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Use of High-Sensitivity Cardiac Troponin for the Exclusion of Inducible Myocardial Ischemia:

A Cohort Study

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Abstract

Background: Many patients with coronary artery disease (CAD) are routinely referred for surveillance stress testing despite recommendations against it.

Objective: To determine whether low levels of resting high-sensitivity cardiac troponin I (hs-cTnI) can identify persons without inducible myocardial ischemia.

Design: Observational study.

Setting: A university-affiliated hospital network.

Patients: Persons with stable CAD: 589 in the derivation group and 118 in the validation cohort.

Measurements: Presence of inducible myocardial ischemia was determined by myocardial perfusion imaging with technetium-99m single-photon emission computed tomography during either treadmill or pharmacologic stress testing. Resting plasma hs-cTnI was measured within 1 week of the stress test, and the negative predictive value (NPV) for inducible ischemia was calculated. The derivation cohort was followed for 3 years for incident cardiovascular death and myocardial infarction.

Results: In the derivation cohort, 10 of 101 patients with an hs-cTnI level below 2.5 pg/mL had inducible myocardial ischemia (NPV, 90% [95% CI, 83% to 95%]) and 3 of 101 had inducible ischemia involving at least 10% of the myocardium (NPV, 97% [CI, 92% to 99%]). In the validation cohort, 4 of 32 patients with an hs-cTnI level below 2.5 pg/mL had inducible ischemia (NPV, 88% [CI, 71% to 96%]) and 2 of 32 had ischemia of 10% or greater (NPV, 94% [CI, 79% to 99%]). After a median follow-up of 3 years in the derivation cohort, no adverse events occurred in patients with an hs-cTnI level below 2.5 pg/mL, compared with 33 (7%) cardiovascular deaths or incident myocardial infarctions among those with an hs-cTnI level of 2.5 pg/mL or greater.

Limitation: The data may not be applicable to a population without known CAD or to persons with unstable angina, and the modest sample sizes warrant further validation in a larger cohort.

Conclusion: Very low hs-cTnI levels may be useful in excluding inducible myocardial ischemia in patients with stable CAD.

Primary Funding Source: National Institutes of Health.

Although cardiac stress testing is useful in diagnosing and managing coronary artery disease (CAD), it is expensive and commonly overused (1). Of the 3.8 million cardiac stress tests performed annually in the United States, 30% of those with imaging and 14% of those without it are considered inappropriate (2). In particular, the current guidelines recommend

against routine surveillance cardiac stress testing in persons with known, stable ischemic heart disease unless it is done to evaluate new or progressive symptoms (3). Yet, evidence suggests that inappropriate use of surveillance stress testing continues, even among persons with known, stable CAD. For example, 40% to 50% of patients who underwent recent coronary revascularization had elective stress testing within 2 years of the procedure (4, 5), despite the low diagnostic yield of such testing (6). Thus, more effective risk stratification of patients with known, stable CAD would be useful to reduce unnecessary stress testing.

The newly developed high-sensitivity cardiac troponin (hs-cTn) assays can measure troponin concentrations substantially lower than those detected by conventional assays (7–9). With improved sensitivity and precision at low concentrations, the hs-cTn assay is useful to stratify risk in patients with CAD in various clinical settings. The U.S. Food and Drug Administration approved hs-cTn to diagnose acute myocardial infarction (10, 11). A level lower than 5 pg/mL identifies low-risk patients in whom myocardial infarction can be safely excluded (12). In patients with stable CAD, higher hs-cTn levels can predict atherosclerotic severity (13–16), CAD progression (15), and incident adverse outcomes (15, 17–19). Finally, among patients undergoing cardiac stress testing, higher levels of hs-cTnI are associated with inducible myocardial ischemia (20–28). Therefore, in light of the overuse of cardiac stress testing in patients with stable CAD, the hs-cTnI assay may offer a valuable strategy to effectively identify a low-risk subgroup without inducible myocardial ischemia.

Using separate derivation and validation cohorts, we sought to test the diagnostic performance of hs-cTnI levels in ruling out inducible myocardial ischemia in patients with largely asymptomatic, stable CAD. We hypothesized that a low hs-cTnI level would identify patients with CAD who have a low likelihood of inducible myocardial ischemia.

Methods

Study Population

The current investigation examined 2 similar but distinct cohorts of patients with CAD. The derivation cohort was enrolled in the Mental Stress Ischemia Prognosis Study, which recruited patients with stable CAD between June 2011 and August 2014 at Emory University–affiliated hospitals (29). Presence of CAD in the derivation cohort was defined by an abnormal coronary angiogram demonstrating evidence of atherosclerosis with at least luminal irregularities, documented previous percutaneous or surgical coronary revascularization, documented myocardial infarction, or a positive stress test result. The validation cohort was enrolled between June 2012 and May 2016 in the MIMS (Mental Stress and Myocardial Ischemia After MI: Sex Differences and Mechanisms) study, which recruited patients who survived a myocardial infarction in the past 6 months. In both groups, patients with acute coronary syndrome or decompensated heart failure in the past 2 months, end-stage renal disease, or unstable psychiatric conditions were excluded. Clinical information, including previous CAD events, CAD risk factors, coronary angiography results, and current medications, was documented by using standardized questionnaires and chart reviews. Estimated glomerular filtration rate was calculated by means of the Chronic Kidney Disease Epidemiology Collaboration equation (30). The research protocols were approved by the institutional review board at Emory University, and all participants provided

informed consent. In both studies, patients were tested in the morning after a 12-hour fast. Antianginal medications (β -blockers, calcium-channel blockers, and long-acting nitrates) were withheld for 24 hours before stress testing. Angina frequency during daily life was assessed with the validated Seattle Angina Questionnaire angina frequency subscale ($n = 586$), which measures the frequency of angina and use of nitroglycerin for chest pain during the previous 4 weeks (31, 32).

