

# openheart Associations between cardiac troponin, mortality and subsequent use of cardiovascular services: differences in sex and ethnicity

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## ABSTRACT

**Background** The impact of cardiac troponin (cTn) testing on the downstream use of cardiovascular services is not well understood. We conducted this large-scale single centre cohort study to investigate the patterns of testing that result from the use of cTn.

**Methods** We conducted this investigation using data collected between 1 January 2013 and 18 December 2015 from an academically affiliated tertiary care centre. Data from all hospitalised patients evaluated with cTn (Roche Elecsys cTn-T) assay were collected from our integrated data repository and divided into two cohorts: all cTn assays negative (<0.03 µg/L) versus at least one elevated (≥0.03 µg/L). The main outcomes were the frequency of use cardiovascular services and mortality.

**Results** Among 26 663 subjects, 18.6% had at least one elevated cTn assay; acute myocardial infarction was diagnosed in 3.9% overall. More men received cardiac catheterisation and cardiology consultation (OR 1.29, 95% CI 1.20 to 1.39 and OR 1.45, 95% CI 1.31 to 1.61) while African-American patients were less likely to have either catheterisation (OR 0.85, 95% CI 0.77 to 0.93) or consultation (OR 0.72, 95% CI 0.63 to 0.82) performed. Mortality was associated with detectable cTn (HR 2.05, P<0.0001).

**Conclusions** Among hospitalised patients evaluated with cTn, we observed patterns of underuse and overuse of cardiovascular services. These patterns may have further relevance when high-sensitivity cTn assays are available in the USA. Sex and race-based disparities in cardiovascular services persist.

## BACKGROUND

Myocardial ischaemia and acute myocardial infarction (AMI) are common diagnoses with potentially serious morbidity and mortality. Missed AMI is a common reason for medical malpractice lawsuits in the inpatient and outpatient settings. Symptoms of AMI can be protean, ranging from silent to haemodynamic collapse.<sup>1</sup> Critically ill patients may not be able to report their symptoms, potentially perplexing physicians if their clinical status suddenly deteriorates. Despite documents

## Key messages

### What is already known about this subject?

Physicians are aware that a substantial proportion of hospitalised patients are evaluated with cardiac troponins and other cardiovascular tests; the scope and magnitude of such testing is not well documented.

### What does this study add?

This study demonstrates that contemporary use of cardiac troponin results in a low diagnostic yield for acute myocardial infarction. Elevation in cardiac troponin is associated with substantial demand for cardiovascular services as well as sex and ethnicity-based disparities in care.

### How might this impact on clinical practice?

Health systems should work to minimise disparities in cardiovascular care. Indiscriminate use of cardiac troponin and downstream testing may be a focus for reducing low-value care. Adoption of higher sensitivity troponin assays may strain available cardiac testing resources.

such as the universal definition of MI, which guides clinicians towards a common understanding about myocardial pathology and encourage judicious use of cardiac troponin (cTn), concern about missed diagnoses contributes to the use of cTn to assess for myocardial damage in a wide array of patients.<sup>2</sup>

Investigators have evaluated the test performance characteristics of cTn for decades. In general, cTn is a highly sensitive marker of myocardial damage with poor specificity for AMI. Because the positive and negative predictive values of a given test are dependent on the prevalence of the condition being tested for, the diagnostic value of a given test is degraded if used indiscriminately.<sup>3</sup> While cTn is a quick and easy test to order, subsequent resource use testing such as echocardiography, nuclear myocardial perfusion

imaging, cardiac catheterisation and cardiology consultation are associated with non-trivial risks and costs.

The impact of using cTn in minimally selected populations, which may then drive demand for cardiovascular services, has not been well studied. Cardiovascular service demand may dramatically change with the approval of high-sensitivity cTn (hs-cTn) assays for use in the USA. We conducted a large-scale cohort study to investigate the association between cardiovascular services use and the real-world use of cTn assays. We hypothesised that patients with elevated cTn levels would undergo more cardiovascular testing compared with patients without elevation in cTn.

## METHODS

We conducted a retrospective cohort study using data gathered from a single, academic, tertiary care centre. Subjects were identified using our integrated data repository based on the search characteristics that they were 18 years of age or older, inpatient status and had at least one cTn assay performed during their hospitalisation between 1 January 2013 and 18 December 2015. The cTn assay used at our facility is the Elecsys cTn-T assay (Roche Diagnostics, Indianapolis, Indiana, USA). Our institution defines  $0.03 \mu\text{g/L}$  (99th percentile) as the cutpoint for abnormal. We defined two cohorts: (1) any cTn value greater than or equal to the  $0.03 \mu\text{g/L}$  threshold and (2) all values normal. For feasibility of the statistical analysis, only the first five sample values were considered. Our institutional review board reviewed and approved the research protocol with a waiver for obtaining informed consent. Roche Diagnostics funded the study through an investigator-initiated funding request. Roche had no role in the study design or conduct, data analysis or drafting of the manuscript.

