Relation of High-sensitivity Cardiac Troponin I Elevation With Exercise to Major Adverse Cardiovascular Events in Patients With Coronary Artery Disease

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High sensitive cardiac troponin I (hs-cTnI) increases with inducible myocardial ischemia in patients with coronary artery disease (CAD). We aimed to assess if the change in hs-cTnI levels with exercise stress testing is associated with major adverse cardiac events (MACE). A cohort of 365 (age 62 ± 9 years, 77% men) patients with stable CAD underwent 99mTc sestamibi myocardial perfusion imaging with treadmill testing. Plasma hs-cTnI level was measured at rest and at 45 min after stress. Multivariable Fine & Gray's subdistribution hazards models were used to determine the association between the change in hs-cTnI and MACE, a composite end point of cardiovascular death, myocardial infarction, and unstable angina requiring revascularization. During a median follow-up of 3 years, 39 (11%) patients experienced MACE. After adjustment, for each two-fold increment in hs-cTnI with stress, there was a 2.2 (95% confidence interval 1.3-3.6)-fold increase in the hazard for MACE. Presence of both a high resting hs-cTnI level (>median) and ≥ 20% stress-induced hs-cTnI elevation was associated with the highest incidence of MACE (subdistribution hazards models 4.6, 95% confidence interval 1.6 to 13.0) compared with low levels of both. Risk discrimination statistics significantly improved after addition of resting and change in hs-cTnI levels to a model including traditional risk factors and inducible ischemia (0.67 to 0.71). Conversely, adding inducible ischemia by SPECT did not significantly improve the C-statistic from a model including traditional risk factors, baseline and change in hs-cTnI (0.70 to 0.71). In stable CAD patients, higher resting levels and elevation of hs-cTnI with exercise are predictors of adverse cardiovascular outcomes beyond traditional cardiovascular risk factors and presence of inducible ischemia. **(Am J Cardiol 2020;136:1−8)**

Cardiac troponin (cTn) I and T are regulatory proteins that constitute the contractile apparatus of cardiomyocytes.[1] High circulating levels of these proteins, measured using conventional assays, signify myocardial necrosis, and form the cornerstone for the diagnosis of myocardial infarction (MI) and for guiding treatment strategies.[2] Recent technical advances have resulted in development of high-sensitivity (hs) assays that permit measurements of troponins at levels below the detection limits of conventional assays.[3] Recent findings from our group and others have shown that hs-cTn levels increase with exercise, with mental stress and with rapid atrial pacing in patients with coronary artery disease

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This work was supported by the NIH through the following grants: P01 HL101398, R01 HL109413, R01HL109413-02S1, R01HL125246, K24HL077506, K24 MH076955, UL1TR000454, KL2TR000455, K23HL127251, and T32HL130025A. High-sensitivity troponin I assays were kindly provided by Abbott Laboratories.

Disclosures: The authors A.B. and G.M. are full-time employees at Abbott. Otherwise, the authors report no biomedical financial interests or potential conflicts of interest. The sponsors of this study had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.09.019

(CAD), and these changes correlate with the magnitude of myocardial ischemia.[4,5] However, whether the magnitude of change in hs-cTn levels in patients with CAD has prognostic significance remains unknown. Our objective was to investigate the prognostic significance of an increase in hs-cTnI level with exercise testing in patients with stable CAD. We hypothesized that an increase in hs-cTnI level with exercise will be associated with adverse outcomes in patients with stable CAD, irrespective of the presence or absence of inducible myocardial ischemia.

Methods

Patients were enrolled into the MIPS (Mental Stress Ischemia Prognosis Study), a prospective study that recruited 695 patients with stable CAD between June 23, 2011 and August 5, 2014 at Emory University−affiliated hospitals. We included in the final analysis only patients that had treadmill stress testing, since we previously demonstrated that pharmacological stress testing did not significantly increase hs-cTnI levels.[4] The research protocol was approved by the institutional review board of Emory University and all participants provided informed consent. For a complete description of the study population, see Appendix S1 in the Supplementary data online.