Myocardial Perfusion Imaging

Myocardial perfusion imaging with technetium-99m (^{99m}Tc)-sestamibi single-photon emission computed tomography (SPECT) was performed during conventional (exercise or pharmacologic) stress according to standard protocols (33). Exercise stress testing was conducted according to the Bruce protocol; patients in whom exercise stress was contraindicated had pharmacologic testing with regadenoson. Xanthine derivatives and caffeine-containing products were discontinued 48 and 12 hours, respectively, before testing. About 20 to 30 mCi of ^{99m}Tc radioisotope was injected at peak exertion during the exercise test or immediately after the regadenoson injection. Patients continued exercising for at least 1 minute after the injection. Stress images were acquired 30 to 60 minutes later by conventional methods (34). Studies were interpreted by 2 experienced readers without previous knowledge of CAD severity or other patient medical history. Discrepancies in interpreting SPECT images were resolved by consensus. Rest and stress images were compared visually for number and severity of perfusion defects by using a 17-segment model. Each segment was scored from 0 to 4, with 0 being normal uptake; 1, possibly normal perfusion; 2, definitely abnormal perfusion; 3, severe perfusion defect; and 4, no uptake. Inducible myocardial ischemia was defined as a new perfusion defect with a score of 2 or greater in any segment during exercise that was not present at rest, or as worsening of a preexisting impairment by at least 2 points if in a single segment or at least 1 point if in 2 or more contiguous segments (35). We calculated the percentage of myocardium with resting perfusion defects as $[\text{stress resting score} \div 68] \times 100$ and percentage of ischemic myocardium as $[\text{stress difference score} \div 68] \times 100$, as previously described (36).

hs-cTnI Assay

Patients had fasting venous blood drawn at rest on a separate visit within 1 week of their stress test. For 60% of the derivation and 78% of the validation cohorts, the blood draw preceded the stress test, whereas for 40% of the derivation and 22% of the validation cohorts, the stress test preceded the blood draw. Samples were processed and stored at -80°C . Plasma hs-cTnI was measured by using the Architect STAT Troponin-I assay (Abbott Laboratories), which has a lower limit of detection of 1.2 pg/mL and an interassay coefficient of variation of less than 10% at 4.7 pg/mL. The upper reference limit (99th centile) ranges from 24 to 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 (9, 37–39).

Long-Term Follow-up

Adjudicated events (cardiovascular death; myocardial infarction; and coronary revascularization, including percutaneous coronary intervention or coronary artery bypass grafting) were ascertained for the derivation cohort after enrollment. Mortality data were

collected during follow-up clinic visits at 1 and 2 years, phone calls at 3 years, medical records review, and queries to the Social Security Death Index. The primary end point of follow-up was a combined outcome of cardiovascular death or myocardial infarction. Cardiovascular death was defined as death attributable to an ischemic cardiovascular cause (fatal myocardial infarction), cardiac arrhythmia (including resuscitated), congestive heart failure, or a cardiac procedure (coronary artery bypass grafting or angioplasty). All events identified were adjudicated by study investigators (A.A.Q., A.J.S., and M.H.) who were blinded to the stress test data.

Statistical Analysis

Levels of hs-cTnI are reported as median (interquartile range [IQR]), and Mann–Whitney and Kruskal–Wallis tests were used to compare hs-cTnI levels between participants with and those without inducible myocardial ischemia as well as according to the severity of ischemic burden. Natural log transformation was applied to hs-cTnI, and linear regression was used to study factors associated with hs-cTnI. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with 95% exact binomial CIs for all cutoff values of hs-cTnI from 1.5 to 3.0 pg/mL in increments of 0.1 pg/mL. We identified the hs-cTnI value that yielded a clinically acceptable NPV (>90%) and had the largest total number of negative results while meeting the minimum acceptable sensitivity (>90%) for detecting ischemia. Finally, we calculated the aforementioned parameters in relation to ischemia involving at least 10% of the myocardium, a cut point of clinically high-risk ischemia used in the literature, with an approximately 4.9% annual rate of adverse cardiac events (40). We compared the numbers of incident adverse events during follow-up between participants with hs-cTnI levels below and above the selected cutoff. Of note, because the nature of our investigation was a secondary exploratory analysis using existing data sets, we did not perform power calculation beforehand. All analyses were conducted by using R, version 3.5.1 (The R Foundation). Statistical significance was defined as $P < 0.050$ for all analyses.

Role of the Funding Source

The National Institutes of Health (NIH) had no role in the design, conduct, data management, or interpretation of the analysis or in the decision to submit the manuscript for publication.

Results

Derivation Cohort

The 589 patients enrolled in the derivation cohort had a mean age of 63 years (SD, 9); 76% were men, 36% had a previous myocardial infarction, and 69.3% underwent exercise treadmill testing while the remainder had pharmacologic stress testing. Most patients were asymptomatic, with no chest pain (72%) or nitroglycerin use (88%) during the previous 30 days. Thirty-five percent of patients had a reversible perfusion defect during stress testing, indicating inducible myocardial ischemia. These patients had a higher prevalence of coronary artery bypass grafting and heart failure and a slightly lower ejection fraction (Table 1).