We gathered the data elements from the electronic health record using automated data extraction. Baseline characteristics included age, sex, African American race (self-reported), chronic kidney disease (CKD), coronary artery disease (CAD), hypertension (HTN), congestive heart failure (CHF), atrial fibrillation/flutter, current tobacco use, stroke/transient ischaemic attack and chronic obstructive pulmonary disease. Data on body mass index were not reliably recorded and therefore not used for this investigation. Prior medical diagnoses were taken from the 'problem list' input by clinicians, no secondary definitions were applied. The Charlson Comorbidity Index is automatically calculated by the data repository software; we used the Charlson score as a binary variable ( $\leq 4$  vs  $> 4$ ).<sup>4,5</sup> Subsequent hospital diagnoses were identified based on International Classification of Disease-9 codes provided in online supplementary table S1: AMI, chronic CAD, arrhythmia including atrial or ventricular, CHF, takotsubo cardiomyopathy, sepsis, CKD, acute kidney injury, haemorrhagic stroke, thrombotic stroke, aortic dissection and acute pulmonary embolus. Cardiovascular procedures performed during

hospitalisation were identified using Current Procedural Terminology codes and are provided in online supplementary table S1, and include cardiac MRI, cardiac CT, other chest CT, single photon emission CT (SPECT), ventilation/perfusion scan, cardiopulmonary resuscitation, cardioversion, ECG, exercise treadmill test, transthoracic echocardiogram (TTE), transoesophageal echocardiogram, cardiac catheterisation, coronary bypass surgery and percutaneous coronary intervention. We determined from billing data if cardiology consultation was performed for each subject. Vital status from the Social Security Death Index is incorporated into our integrated data repository. We conducted our search for mortality data greater than 6 months after the final hospitalisation date.

The main outcomes were the frequency of use of ECG, non-invasive imaging, cardiac catheterisation and cardiology consultation between the cohorts. Binary associations were calculated using Mantel-Haenszel  $X^2$  test. We performed a secondary manual chart review on a 5% sample of patients who did not have a documented ECG in our administrative to confirm the prevalence of cardiovascular service use. As secondary outcomes, we used the log-rank test and constructed a model of Cox proportional HR for mortality; logistic regression models were used to determine independent associations with cardiology consultation and cardiac catheterisation. Variables eligible for entry to the Cox proportional hazard model for mortality included all baseline medical condition, new diagnoses during hospitalisation, age (by year), African-American race, female sex and elevation of troponin. Kaplan-Meier plots were created to display the risk of mortality related to elevated troponin. ORs were calculated with logistic regression models; variables included in the models of catheterisation and consultation were all baseline medical conditions, age (by year), African-American race, female sex and elevation of troponin. Power calculations were not performed a priori for this population-based investigation. All statistical analyses were performed two-sided, using SAS V.9.4 (Cary, North Carolina, USA) The investigation and manuscript were conducted in accordance with the STROBE guidelines for observational studies.<sup>6</sup>

## RESULTS

### Baseline characteristics

Data on the 26 663 subjects are described in table 1. A total of 4962 (18.6%) patients had a cTn elevation. African-American race was not different between the groups (22.0% for both cohorts). Male sex was prevalent in 50.1% of the population and more common in the elevated cTn cohort (58.0% vs 48.3%,  $P < 0.0001$ ). Rates of medical history were as follows: HTN (19.5%), diabetes mellitus (9.8%), CAD (6.3%) and CHF (2.9%). Only 3.93% of patients with a cTn ordered were subsequently diagnosed with myocardial infarction.