Myocardial perfusion imaging with technetium Tc 99m sestamibi−−single-photon emission computed tomography (SPECT) was performed at rest and 60 min after physical stress according to standard protocols.[6−8] Testing was done on a dedicated SPECT camera (Philips Cardio MD) without attenuation correction. For a complete description of the SPECT images interpretation and high-sensitivity cardiac troponin I (hs-cTnI) assay, see Appendix S2 in the Supplementary data online.

Adjudicated events (cardiovascular death, MI, and unstable angina with coronary revascularization) were ascertained after enrollment. Mortality data were collected during follow-up visits at 1 and 2 years, phone calls at 3 years, medical records review, and queries from the Social Security Death Index. The primary end point of follow-up was a combined outcome of major adverse cardiovascular events (MACE) including cardiovascular death, MI, and unstable angina with coronary revascularization. Cardiovascular death was defined as death attributable to an ischemic cardiovascular cause (fatal MI), cardiac arrhythmia (including resuscitated), congestive heart failure, or a cardiac procedure (coronary artery bypass grafting or angioplasty). The patient management team did have access to the results of the exercise SPECT, but didn't have access to hs-cTn results. 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 as described previously.[9]

Descriptive data were summarized as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Two-sample Student's *t* tests and Kruskal-Wallis tests for continuous variables, and chi-square tests for categorical variables, were performed to compare those with < 20% versus ≥ 20% hs-cTnI increase with exercise. The cut-off of 20% increase in hs-cTnI was chosen in accordance with the National Academy of Clinical Biochemistry laboratory medicine practice guidelines which represents a significant (3 SD) change in hs-cTnI level on the basis of a 5% to 7% analytical coefficient of variance typical for most assays in the concentration range indicating acute MI.[10] This cut-off also approximately corresponds to the upper quartile in this population. The logarithmic transformation (base 2) was used for non-normally distributed variables (resting hs-cTnI, change in hs-cTnI, and Gensini score). Linear mixed models were used to study factors associated with the change (post-stress minus resting) in hs-cTnI levels.

To investigate the association between the change in hs-cTnI level with exercise and cardiovascular events, change in hs-cTnI was examined both as a continuous and a dichotomized (below or ≥ 20% increase) variable in Fine and Gray's subdistribution hazard models with non-cardiovascular death treated as competing risk.[11] Subjects were also divided with respect to the median resting hs-cTnI level (4 ng/L). Finally, we divided the subjects into 4 groups based on both the resting and exercise-induced change in hs-cTnI levels: (1) low resting hs-cTnI and < 20% hs-cTnI increase with stress; (2) low resting hs-cTnI and ≥ 20% hs-cTnI increase with stress; (3) high resting hs-cTnI and < 20% hs-cTnI response to stress; (4) high resting hs-cTnI and ≥ 20% hs-cTnI response to stress. Selection of factors to be included in the models was based on previous evidence of an association with hs-cTnI or cardiovascular disease events.[12] The covariates retained in the fully adjusted models included demographics factors (age, gender, and race), resting hs-cTnI, exercise-induced ischemia status, lifestyle, and clinical cardiovascular risk factors (smoking, BMI, dyslipidemia, diabetes, hypertension, heart failure, previous MI, creatinine clearance [CrCl], and Gensini score).

The C-statistic, the category-free net reclassification improvement (NRI), the NRI at the event rate, and the integrated discrimination improvement were calculated as measures of risk discrimination.[13] The NRI computes the proportions moving up or down in risk strata in cases and noncases separately. The overall NRI is the sum of improvement in each set. If cut points are based on clinical criteria, the NRI can indicate whether there are changes in risk stratification that can affect decisions regarding clinical care. The significance level for main effects and interactions was set at $p < 0.05$. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Of 365 patients with stable CAD underwent myocardial perfusion imaging with treadmill stress testing, 30% (n = 110) had exercise-induced myocardial ischemia. The sample mean age (± SD) was 62 ± 9 years, 77% were men, and 25% Black (Table 1). Patients with ≥ 20% increase in hs-cTnI with stress, compared with those with <20% increase, shared similar clinical characteristics with the exception of the presence of inducible myocardial ischemia (Table 1). In the patients with inducible myocardial ischemia, 37% had >20% increase in hs-cTnI with stress.