All patients had detectable hs-cTnI levels, ranging from 1.3 to 377.9 pg/mL, with a median value of 4.3 pg/mL (IQR, 2.8 to 7.2 pg/mL). Only 24 patients had an hs-cTnI level above the assay's 99th percentile cutoff of 24 pg/mL. Black race, lower estimated glomerular filtration rate, lower ejection fraction, and resting perfusion defects (myocardial scar) were all independently associated with higher hs-cTnI levels (Appendix Table 1, available at [Annals.org](https://www.annals.org)).

hs-cTnI Levels and Inducible Myocardial Ischemia—As we previously reported in this cohort (27), patients with inducible myocardial ischemia had higher hs-cTnI levels than those without it (5.4 pg/mL [IQR, 3.9 to 9.2 pg/mL] vs. 3.9 pg/mL [IQR, 2.5 to 6.5 pg/mL]; $P < 0.001$), even after adjustment for the aforementioned covariates ($P < 0.001$).

Furthermore, patients with a larger ischemic burden had higher hs-cTnI levels; thus, compared with patients without inducible ischemia, those with perfusion defects involving 1% to 10% ($n = 137$) or 10% or more ($n = 88$) of the myocardium had approximately 32% and 51% higher hs-cTnI levels, respectively (Kruskal–Wallis test, $P < 0.001$; post hoc pairwise test, $P < 0.001$ for both).

Performance Characteristics—The specificity, sensitivity, NPV, and PPV for inducible myocardial ischemia were calculated for hs-cTnI levels between 1.5 pg/mL and 3.0 pg/mL (Table 2). With the minimum sensitivity threshold of 90%, the cutoff of 2.5 pg/mL provided the highest NPV—90% (95% CI, 83% to 95%)—with the largest number of total negative results (17%). Likewise, to detect ischemia of 10% or greater, a cutoff below 2.5 pg/mL had an NPV of 97% (CI, 92% to 99%) with the largest number of total negatives (17%) within the minimum sensitivity threshold of 90% or greater. Thus, among patients with an hs-cTnI level below 2.5 pg/mL (17% of the total cohort), 10% (CI, 5% to 17%) had an inducible ischemic defect and 3% (CI, 1% to 8%) had ischemia involving 10% or more of the myocardium, whereas the remaining 90% and 97%, respectively, did not.

We performed further sensitivity analyses to compare the performance of the 2.5-pg/mL cutoff across various patient phenotypes and observed a relatively consistent NPV across different groups (Table 3). However, our results suggest higher NPVs among patients without underlying myocardial scar (resting defect). For example, among patients without a resting perfusion defect ($n = 338$), 79 of 85 with an hs-cTnI level below 2.5 pg/mL had no inducible ischemia (NPV, 93% [CI, 85% to 97%]), whereas 12 of 16 of those with a resting defect did not have inducible ischemia (NPV, 75% [CI, 48% to 93%]). A similar pattern was observed in the NPVs of the 2.5-pg/mL cutoff for ruling out ischemia of 10% or greater: 99% (CI, 94% to 100%) and 88% (CI, 62% to 98%), respectively. Also, the performance of this cutoff value seemed to be similar when examined within subgroups meeting the individual inclusion criteria of stable CAD (Table 3).

Validation Cohort

In the 118-patient validation cohort, the median hs-cTnI level was 4.8 pg/mL (IQR, 2.4 to 12.7 pg/mL) and 28 patients (24%) developed inducible myocardial ischemia during stress testing (Appendix Table 2, available at [Annals.org](https://www.annals.org)). Compared with participants in the derivation cohort, those in the validation group tended to be younger (51 years [SD, 7]) and

were less likely to be male (56%). In addition, by the cohort inclusion criteria, all participants had survived a recent myocardial infarction and more patients had previous percutaneous coronary intervention (70%) and were receiving clopidogrel (70%).

Patients with inducible myocardial ischemia had higher hs-cTnI levels (median, 8.2 pg/mL [IQR, 4.1 to 14.1 pg/mL] vs. 3.6 pg/mL [IQR, 2.2 to 9.7 pg/mL]; $P < 0.016$), and the levels increased with the percentage of ischemic defect (10% higher hs-cTnI level with each 10% increase in inducible ischemic defect size). Appendix Table 3 (available at [Annals.org](https://www.annals.org)) shows the sensitivity, specificity, PPV, and NPV for inducible ischemia at different hs-cTnI cutoff values. Among 32 patients (27%) in the validation cohort who had an hs-cTnI level below the cutoff derived from the derivation cohort (<2.5 pg/mL), 4 had inducible ischemia (NPV, 88% [CI, 71% to 96%]) (90% in the derivation cohort) and 2 had an inducible ischemic defect of 10% or greater (NPV, 94% [CI, 79% to 99%]) (97% in the derivation cohort). As in the derivation cohort, these results suggest that a potentially higher NPV for excluding inducible ischemia was found among patients without a resting perfusion defect. Of 28 participants with an hs-cTnI level below 2.5 pg/mL and no resting perfusion defect, only 1 had inducible ischemia and none had ischemia of 10% or greater.

hs-cTnI Levels and Adverse Cardiovascular Events in the Derivation Cohort

After a median follow-up of 3.0 years (IQR, 3.0 to 3.1 years), 79 patients had adverse cardiovascular events (14 cardiovascular deaths, 23 myocardial infarctions, and 69 revascularizations) whereas 8 died of non-cardiovascular causes. During follow-up, no patients (0%) with an hs-cTnI level below 2.5 pg/mL and 33 (7%) with a level of 2.5 pg/mL or greater had cardiovascular death or myocardial infarction (Table 4). Ten patients (10%) with an hs-cTnI level below 2.5 pg/mL and 59 (12%) with a level of 2.5 pg/mL or greater required coronary revascularization during follow-up. Among the 10 patients who had an hs-cTnI level below 2.5 pg/mL and required revascularization during follow-up, only 1 patient had inducible myocardial ischemia at enrollment.