**Table 1** Baseline characteristics and medical history for n=26 663 subjects

	Troponin <0.03 n=21 701		Troponin ≥0.03 n=4962		P	OR	95% CI
Age (years)	60.2	16.2	64.9	15.4	<0.0001		
African-American	4745	22.0%	1076	22.0%	0.95	0.96	0.93 to 1.08
Male	10 481	48.3%	2879	58.0%	<0.0001	1.48	1.39 to 1.57
Diabetes mellitus	1976	9.1%	624	12.6%	<0.0001	1.44	1.30 to 1.58
Chronic kidney disease	583	2.7%	516	10.4%	<0.0001	4.20	3.71 to 4.75
Coronary artery disease	1207	5.6%	486	9.8%	<0.0001	1.84	1.65 to 2.06
Hypertension	4175	19.2%	1011	20.4%	0.07	1.07	1.00 to 1.16
Congestive heart failure	520	2.4%	266	5.4%	<0.0001	2.31	1.98 to 2.68
Atrial fibrillation or flutter	992	4.6%	339	6.8%	<0.0001	1.53	1.35 to 1.74
Current tobacco use	775	3.6%	125	2.5%	0.0002	0.70	0.58 to 0.85
Stroke or transient ischaemic attack	1546	7.1%	382	7.7%	0.16	1.09	0.97 to 1.22
Chronic obstructive pulmonary disease	1148	5.3%	255	5.1%	0.67	0.97	0.84 to 1.12
Charlson Comorbidity Index >4	1990	9.2%	717	14.5%	<0.0001	1.67	1.53 to 1.83

### CARDIOVASCULAR SERVICES

The most common test performed in our study population was an ECG. In our administrative data, ECG was documented for 75.6% of subjects. When we performed a manual review of charts for patients without a documented ECG, we found the correct estimate to be 4.9%. Undercounting in administrative data was due to ECGs being performed in the prehospital setting or by unit staff without an official order. When ECG was truly not performed, it was typically because of another evident diagnosis (eg, stroke, pulmonary embolus or trauma). TTE was the second most common test, performed in 57.6% of all patients (79.4% for elevated cTn vs 52.6%,  $P<0.0001$ ) (table 2). Cardiology consultation was performed in the minority of both cohorts (13.8% overall; 29.6% for the elevated cTn cohort vs 10.2% for the not elevated cTn cohort,  $P<0.0001$ ). If the cTn was elevated, invasive coronary angiography and revascularisation procedures were more common, with non-invasive diagnostics occurring less often (table 2). In the secondary chart review, the use of cardiology consultation, nuclear stress testing and TTE were not different from the observations in the administrative data.

### HOSPITAL DIAGNOSES

AMI was an uncommon diagnosis (3.9% overall) and was more frequent in the elevated cTn cohort (20.0% vs 0.3%,  $P<0.0001$ ) (table 2). The sensitivity, specificity, positive predictive value and negative predictive values for a diagnosis of AMI, based on the elevation of at least one cTn assay, were 94.8%, 84.5%, 20.0% and 99.7%, respectively. Chronic cardiovascular disease, CHF, arrhythmia, and both acute and chronic kidney disease were common in both elevated and non-elevated cTn cohorts with higher likelihood of each seen in the elevated cTn

cohort. Takotsubo cardiomyopathy was seen in 2.0% of those with elevated cTn.

### MORTALITY

Overall, 4697 patients died during the study period. In unadjusted comparison, subjects with elevated cTn had more than twice the likelihood of mortality compared with those with no cTn elevation (35.9% vs 13.8%, OR 3.49, 95% CI 3.25 to 3.74,  $P<0.0001$ ). In our Cox proportional hazard model, several baseline characteristics and hospital diagnoses were associated with mortality (table 3). Elevated Charlson Comorbidity Index (HR 3.328,  $P<0.0001$ ) and elevated cTn (HR 2.05,  $P<0.0001$ ) were two of the strongest independent associations with mortality. Some individual hospital diagnoses, including haemorrhagic stroke (HR 2.49,  $P<0.0001$ ) and sepsis (2.37,  $P<0.0001$ ), were associated with mortality. The risk of death associated with elevated cTn diverged early and persisted out to maximum of 3 years of follow-up (log rank  $P<0.0001$ ) (figure 1).

### PREDICTORS OF CATHETERISATION AND CONSULTATION

Overall, 3672 (13.8%) patients had a cardiology consultation during their hospitalisation and those with elevated cTn were more likely to have a consult (29.6% vs 10.2%,  $P<0.0001$ ). Cardiac catheterisation was performed on 1800 subjects (6.8% overall) and was more likely in those with elevated cTn (20.8% vs 3.5%,  $P<0.0001$ ). In our logistic regression models, we observed that elevated cTn was the variable with the strongest association to consultation (OR 3.44,  $P<0.0001$ ) and to catheterisation (OR 8.16,  $P<0.0001$ ) (table 4). In both models, men were more likely to have a consult (OR 1.29,  $P<0.0001$ ) or catheterisation (OR 1.45,  $P<0.0001$ ), while African-American subjects were less likely to have either (OR for