During exercise stress testing, compared with patients with <20% increase in hs-cTnI, those with ≥20% hs-cTnI

Table 1
Characteristics of the study population by High-Sensitivity Cardiac Troponin I (hs-cTnI) response to exercise stress testing

	Total	hs-cTnI Response		p-value*
		<20%	≥ 20%	
Variable	365	268	97	
Age (Years), Mean (SD)	62 ± 9	62 ± 9	63 ± 9	0.29
Men	282 (77%)	216 (81%)	72 (74%)	0.28
Black	92 (25%)	64 (24%)	21 (22%)	0.87
Medical history and CAD risk factors				
Current smoker	39 (11%)	27 (10%)	9 (9%)	0.94
Diabetes mellitus	100 (28%)	71 (27%)	27 (28%)	0.76
Hypertension	272 (75%)	198 (74%)	74 (76%)	0.87
Dyslipidemia	300 (83%)	218 (82%)	81 (84%)	0.75
BMI (kg/m^2), Mean (SD)	39 ± 5	29 ± 5	30 ± 4	0.24
Prior MI	141 (39%)	112 (42%)	28 (29%)	0.07
Heart failure	50 (14%)	42 (16%)	9 (9%)	0.17
Prior revascularization	190 (52%)	145 (54%)	45 (46%)	0.24
Gensini score, Median (IQR)	23 ± 42	23 ± 41	22 ± 43	0.92
CrCl (ml/min per 1.73 m^2), Mean (SD)	80 ± 18	79 ± 17	83 ± 20	0.08
Ejection fraction (%), Mean (SD)	55 ± 11	54 ± 9	56 ± 11	0.16
Inducible Ischemia	110 (30%)	73 (28%)	39 (41%)	0.03
Baseline hs-cTnI (ng/L), Median (IQR)	4.0 ± 4	4.0 ± 4	3.5 ± 3	0.49
Medications				
Aspirin	319 (88%)	239 (90%)	83 (86%)	0.51
P2Y12 inhibitors	129 (35%)	99 (37%)	30 (31%)	0.47
Beta-Blocker	257 (71%)	191 (72%)	68 (70%)	0.76
ACE Inhibitors or ARB	233 (64%)	172 (64%)	61 (63%)	0.87
Statin use	322 (89%)	239 (90%)	82 (85%)	0.23

Abbreviations - ACE = Angiotensin Converting Enzyme; ARB = Angiotensin Receptor Block; BMI = Body Mass Index; CrCl = Creatinine Clearance; Hs-cTnI = High-sensitivity Cardiac Troponin I; MI = Myocardial Infarction.

* Statistical tests - categorical variables: chi−square or Fisher's exact test; continuous variables: Student *t* test or Wilcoxon−Mann−Whitney U test, when appropriate.

in response to exercise demonstrated a significantly higher poststress systolic blood pressure (159 vs 166 mm Hg, p = 0.05) and more myocardial perfusion defects (summed stress percent, 9.3% vs. 11.7%, p=0.03) (Table 2). In linear mixed model analysis that included CAD risk factors, only the presence of inducible myocardial ischemia was independently associated with a higher increase in hs-cTnI level with stress, Supplementary data online, Table S1.

Patients were followed up for a median (interquartile range) period of 3.0 (2.9 to 3.1) years. A total of 39 patients (11%) had adverse events, including 3 cardiovascular deaths, 11 MIs, and 26 unstable angina events followed by revascularization. In both bivariate and fully adjusted Fine & Gray's models, resting hs-cTnI levels were associated with increased risk for MACE (Table 3, Figure 1). In a multivariate model adjusting for inducible ischemia, demographics, lifestyle, and clinical cardiovascular risk factors, each two-fold increment in the resting hs-cTnI level was associated with an adjusted 56% (subdistribution hazard ratio [sHR] 1.56, 95% CI 1.08 to 2.25, p = 0.02) increase in the hazard of MACE (Table 3).

When dichotomized by the median resting value of hs-cTn (4 ng/L), those with higher resting levels had worse outcomes compared with those with lower resting levels (sHR 1.66, 95% CI 1.01 to 2.73, p = 0.04), Figure 1. The results were consistent when the hs-cTnI response to the exercise stress test was dichotomized into < 20% or ≥ 20% increase. The presence of ≥ 20% hs-cTnI level increase in response to stress was associated with an adjusted sHR of 2.31 (95% CI 1.12 to 4.77, p = 0.008), Figures 1.