Discussion

In patients with established CAD, we found that low circulating levels of hs-cTnI have a high NPV for excluding inducible myocardial ischemia during stress testing. In the derivation and validation cohorts, 17% and 27% of patients, respectively, had hs-cTnI levels below 2.5 pg/mL. Of these, only 10% and 12% had any evidence of inducible myocardial ischemia, whereas 3% and 6% had evidence of clinically significant inducible ischemia ($>10\%$ defect). Thus, on the basis of the CIs of our estimates, this cutoff value ruled out inducible myocardial ischemia in at least 71% to 83% of patients and ischemic defect of 10% or greater in 79% to 92% of patients. To our knowledge, this is the first study in patients with known, stable CAD to show that an hs-cTnI cutoff below 2.5 pg/mL identifies those who are very unlikely to develop myocardial ischemia and who have no risk for adverse cardiovascular outcomes during medium-term follow-up.

Previous studies tested the performance of hs-cTn levels in excluding inducible myocardial ischemia during stress testing in patients with chest pain, but mostly in populations without CAD. In 2 studies of 138 and 714 patients with no history of CAD who were undergoing

SPECT stress testing, those with hs-cTnT levels below 4.26 pg/mL had an NPV greater than 96% and those with hs-cTnI levels lower than 1.54 pg/mL had an NPV of 92% for inducible myocardial ischemia (22, 28). In a study of 819 participants, 30% of whom had CAD, those with inducible myocardial ischemia had higher resting hs-cTnI levels, as in our study, and low hs-cTnI levels had a high NPV for ruling out inducible myocardial ischemia (26). These studies differed from ours in that they had a low prevalence of inducible myocardial ischemia and were not performed in patients with known CAD. Because the NPV of a test is inversely related to the prevalence of the disease in the population of interest, the high NPVs reported in the aforementioned studies may have been driven primarily by the low prevalence of CAD and inducible myocardial ischemia, thereby limiting their applicability to a population with CAD. In contrast, we believe our study was the first to test the performance of hs-cTnI levels exclusively in patients with known CAD or recent myocardial infarction, among whom inducible myocardial ischemia is substantially prevalent.

Conditions known to be associated with elevated hs-cTnI levels include myocarditis, severe heart failure, CAD, hypertensive crisis, and pulmonary embolism (17, 41–45). We demonstrated that hs-cTnI levels also are persistently elevated in patients with CAD who have stress-inducible myocardial ischemia. Cardiac troponins are present in the cytosol as largely structural or bound proteins with a small free cytosolic pool (6% to 8% for troponin T and 3.5% for troponin I) (46). Repeated episodes of ischemia during daily life, which often are silent, probably increase cell wall permeability as the result of wall injury or stress and release cytosolic troponin (47). Alternatively, myocardial ischemia in the presence of obstructive plaque may result in microinfarctions, leading to sustained structural troponin degradation (43, 48–50). Finally, as we showed earlier, myocardial scar, possibly as the result of ongoing myocardial stretching and remodeling, contributes to hs-cTn elevation in persons with CAD (27). Thus, low hs-cTn levels have a higher NPV in those with normal resting perfusion.

Currently, risk estimation based on age, sex, and presenting symptoms has been adopted by clinical guidelines on ischemic heart disease to guide decision making for cardiac stress testing. The American Heart Association recommends further work-up for patients with a pretest probability of 20% to 70% for obstructive CAD (3). However, many patients who are considered low risk or asymptomatic are still referred for cardiac stress testing, and intermittent stress testing is performed routinely in patients with stable CAD (2). Thus, an unmet need exists for more effective decision support tools to help physicians identify patients with stable CAD who are likely to benefit from cardiac stress testing. Unlike the 99th percentile cutoff for ruling in myocardial infarction, no predefined cutoff has been determined for ruling out inducible myocardial ischemia. Our data suggest that in patients with CAD without known myocardial scar, an hs-cTnI level below 2.5 pg/mL, which is present in approximately a quarter of this population, identifies a group with a 99% chance of having no clinically significant ischemia (10% of the myocardium). Moreover, none of these patients died or had an acute myocardial infarction during 3 years of follow-up.

Despite the strong NPV and sensitivity of hs-cTnI levels, the specificity (23.8%) and PPV (40.2%) for diagnosing inducible myocardial ischemia at a cutoff value of 2.5 pg/mL were low. Thus, hs-cTnI levels are not useful for determining whether inducible myocardial

ischemia is present, and if clinical suspicion exists, the patient should probably still have conventional stress testing.