**Table 2** Procedures performed and diagnoses made during hospitalisation

	Troponin <0.03 n=21 701		Troponin ≥0.03 n=4962		P	OR	95% CI
<b>Procedures</b>							
Cardiology consult	2203	10.2%	1469	29.6%	<0.0001	3.72	3.45 to 4.01
Cardiac MRI	60	0.3%	36	0.7%	<0.0001	2.64	1.74 to 3.99
Coronary CT angiography	363	1.7%	30	0.6%	<0.0001	0.36	0.25 to 0.52
Chest CT (non-coronary)	5304	24.4%	1472	29.7%	<0.0001	1.30	1.22 to 1.40
Single photon emission CT	2169	10.0%	324	6.5%	<0.0001	0.63	0.56 to 0.71
Ventilation/perfusion scan	174	0.8%	67	1.4%	0.0002	1.69	1.28 to 2.25
Cardiopulmonary resuscitation	48	0.2%	95	1.9%	<0.0001	8.81	6.21 to 12.48
Cardioversion	135	0.6%	74	1.5%	<0.0001	2.42	1.82 to 3.22
Exercise treadmill testing	2341	10.8%	324	6.5%	<0.0001	0.58	0.51 to 0.65
Transthoracic echocardiogram	11 421	52.6%	3938	79.4%	<0.0001	3.46	3.22 to 3.73
Transoesophageal echocardiogram	463	2.1%	342	6.9%	<0.0001	3.40	2.94 to 3.92
Coronary catheterisation	769	3.5%	1031	20.8%	<0.0001	7.14	6.46 to 7.88
Percutaneous coronary intervention	122	0.6%	478	9.6%	<0.0001	18.86	15.42 to 23.06
Coronary bypass	44	0.2%	118	2.4%	<0.0001	11.99	8.47 to 16.97
<b>Hospital diagnoses</b>							
Acute myocardial infarction	55	0.3%	993	20.0%	<0.0001	98.47	74.90 to 129.45
Chronic cardiovascular disease	5145	23.7%	2374	47.8%	<0.0001	2.95	2.77 to 3.15
Arrhythmia*	3484	16.1%	1530	30.8%	<0.0001	2.33	2.17 to 2.50
Acute/chronic heart failure	3305	15.2%	1936	39.0%	<0.0001	3.56	3.33 to 3.81
Takotsubo cardiomyopathy	27	0.1%	101	2.0%	<0.0001	16.68	10.90 to 25.53
Sepsis	1905	8.8%	1132	22.8%	<0.0001	3.07	2.83 to 3.33
Chronic kidney disease	2270	10.5%	1771	35.7%	<0.0001	4.75	4.42 to 5.11
Acute kidney injury	2962	13.7%	1729	34.8%	<0.0001	3.38	3.15 to 3.63
Stroke, haemorrhagic	618	2.9%	180	3.6%	0.004	1.28	1.08 to 1.52
Stroke, thrombotic	1700	7.8%	446	9.0%	0.007	1.16	1.04 to 1.30
Aortic dissection	125	0.6%	35	0.7%	0.29	1.23	0.84 to 1.79
Acute pulmonary embolus	477	2.2%	168	3.4%	<0.0001	1.56	1.30 to 1.86

\*Atrial or ventricular arrhythmia.

consultation 0.85,  $P=0.0006$ ; OR for catheterisation 0.72,  $P<0.0001$ ).

## DISCUSSION

In this large, single centre cohort study examining the real-world use of cTn, we made several novel and confirmatory observations. Some of these observations suggest patterns of care that appear discordant with best clinical practices. While appropriate use criteria have established standards for use for many cardiovascular tests, the terms overuse and underuse remain difficult to apply. These terms may be relevant when our data are considered in the context of clinical guidelines and other data sources.