Finally, when subjects were divided into 4 groups based on their resting hs-cTnI levels (below or above median) and its change with exercise (<20% and ≥ 20% increase), the subgroup with concurrently high resting hs-cTnI level (≥ 4 ng/L) and ≥ 20% hs-cTnI level elevation with stress had the greatest increase in the MACE incidence (adjusted sHR 4.57, 95% CI 1.61 to 12.97, p = 0.005) compared with the reference group (low resting hs-cTnI level and < 20% increase with stress), Figure 1. The interaction between resting and change in hs-cTnI was not significant (p = 0.23).

We tested the incremental value of adding the presence of resting hs-cTnI level, change in hs-cTnI level and inducible ischemia to a model with traditional risk factors and clinical characteristics as previous models for predicting incident MACE. The C-statistic for incident MACE increased significantly when we added baseline plus change in hs-cTnI levels with exercise (from 0.67 to 0.71, p = 0.007) in a model including inducible ischemia by SPECT. However, including inducible ischemia by SPECT did not significantly improve the C-statistic from a model including baseline plus change in hs-cTnI (0.70 to 0.71, p = 0.21), Supplementary data online, Table S2. Furthermore, the NRI at the average event rate showed significant reclassification of subject risk by addition of hs-cTnI response to exercise (NRI 0.30, 95% CI 0.09 to 0.51, p = 0.006), Table 4.

Table 2
Hemodynamic responses and perfusion defects with exercise stress testing

Variable	hs-cTnI Response to Exercise		
	<20% Increase	≥ 20% Increase	p-value
Systolic blood pressure (mm Hg), Mean (SD)			
Rest	137 ± 18	138 ± 19	0.70
Post-stress	159 ± 20	166 ± 23	0.05
Systolic blood pressure reactivity	22 ± 20	26 ± 21	0.08
Diastolic blood pressure (mm Hg), Mean (SD)			
Rest	79 ± 10	80 ± 11	0.47
Post-stress	82 ± 11	85 ± 12	0.41
Diastolic blood pressure reactivity	3 ± 12	4 ± 13	0.45
Heart Rate (bpm), Mean (SD)			
Rest	66 ± 11	65 ± 12	0.82
Post-stress	116 ± 14	117 ± 14	0.46
Heart rate reactivity	50 ± 14	49 ± 14	0.45
Rate pressure product (mm Hg* bmp), Mean (SD)			
Rest	9,020 ± 2,045	9,038 ± 2,067	0.95
Post-stress	17,952 ± 4,460	18,412 ± 4,779	0.66
Rate pressure product reactivity	8,941 ± 4,294	9,374 ± 4,473	0.46
Maximum work level (MET), Median (IQR)	8.2 ± 3.7	8.7 ± 3.1	0.67
Minutes on treadmill (min), Median (IQR)	7.1 ± 3.5	7.4 ± 2.7	0.75
Perfusion defects, % of LV, Median (IQR)			
Summed rest percent (SR%)	8.0 ± 7.5	8.9 ± 7.9	0.29
Summed stress percent (SS%)	9.3 ± 8.1	11.7 ± 10.1	0.03
Summed difference percent (SD%)	3.7 ± 4.0	4.8 ± 5.1	0.05

Abbreviations - bpm = Beats per Minute; Hs-cTnI = High-sensitivity Cardiac Troponin I; IQR = Interquartile Range; MET = Metabolic Equivalent; min = Minute; mmHg = Millimeter of Mercury; SD = Standard Deviation.

* Statistical tests: Student *t* test or Wilcoxon−Mann−Whitney U test, when appropriate.