Three-year follow-up of the derivation cohort demonstrated that patients with an hs-cTnI level below 2.5 pg/mL had a much lower risk for adverse cardiovascular outcomes than those with a level above this value, suggesting that low hs-cTnI levels not only safely identify patients at low risk for inducible myocardial ischemia they also predict a low incident adverse event rate. With the ability to detect lower levels of cardiac troponin than traditional troponin assays, hs-cTn measurement has emerged as a prognostic tool in patients without acute coronary syndrome. Studies have consistently shown a dose-dependent association between higher hs-cTn levels and higher adverse event rates in both the general population (51, 52) and persons with stable CAD (15, 17–19). The unique contribution of our study to the growing body of literature is the illustration that patients with low hs-cTnI levels have a very low prevalence of inducible myocardial ischemia.

Our data, however, may not be applicable to a population with unstable angina or without known CAD. Moreover, the NPV of hs-cTnI is greater in patients with asymptomatic CAD whose left ventricular function is normal and seems to be noticeably decreased in those with myocardial scar. Furthermore, given the relatively modest size of our patient samples, replication in larger cohorts would be helpful to validate our findings. Also, a subset of participants had stress testing first, followed by blood sampling within 1 week. However, previous studies showed that exercise-induced elevations in troponin levels normalize within 24 hours (53, 54), and the order of stress testing and blood sampling did not affect our results substantially. Finally, given the variability of high-sensitivity troponin assays (9), our findings may not apply to other hs-cTn testing products.

A low plasma level of hs-cTnI identifies patients with CAD who have a very low risk for myocardial ischemia during stress testing and a low medium-term risk for adverse cardiovascular events.

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Appendix

Appendix Table 1.

Demographic and Clinical Predictors of hs-cTnI Levels After Multivariable Analysis*

Demographic and Clinical Variables	Percentage of Change (95% CI)	P Value [†]
Age, per 10 years	5.73 (−1.68 to 13.71)	0.134
Male vs. female	12.39 (−2.70 to 29.82)	0.113
Race: black vs. nonblack	17.42 (1.94 to 35.26)	0.026
Previous myocardial infarction	2.90 (−9.15 to 16.54)	0.65
Hypertension	14.73 (−0.45 to 32.22)	0.058

Demographic and Clinical Variables	Percentage of Change (95% CI)	P Value [‡]
Dyslipidemia	−0.70 (−14.75 to 15.66)	0.93
Diabetes	12.12 (−1.43 to 27.52)	0.082
Smoking history [‡]	8.54 (−3.31 to 21.85)	0.165
Body mass index, per 5 kg/m ²	2.17 (−3.65 to 8.35)	0.47
eGFR, per 10 mL/min/1.73 m ² [§]	−0.43 (−0.76 to −0.09)	0.013
Ejection fraction, 10% change	−17.55 (−21.74 to −13.14)	<0.001
Resting myocardial perfusion defect	18.89 (4.08 to 35.81)	0.011

eGFR = estimated glomerular filtration rate; hs-cTnI = high-sensitivity cardiac troponin I.

* Natural log-transformed resting hs-cTnI level was regressed on the variables shown in the table by using a linear regression. Estimated percentage of change in hs-cTnI was reported.

[‡] Boldface indicates $P < 0.050$.

[‡] Data were missing for 3 participants and were excluded from the analysis.

[§] Data were missing for 18 participants and were excluded from the analysis.

Appendix Table 2.

Demographic and Clinical Characteristics of the Validation Cohort According to the Presence of Inducible Ischemia*

Characteristic	All (n = 118)	Inducible Ischemia	
		Negative (n = 90)	Positive (n = 28)
Mean age (SD), y	51 (7)	51 (7)	52 (6)
Male, n (%)	66 (56)	51 (57)	15 (54)
Black, n (%)	79 (67)	60 (67)	19 (68)
Mean body mass index (SD), kg/m ²	32 (8)	32 (8)	31 (9)
Ever smoking, n (%)	71 (60)	52 (58)	19 (68)
Hypertension, n (%)	93 (79)	70 (78)	23 (82)
Dyslipidemia, n (%)	98 (83)	74 (82)	24 (86)
Diabetes, n (%)	33 (33)	28 (31)	11 (39)
Prior myocardial infarction, n (%)	118 (100)	90 (100)	28 (100)
Prior PCI, n (%)	82 (70)	63 (70)	19 (68)
Heart failure, n (%)	12 (10)	10 (11)	2 (7)
Mean ejection fraction (SD), %	50 (12)	50 (12)	49 (12)
Medications			
ACE inhibitor, n (%)	57 (48)	42 (47)	15 (54)
Aspirin, n (%)	93 (79)	71 (79)	22 (79)
β -Blocker, n (%)	100 (85)	76 (84)	24 (86)
Calcium-channel antagonist, n (%)	21 (18)	17 (19)	4 (14)
Clopidogrel, n (%)	82 (70)	61 (68)	21 (75)
Statins, n (%)	100 (85)	75 (83)	25 (89)

ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention.

* No data are missing for any variables.

Appendix Table 3.