Some have suggested that the contemporary application of cardiac biomarker testing for ischaemia is an example of testing overuse.<sup>3</sup> In our sample of 26 663 subjects with cTn testing performed, the proportion with

elevation and the positive predictive value of cTn was low. Furthermore, during our study period there were 67 829 inpatient admissions. This corresponds to a total of 39.3% of all inpatients having their cTn measured at some point during their stay. Because of the pattern of pervasive cTn use, which results in a low positive predictive value for diagnosing MI, more judicious use of cTn has been encouraged in editorials and has been the subject of quality improvement initiatives seeking to reduce waste.<sup>7,8</sup>

The data on ECG use in our cohort raise multiple points for discussion. First, the discrepancy in documentation of ECG between the administrative and manual chart reviews is substantial. As we noted, this is often due to clinically available data (eg, prehospital ECG) not captured because our facility did not have the necessary billing infrastructure. For higher cost testing, such



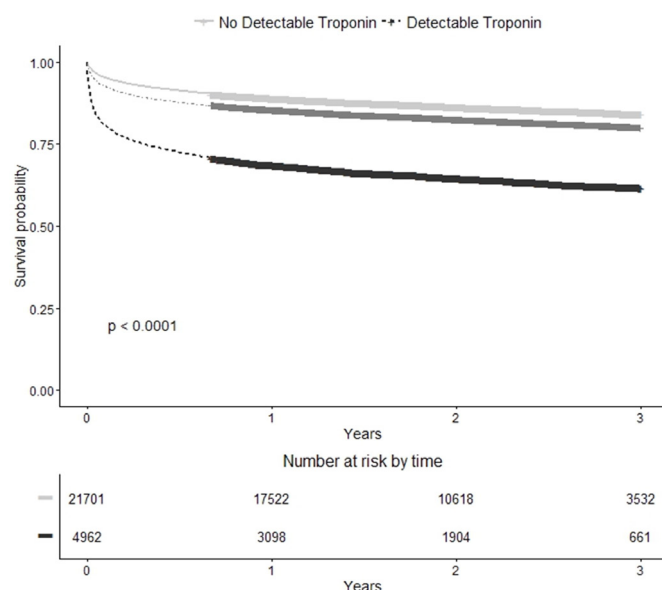
**Table 3** Cox proportional hazards model for mortality

	HR	P
Elevated troponin	2.05	<0.0001
African-American race	0.86	<0.0001
Male	1.14	<0.0001
Hypertension*	0.92	0.03
Congestive heart failure*	1.27	0.0004
Stroke or transient ischaemic attack*	1.16	0.009
Chronic obstructive pulmonary disease*	1.21	<0.0001
Age (per year)	1.02	<0.0001
Elevated Charlson Comorbidity Index (>4)	3.33	<0.0001
Aortic dissection†	1.83	0.0002
Acute kidney injury†	1.31	<0.0001
Arrhythmia†	1.29	<0.0001
Chronic cardiovascular disease†	0.85	<0.0001
Stroke, haemorrhagic†	2.49	<0.0001
Pulmonary embolus†	1.35	<0.0001
Sepsis†	2.37	<0.0001

\*Diagnosis present at time of admission.

†Diagnosis made during hospitalisation.

as echocardiography and nuclear stress testing, we did not observe any discrepancy. Even after manual review, however, some 5% of patients evaluated with cTn did not have an ECG performed. Given the simplicity and ubiquity of ECG in the hospital setting, it is perplexing why patients evaluated with cTn, presumably to diagnose myocardial damage, would not undergo an ECG as well.



**Figure 1** Kaplan-Meier curve for mortality. The light grey line represents the risk of mortality for patients without elevation in cardiac troponin and the dark grey line represents risk for those with elevation in troponin. The medium grey line in between is the risk for the overall population.

Guidelines give a class I recommendation for performing an ECG promptly in patients for whom acute coronary syndrome is suspected. This has a ‘C’ level of evidence, as there does not seem to be any reason why this recommendation should be empirically tested. The message worth communicating is that patients being evaluated for myocardial ischaemia should be evaluated clinically and augmented with both biomarkers and ECG.

The use of cardiology consultation differed nearly threefold between our cohorts. Unlike non-invasive testing, use of expert consultation is much more nuanced and does not lend itself to categorisation schema such as appropriate use criteria. Thus, we cannot comment as to whether consultation was overused or underused. Some patients with elevated cTn and without cardiology consult may have benefited from cardiology care; we cannot ascertain this from our dataset. We observed greater use of echocardiography with elevated cTn, which is reasonably expected. We saw less use of cardiac CT and SPECT with elevated cTn, which is also expected as patients without elevated cTn would be more likely to undergo a non-invasive ischaemia evaluation. These data would be stronger if we had been able to extract information on appropriateness of testing.<sup>9</sup>