Discussion

In subjects with stable CAD, we demonstrated for the first time that the magnitude of change in hs-cTnI level after exercise stress testing is associated with adverse cardiovascular outcomes, independent of, and in addition to, the resting hs-cTnI level and the presence of myocardial ischemia detected by perfusion imaging. For each two-fold increase in cTn level with exercise, incident MACE rate more than doubled. Our results not only confirm findings from previous reports regarding the prognostic value of resting hs-cTn levels in patients with CAD, but demonstrate the added value of measuring the change in cTn levels with exercise.[6,14] Both rest and the change in hs-cTnI levels with stress were independently associated with MACE, even

Table 3
Bivariate and multivariate Sub-Distribution Hazard Ratios (sHR) and 95% Confidence Intervals (CI) for Major Adverse Cardiovascular Event (MACE) incidence by fine & gray's proportional sub-distribution hazards models

	Bivariate sHR (95% CI)	p-value	Multivariate sHR (95% CI)	p-value
Change in hs-cTnI*, per 2-fold increment	2.86 (1.37−5.94)	0.005	2.17 (1.29−3.65)	0.003
Resting hs-cTnI, per 2-fold increment	1.77 (1.31−2.41)	<0.001	1.56 (1.08−2.25)	0.02
Inducible myocardial ischemia	2.40 (1.25−4.60)	0.009	2.18 (1.04−4.57)	0.04
Age	0.99 (0.95−1.02)	0.47	1.00 (0.96−1.05)	0.90
Men	1.34 (0.59−3.06)	0.48	1.02 (0.98−1.06)	0.87
Black	1.42 (0.72−2.80)	0.32	0.99 (0.42−2.34)	0.97
Previous MI	1.29 (0.67−2.26)	0.44	1.29 (0.59−2.81)	0.52
Hypertension	0.76 (0.38−1.54)	0.44	0.66 (0.29−1.52)	0.33
Dyslipidemia	0.74 (0.34−1.62)	0.45	0.61 (0.26−1.46)	0.27
Diabetes Mellitus	1.51 (0.77−2.97)	0.22	1.47 (0.66−3.30)	0.35
Current smoker	1.74 (0.87−3.48)	0.11	1.36 (0.65−2.87)	0.42
BMI, 1 unit change	1.00 (0.94−1.06)	0.93	0.99 (0.92−1.08)	0.88
Heart failure	1.51 (0.66−3.45)	0.32	1.44 (0.57−3.67)	0.98
Creatinine clearance, 10 units change	1.27 (1.07−1.51)	0.006	1.29 (1.01−1.65)	0.04
Log CAD severity score (Gensini)	1.33 (0.94−1.91)	0.10	1.33 (0.84−1.74)	0.10

Abbreviations - BMI: Body Mass Index; CAD: Coronary Artery Disease; MI: Myocardial Infarction.

MACE defined as a combination of CV death, MI, and unstable angina with revascularization. sHR represents the risk of end points for the comparison versus the reference groups while treating non-cardiovascular death as competing risk.

* Change in hs-cTnI defined as post-stress minus baseline hs-cTnI levels.