Performance of hs-cTnI Level in Excluding the Presence of Any Inducible Myocardial Ischemia and 10% Ischemic Defect in the Validation Cohort

Cutoff, pg/mL	True Positive, %	False Positive, %	False Negative, %	True Negative, %	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Any ischemia								
1.0	28 (24)	86 (73)	0 (0)	4 (3)	100 (88–100)	4 (1–11)	25 (17–34)	100 (40–100)
1.5	27 (23)	83 (70)	1 (1)	7 (6)	96 (82–100)	8 (3–15)	25 (17–34)	88 (47–100)
2.0	26 (22)	73 (62)	2 (2)	17 (14)	93 (76–99)	19 (11–29)	26 (18–36)	89 (67–99)
2.5	24 (20)	62 (53)	4 (3)	28 (24)	86 (67–96)	31 (22–42)	28 (19–39)	88 (71–96)
3.0	23 (19)	54 (46)	5 (4)	36 (31)	82 (63–94)	40 (30–51)	30 (20–41)	88 (74–96)
3.5	23 (19)	47 (40)	5 (4)	43 (36)	82 (63–94)	48 (37–59)	33 (22–45)	90 (77–97)
10% ischemia								
1.0	9 (8)	105 (89)	0 (0)	4 (3)	100 (66–100)	4 (1–9)	8 (4–14)	100 (40–100)
1.5	9 (8)	101 (86)	0 (0)	8 (7)	100 (66–100)	7 (3–14)	8 (4–15)	100 (63–100)
2.0	9 (8)	90 (76)	0 (0)	19 (16)	100 (66–100)	17 (11–26)	9 (4–17)	100 (82–100)
2.5	7 (6)	79 (67)	2 (2)	30 (25)	78 (40–97)	28 (19–37)	8 (3–16)	94 (79–99)
3.0	7 (6)	70 (59)	2 (2)	39 (33)	78 (40–97)	36 (27–46)	9 (4–18)	95 (83–99)
3.5	7 (6)	63 (53)	2 (2)	46 (39)	78 (40–97)	42 (33–52)	10 (4–20)	96 (86–99)

hs-cTnI = high-sensitivity cardiac troponin I; NPV = negative predictive value; PPV = positive predictive value.

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Table 1.
Demographic and Clinical Characteristics of the Derivation Cohort, by the Presence of Inducible Ischemia

Characteristic	All (<i>n</i> = 589)*	Inducible Ischemia	
		No (<i>n</i> = 383)	Yes (<i>n</i> = 206)
Mean age (SD), <i>y</i>	63 (9)	63 (9)	63 (9)
Male, <i>n</i> (%)	449 (76)	283 (74)	166 (81)
Black, <i>n</i> (%)	159 (27)	101 (26)	58 (28)
Mean body mass index (SD), <i>kg/m</i> ²	30 (5)	30 (5)	30 (5)
Ever smoking, <i>n</i> (%) [†]	345 (59)	220 (58)	125 (61)
Hypertension, <i>n</i> (%)	442 (75)	286 (75)	156 (76)
Dyslipidemia, <i>n</i> (%)	477 (81)	306 (80)	171 (83)
Mean eGFR (SD), <i>mL/min/1.73 m</i> ² [‡]	79 (19)	78 (18)	80 (20)
Diabetes, <i>n</i> (%)	186 (32)	112 (29)	74 (36)
Heart failure, <i>n</i> (%)	136 (23)	72 (19)	64 (31)
Mean ejection fraction using SPECT (SD), %	68 (13)	70 (13)	66 (14)
CAD history (inclusion criteria), <i>n</i> (%) [§]			
Abnormal findings on angiography	358 (66)	245 (69)	113 (60)
Prior myocardial infarction	213 (36)	140 (37)	73 (35)
Coronary artery bypass grafting	191 (32)	101 (26)	90 (44)
PCI	322 (55)	205 (54)	117 (57)
Abnormal results on exercise stress testing	72 (13)	53 (15)	19 (10)
Abnormal results on nuclear stress testing	70 (13)	43 (12)	27 (14)
Medications, <i>n</i> (%)			
ACE inhibitor	271 (46)	170 (44)	101 (49)
Angiotensin-receptor antagonists	94 (16)	64 (17)	30 (15)
Aspirin	508 (86)	331 (86)	177 (86)
β -Blocker	435 (74)	281 (73)	154 (75)
Calcium antagonist	128 (22)	88 (23)	40 (20)
Clopidogrel	203 (35)	124 (32)	79 (39)
Statins	502 (85)	326 (85)	176 (86)

Characteristic	All (<i>n</i> = 589) [*]	Inducible Ischemia No (<i>n</i> = 383)	Yes (<i>n</i> = 206)
Responses on the angina questionnaire, <i>n</i> (%) [†]			
Any chest pain in the past 30 d	165 (28)	98 (26)	67 (33)
Nitroglycerin use in the past 30 d	71 (12)	39 (10)	32 (16)

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography.

^{*}Data overlap with those from a previous publication using the same cohort (27).

[†]Data were unavailable for 3 participants without inducible ischemia.

[‡]Data were unavailable for 12 and 6 participants without and with inducible ischemia, respectively.

[§]Participants had to meet 1 criterion to enroll in the cohort. Data from previous angiography and stress testing were unavailable for 45 participants.

^{||}Data were unavailable for 1 participant with inducible ischemia.

Table 2.