A key question raised by our observations is: What is the likely impact of hscTn assays on demand for cardiovascular services?<sup>10</sup> In 2001, a randomised trial compared the evaluation of emergency department patients with cTn with the then-standard-of-care, Creatine kinase-MB (CKMB).<sup>11</sup> While subgroup analyses showed significant differences in hospitalisation and hospital costs, these were not different for the cohort as a whole. A more contemporary study from Spain compared conventional and hscTn finding that the newer assay resulted in some improvement of acute triage offset by higher use of invasive procedures and longer hospitalisations.<sup>12</sup> A large registry study from Sweden compared use of cardiovascular services after adoption of a hscTn assay finding modest increases in demand for echocardiography and catheterisation, which did not persist after multivariate regression.<sup>13</sup> Other studies evaluating adoption of hscTn found no difference in cardiovascular service demand.<sup>14,15</sup> We could only speculate as to how demand for cardiovascular services will change with the transition to hscTn; however, our data on prevalence are informative for future study of this transition. As technology continues to advance rapidly, the medical community and industry partners should consider not just the accuracy of a new test, but also whether the procedure improves outcomes for patients.<sup>16</sup>

Our investigation adds to the body of literature documenting that elevation in cTn is clinically a poor prognostic indicator associated with mortality in both cardiac and non-cardiac conditions.<sup>17-19</sup> While this mortality risk appears to differ based on the aetiology of the elevation,<sup>1,20</sup> our data did not allow for this degree of detailed investigation. We did observe a decreased risk of mortality for African-American patients. A review of literature on

**Table 4** Logistic regression models of factors\* associated with cardiology consultation and cardiac catheterisation

Cardiology consultation	OR	95% CI	P
Elevated troponin	3.44	3.19 to 3.72	<0.0001
African-American race	0.85	0.77 to 0.93	0.0006
Male	1.29	1.20 to 1.39	<0.0001
Congestive heart failure	1.99	1.67 to 2.36	<0.0001
Atrial fibrillation/flutter	2.10	1.84 to 2.40	<0.0001
Chronic obstructive pulmonary disease	0.82	0.69 to 0.97	0.0193
Age (per year)	1.01	1.00 to 1.01	<0.0001
Cardiac catheterisation	OR	95% CI	P
Elevated troponin	8.16	7.35 to 9.06	<0.0001
African-American race	0.72	0.63 to 0.82	<0.0001
Male	1.45	1.31 to 1.61	<0.0001
Chronic kidney disease	0.39	0.29 to 0.53	<0.0001
Coronary artery disease	2.44	2.05 to 2.91	<0.0001
Hypertension	0.83	0.72 to 0.96	0.0118
Atrial fibrillation/flutter	0.66	0.51 to 0.86	0.0022
Stroke or transient ischaemic attack	0.41	0.31 to 0.54	<0.0001
Chronic obstructive pulmonary disease	0.59	0.44 to 0.78	0.0002
Age (per year)	0.99	0.99 to 0.99	<0.0001
Elevated Charlson Comorbidity Index (>4)	0.44	0.35 to 0.54	<0.0001

\*Medical conditions listed are diagnoses that were present at time of admission.

inpatient mortality and race yields non-uniform findings; some finding African-Americans to have higher mortality, some with lower mortality and some where race was not a relevant factor.<sup>21–24</sup> Another study evaluating disparities in care and mortality found that women were more likely to receive suboptimal care and that both African-American and female patients have higher AMI mortality than white men.<sup>25</sup> We observed that use of cardiovascular services was less for women and African-Americans; however, we cannot determine if this represents underuse of services in these groups or overuse in white, male patients. It also remains unclear what impact race and sex will have on hscTn adoption given ongoing disagreement whether hscTn assays should have different cut-offs for different populations.<sup>26–28</sup>

Our study is not without limitations. We were not able to derive a statistical method to determine rise and fall of cTn, as would be preferred for verifying the diagnosis of AMI, within our data set. The data on pre-existing conditions are subject to the limitation of whether they were documented correctly by care providers; data on new hospital diagnoses are drawn from billing and coding. We did not have information on appropriateness of non-invasive imaging or catheterisation. Regression models are an imperfect method for determining risk associations between variables such as sex and ethnicity with outcomes such as consultation and catheterisation. We cannot ascertain any reasons for the disparities observed

in women and African-American subjects; these findings should be considered hypothesis generating.

## CONCLUSIONS

Our investigation of the real-world use of cTn demonstrates patterns of cardiovascular service use that may be discordant with best clinical practice. Cardiology consultation is far from universal in evaluating these patients. Elevated cTn continues to be associated with higher mortality, although other factors are stronger predictors of death. Racial and sex-based differences in cardiovascular service use and mortality support continued concern about disparities in care.

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