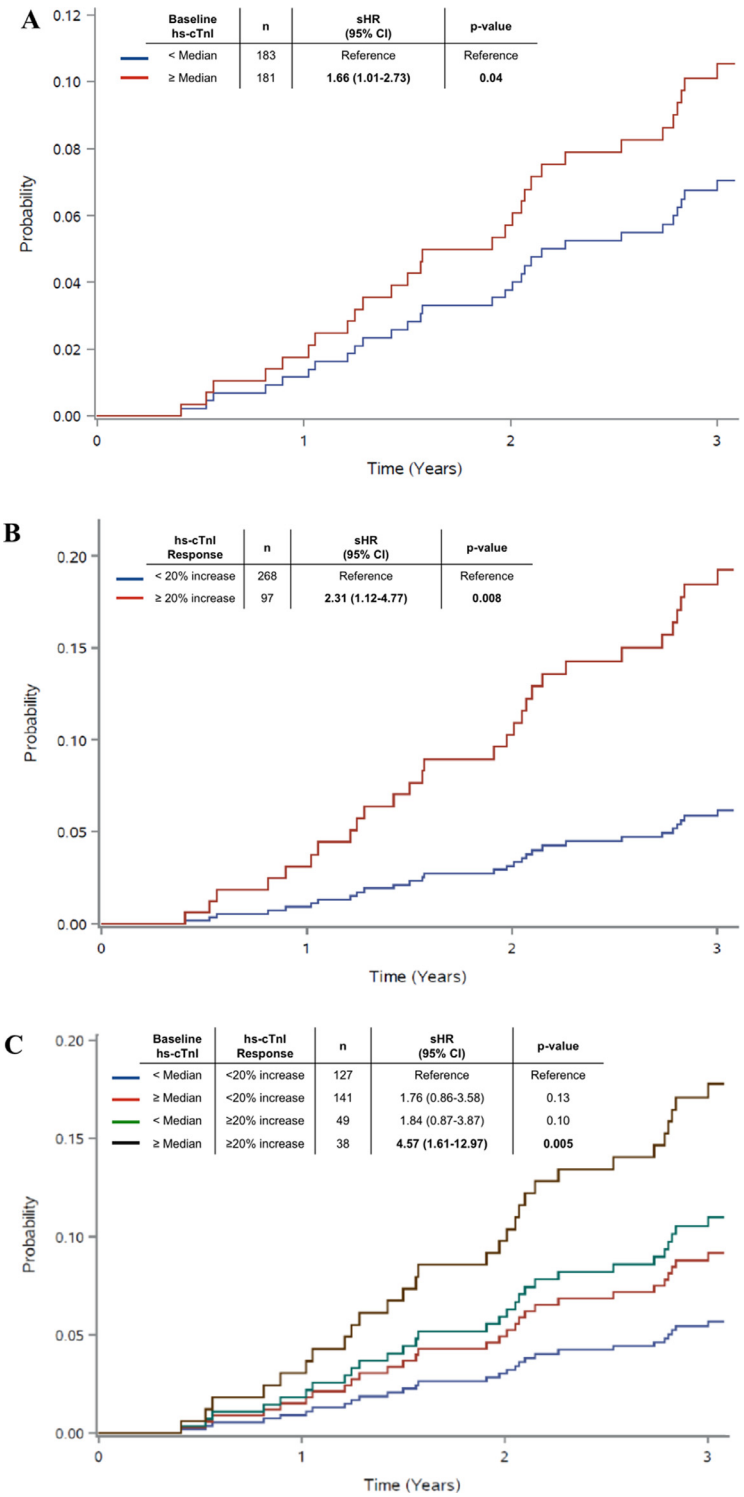

Figure 1. Adjusted cumulative incidence of Major Adverse Cardiovascular Events (MACE) by (A) Baseline (below or above median) high-sensitivity Cardiac Troponin I (hs-cTnI) (B) hs-cTnI Response to exercise stress testing (below or above 20% increase) and (C) four categories combining baseline and hs-cTnI response to stress. MACE defined as a combination of CV death, MI and unstable angina with revascularization. The median baseline hs-cTnI was 4 ng/L. sHR represents the risk of end points for the comparison versus the reference groups while treating non-cardiovascular death as competing risk. P-values were generated from cumulative incidence function homogeneity test of Gray. Abbreviations – sHR: Sub-distribution Hazard Ratio; CI: Confidence Interval.

Table 4
Net Reclassification improvement at event rate of predicted risk with the addition of hs-cTnI response to exercise

	Reclassified Predicted Risk (with hs-cTnI Response)		n (%) of Subjects Reclassified With		Net Correctly Reclassified (%)
Predicted Risk (without hs-cTnI Response)*	< 11%	≥ 11%	Increased Risk	Decreased Risk	
Subjects who experienced MACE (n = 39)					
Low risk (< 11%)	8	11	11 (28%)	4 (10%)	18%
High risk (≥ 11%)	4	16			
Subjects who did not experience MACE (n = 311)					
Low risk (< 11%)	140	41	41 (13%)	78 (25%)	12%
High risk (≥ 11%)	78	52			
Net reclassification improvement (95% CI)					0.30 (0.09−0.51) p = 0.006

Abbreviations - hs-cTnI: High-Sensitivity Cardiac Troponin I; MACE: Major Adverse Cardiovascular Event.
MACE defined as a combination of CV death, MI, and unstable angina with revascularization.
* Predicted risk based on myocardial perfusion imaging, baseline hs-cTnI, and traditional risk factors (sex, race, age, hypertension, dyslipidemia, prior MI, heart failure, body mass index, diabetes, smsoking history, high sensitivity C-reactive protein).

after adjustment for traditional risk factors, the extent of CAD, left ventricular ejection fraction, renal function, and most importantly, the presence/absence of a reversible perfusion defect.