Performance of hs-cTnI Level in Excluding the Presence of Any Inducible Myocardial Ischemia and a 10% Ischemic Defect in the Derivation Cohort*

hs-cTnI Cutoff, pg/mL	True-Positive Result, n (%)	False-Positive Result, n (%)	False-Negative Result, n (%)	True-Negative Result, n (%)	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Any ischemia								
1.5	206 (35)	377 (64)	0 (0)	6 (1)	100 (98–100)	2 (1–3)	35 (31–39)	100 (54–100)
1.6	205 (35)	370 (63)	1 (0)	13 (2)	100 (97–100)	3 (2–6)	36 (32–40)	93 (66–100)
1.7	204 (35)	368 (62)	2 (0)	15 (3)	99 (97–100)	4 (2–6)	36 (32–40)	88 (64–99)
1.8	204 (35)	366 (62)	2 (0)	17 (3)	99 (97–100)	4 (3–7)	36 (32–40)	89 (67–99)
1.9	204 (35)	359 (61)	2 (0)	24 (4)	99 (97–100)	6 (4–9)	36 (32–40)	92 (75–99)
2.0	202 (34)	349 (59)	4 (1)	34 (6)	98 (95–99)	9 (6–12)	37 (33–41)	89 (75–97)
2.1	201 (34)	330 (56)	5 (1)	53 (9)	98 (94–99)	14 (11–18)	38 (34–42)	91 (81–97)
2.2	200 (34)	323 (55)	6 (1)	60 (10)	97 (94–99)	16 (12–20)	38 (34–43)	91 (81–97)
2.3	198 (34)	314 (53)	8 (1)	69 (12)	96 (92–98)	18 (14–22)	39 (34–43)	90 (81–95)
2.4	197 (33)	298 (51)	9 (2)	85 (14)	96 (92–98)	22 (18–27)	40 (35–44)	90 (83–96)
2.5	196 (33)	292 (50)	10 (2)	91 (15)	95 (91–98)	24 (20–28)	40 (36–45)	90 (83–95)
2.6	189 (32)	286 (49)	17 (3)	97 (16)	92 (87–95)	25 (21–30)	40 (35–44)	85 (77–91)
2.7	186 (32)	274 (47)	20 (3)	109 (19)	90 (85–94)	28 (24–33)	40 (36–45)	84 (77–90)
2.8	185 (31)	266 (45)	21 (4)	117 (20)	90 (85–94)	31 (26–35)	41 (36–46)	85 (78–90)
2.9	181 (31)	260 (44)	25 (4)	123 (21)	88 (83–92)	32 (27–37)	41 (36–46)	83 (76–89)
3.0	180 (31)	253 (43)	26 (4)	130 (22)	87 (82–92)	34 (29–39)	42 (37–46)	83 (77–89)
10% ischemia								
1.5	88 (15)	495 (84)	0 (0)	6 (1)	100 (96–100)	1 (0–3)	15 (12–18)	100 (54–100)
1.6	88 (15)	487 (83)	0 (0)	14 (2)	100 (96–100)	3 (2–5)	15 (12–19)	100 (77–100)
1.7	88 (15)	484 (82)	0 (0)	17 (3)	100 (96–100)	3 (2–5)	15 (13–19)	100 (80–100)
1.8	88 (15)	482 (82)	0 (0)	19 (3)	100 (96–100)	4 (2–6)	15 (13–19)	100 (82–100)
1.9	88 (15)	475 (81)	0 (0)	26 (4)	100 (96–100)	5 (3–8)	16 (13–19)	100 (87–100)
2.0	87 (15)	464 (79)	1 (0)	37 (6)	99 (94–100)	7 (5–10)	16 (13–19)	97 (86–100)
2.1	87 (15)	444 (75)	1 (0)	57 (10)	99 (94–100)	11 (9–14)	16 (13–20)	98 (91–100)
2.2	87 (15)	436 (74)	1 (0)	65 (11)	99 (94–100)	13 (10–16)	17 (14–20)	98 (92–100)
2.3	86 (15)	426 (72)	2 (0)	75 (13)	98 (92–100)	15 (12–18)	17 (14–20)	97 (91–100)
2.4	86 (15)	409 (69)	2 (0)	92 (16)	98 (92–100)	18 (15–22)	17 (14–21)	98 (93–100)

hs-cTnI Cutoff, pg/mL	True-Positive Result, <i>n</i> (%)	False-Positive Result, <i>n</i> (%)	False-Negative Result, <i>n</i> (%)	True-Negative Result, <i>n</i> (%)	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
2.5	85 (14)	403 (68)	3 (1)	98 (17)	97 (90–99)	20 (16–23)	17 (14–21)	97 (92–99)
2.6	83 (14)	392 (67)	5 (1)	109 (19)	94 (87–98)	22 (18–26)	17 (14–21)	96 (90–99)
2.7	83 (14)	377 (64)	5 (1)	124 (21)	94 (87–98)	25 (21–29)	18 (15–22)	96 (91–99)
2.8	82 (14)	369 (63)	6 (1)	132 (22)	93 (86–97)	26 (23–30)	18 (15–22)	96 (91–98)
2.9	79 (13)	362 (61)	9 (2)	139 (24)	90 (81–95)	28 (24–32)	18 (14–22)	94 (89–97)
3.0	79 (13)	354 (60)	9 (2)	147 (25)	90 (81–95)	29 (25–34)	18 (15–22)	94 (89–97)

hs-cTnI = high-sensitivity cardiac troponin I; NPV = negative predictive value; PPV = positive predictive value.

* Boldface indicates the cutoff value (2.5 pg/mL) that yielded the highest NPV and the most negative results within the minimum sensitivity threshold of 90%.

Table 3.

