective and observational study, we are unable to establish the association between hsTnI and prospective CAD progression. Given potential selection bias and the paucity of research on CAD progression, this study generates questions that should be answered with large prospective studies.

In conclusion, an elevated hsTnI level is closely associated with more severe CAD, with its accelerated progression, and with incident adverse cardiovascular events, independent of other clinical risk factors and hs-CRP levels. This study provides additional support for the potential role of hsTnI as a

marker of the presence, progression, and outcomes in CAD. Whether more aggressive treatment aimed at reducing hsTnI levels can positively alter disease course requires further investigation.

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Disclosures

None.

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