High-sensitivity troponins are markers of increased risk for major cardiovascular events and mortality in the general population as well as in patients with stable CAD.[15,16] Greater resting hs-cTn levels are indicative of myocardial injury that may be due to a variety of conditions including myocarditis, severe heart failure, hypertensive crises, and pulmonary embolism.[17,18] This is consistent with our results demonstrating the independent prognostic value of resting hs-cTnI levels even after adjustment for traditional risk factors.[19] Importantly, addition of the change in hs-cTnI level to the resting level further improves risk prediction beyond conventional ischemia detection and improves risk reclassification. Taken together, our findings suggest that assessing not only baseline levels, but also the response of hs-cTnI to exercise stress testing, would be superior in risk stratifying patients with stable CAD possibly obviating the need for further invasive testing.

In our study, we demonstrated that hs-cTnI elevation 45 minutes after exercise was strongly associated with the presence of inducible myocardial ischemia. This association was independent of left ventricular ejection fraction, baseline hs-cTnI levels and renal function. Compared with those with < 20% increase, patients with ≥ 20% increase in hs-cTnI level had significantly more exercise-induced myocardial perfusion defects. This is in accordance with previous reports by our group and others showing that circulating levels of hs-cTnI increase after exercise stress are proportionate to the magnitude of ischemia during imaging,[4] although other studies have not confirmed these findings.[20] This discrepancy may be (1) due to differences in characteristics of the populations studied; we studied only patients with CAD whereas most of the other studies were not restricted to this population; (2) older hs-cTnI assays had inferior analytical performance at lower concentrations compared with current assay used; and (3) the timing of poststress measurements varied in the studies.[1,21]

Our findings demonstrate an independent association of MACE with resting and the change in hs-cTnI concentrations with exercise, even after adjusting for the presence of inducible ischemia by SPECT. With recent data demonstrating an association between raised hs-cTnI levels and vulnerable plaque burden, it is possible that rest and poststress hs-cTnI levels could be used to triage patients before more expensive imaging-based stress testing is employed.[22] For instance, a patient with suspected CAD with low baseline hs-cTnI levels who also did not have a significant increase in hs-cTnI with exercise could potentially be managed conservatively without the need of cardiac imaging.[6,23,24] Additionally, increased troponin levels with exercise might be a useful criterion to trigger more intensive secondary prevention strategies in those patients.[25−27] However, further studies are needed to confirm these findings and to prospectively evaluate the risks and benefits of clinical decision making based on exercise-induced changes in hs-cTnI levels for risk stratification of patients with stable CAD.[28−30]

This is the first study to investigate the effects of exercise-induced hs-cTnI elevation and adverse cardiovascular disease outcomes. The use of state-of-the-art myocardial perfusion imaging, the diversity of the population studied, the independent adjudication of outcome events, and prospective design of the study are important strengths. Our study focused on patients with CAD and thus our results cannot be generalized to subjects without CAD. Furthermore, study participants underwent myocardial perfusion imaging for research purposes, and thus results may differ in patients referred for evaluation due to cardiac symptoms, or patients with acute coronary syndromes. In these patients, visualization of affected territory may be important for further intervention. Furthermore, in clinical practice, patients with known CAD who are referred for stress testing generally do not have their antianginal agents held, which could potentially decrease the sensitivity of myocardial perfusion imaging to ischemia. In addition, we measured poststress hs-cTnI levels at a single time point (45 minutes after the stress test). Whether the peak changes after exercise occur at a different time point will need to be further investigated.

In stable CAD patients, an elevation of hs-cTnI with exercise stress testing in combination with baseline hs-cTnI

is associated with adverse cardiovascular outcomes beyond traditional cardiovascular risk factors and inducible ischemia detected by myocardial perfusion imaging. Our results highlight the importance of the assessment of dynamic changes in hs-cTnI levels instead of its resting levels alone to improve the risk stratification of subjects with stable CAD. Whether the adoption of this modality would improve patients' outcomes, or whether patients with exercise-induced hs-cTnI increase would benefit from more intensive intervention to reduce their risk are important questions that require further investigation.

Authors contribution

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.09.019.

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