NPVs of a 2.5-pg/mL hs-cTnI Cutoff in Subsets of Patients Developing Any Ischemia and Those Developing a 10% Ischemic Defect During Stress Testing

Subgroup of Patients	Any Ischemia				10% Ischemia			
	True-Positive Result, n (%)	False-Positive Result, n (%)	False-Negative Result, n (%)	True-Negative Result, n (%)	NPV (95% CI), %	True-Positive Result, n (%)	False-Positive Result, n (%)	False-Negative Result, n (%)
Age								
<65 y	99 (31)	152 (47)	7 (2)	64 (20)	90 (81–96)	39 (12)	212 (66)	3 (1)
65 y	97 (36)	140 (52)	3 (1)	27 (10)	90 (73–98)	46 (17)	191 (72)	0 (0)
Sex								
Female	35 (25)	70 (50)	5 (4)	30 (21)	86 (70–95)	16 (11)	89 (64)	1 (1)
Male	161 (36)	222 (49)	5 (1)	61 (14)	92 (83–97)	69 (15)	314 (70)	2 (0)
Race								
Black	56 (35)	84 (53)	2 (1)	17 (11)	89 (67–99)	26 (16)	114 (72)	1 (1)
Other	140 (33)	208 (48)	8 (2)	74 (17)	90 (82–96)	59 (14)	289 (67)	2 (0)
Diabetes								
No	123 (31)	200 (50)	9 (2)	71 (18)	89 (80–95)	44 (11)	279 (69)	3 (1)
Yes	73 (39)	92 (49)	1 (1)	20 (11)	95 (76–100)	41 (22)	124 (67)	0 (0)
Previous MI								
No	127 (34)	182 (48)	6 (2)	61 (16)	91 (82–97)	58 (15)	251 (67)	2 (1)
Yes	69 (32)	110 (52)	4 (2)	30 (14)	88 (73–97)	27 (13)	152 (71)	1 (0)
Prior coronary artery bypass grafting								
No	109 (27)	202 (51)	7 (2)	80 (20)	92 (84–97)	40 (10)	271 (68)	3 (1)
Yes	87 (46)	90 (47)	3 (2)	11 (6)	79 (49–95)	45 (24)	132 (69)	0 (0)
Resting perfusion defect								
None	59 (17)	194 (57)	6 (2)	79 (23)	93 (85–97)	34 (10)	219 (65)	1 (0)
Any	137 (55)	98 (39)	4 (2)	12 (5)	75 (48–93)	51 (20)	184 (73)	2 (1)
eGFR								

Subgroup of Patients	Any Ischemia				10% Ischemia			
	True-Positive Result, n (%)	False-Positive Result, n (%)	False-Negative Result, n (%)	True-Negative Result, n (%)	NPV (95% CI), %	True-Positive Result, n (%)	False-Positive Result, n (%)	False-Negative Result, n (%)
<60 mL/min/1.73 m ²	28 (32)	53 (60)	0 (0)	7 (8)	100 (59–100)	14 (16)	67 (76)	0 (0)
60 mL/min/1.73 m ²	168 (34)	239 (48)	10 (2)	84 (17)	89 (81–95)	71 (14)	336 (67)	3 (1)
Heart failure								
No	133 (29)	230 (51)	9 (2)	81 (18)	90 (82–95)	59 (13)	304 (67)	3 (1)
Yes	63 (46)	62 (46)	1 (1)	10 (7)	91 (59–100)	26 (19)	99 (73)	0 (0)
Type of stress test								
Exercise	121 (30)	204 (50)	8 (2)	75 (18)	90 (82–96)	56 (14)	269 (66)	3 (1)
Pharmacologic	75 (41)	88 (49)	2 (1)	16 (9)	89 (65–99)	29 (16)	134 (74)	0 (0)
Nitroglycerin use over the past 30 d								
None	166 (32)	262 (51)	8 (2)	79 (15)	91 (83–96)	73 (14)	355 (69)	3 (1)
Any	30 (42)	27 (38)	2 (3)	12 (17)	86 (57–98)	12 (17)	45 (63)	0 (0)
Inclusion criteria								
Abnormal findings on angiography	106 (30)	190 (53)	7 (2)	55 (15)	89 (78–95)	41 (11)	255 (71)	3 (1)
Prior coronary artery bypass grafting	87 (46)	90 (47)	3 (2)	11 (6)	79 (49–95)	45 (24)	132 (69)	0 (0)
Prior abnormal results on nuclear testing	27 (39)	32 (46)	0 (0)	11 (16)	100 (72–100)	12 (17)	47 (67)	0 (0)
Prior PCI	111 (34)	148 (46)	6 (2)	57 (18)	90 (80–96)	44 (14)	215 (67)	2 (1)
Prior abnormal results on exercise testing	18 (25)	42 (58)	1 (1)	11 (15)	92 (62–100)	12 (17)	48 (67)	0 (0)

eGFR = estimated glomerular filtration rate; hs-cTnI = high-sensitivity cardiac troponin I; MI = myocardial infarction; NPV = negative predictive value; PCI = percutaneous coronary intervention.

Table 4.

Adverse Events During Follow-up in the Derivation Cohort, by hs-cTnI Level*

Adverse Event	All (<i>n</i> = 587)	hs-cTnI Level	
		<2.5 pg/mL (<i>n</i> = 101)	≥2.5 pg/mL (<i>n</i> = 486)
Cardiovascular death	14 (2)	0 (0)	14 (3)
All-cause death	22 (4)	0 (0)	22 (5)
Myocardial infarction	23 (4)	0 (0)	23 (5)
Revascularization	69 (12)	10 (10)	59 (12)

hs-cTnI = high-sensitivity cardiac troponin I.

* Values are numbers (percentages).