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Clinical Impact of High-Sensitivity Cardiac Troponin T Implementation in the Community

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ABSTRACT

BACKGROUND Limited U.S. data exist regarding high-sensitivity cardiac troponin (cTn) implementation.

OBJECTIVES This study sought to evaluate the impact of high-sensitivity cardiac troponin T (cTnT) implementation.

METHODS Observational U.S. cohort study of emergency department (ED) patients undergoing measurement of cTnT during the transition from 4th (pre-implementation March 12, 2018, to September 11, 2018) to 5th generation (Gen) cTnT (post-implementation September 12, 2018, to March 11, 2019). Diagnoses were adjudicated following the Fourth Universal Definition of Myocardial Infarction (MI). Resources evaluated included length of stay, hospitalizations, and cardiac testing.

RESULTS In this study, 3,536 unique patients were evaluated, including 2,069 and 2,491 ED encounters pre- and post-implementation. Compared with 4th Gen cTnT, encounters with ≥1 cTnT >99th percentile increased using 5th Gen cTnT (15% vs. 47%; $p < 0.0001$). Acute MI (3.3% vs. 8.1%; $p < 0.0001$) and myocardial injury (11% vs. 38%; $p < 0.0001$) increased. Although type 1 MIs increased (1.7% vs. 2.9%; $p = 0.0097$), the overall MI increase was largely due to more type 2 MIs (1.6% vs. 5.2%; $p < 0.0001$). Women were less likely than men to have MI using 4th Gen cTnT (2.3% vs. 4.4%; $p = 0.008$) but not 5th Gen cTnT (7.7% vs. 8.5%; $p = 0.46$). Overall length of stay and stress testing were reduced, and angiography was increased (all $p < 0.05$). Among those without cTnT increases, there were more ED discharges and a reduction in length of stay, echocardiography, and stress tests (all $p < 0.05$).

CONCLUSIONS High-sensitivity cTnT implementation resulted in a marked increase in myocardial injury and MI, particularly in women and patients with type 2 MI. Despite this, except for angiography, overall resource use did not increase. Among those without cTnT increases, there were more ED discharges and fewer cardiac tests.
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Measurement of cardiac troponin (cTn) is central to the evaluation of patients with suspected acute myocardial infarction (MI) (1). High-sensitivity (hs) assays quantify cTn at lower concentrations with higher precision than prior assays did (2). These analytical improvements enable more rapid and efficient evaluation of patients with suspected MI (3). European Society of Cardiology guidelines have endorsed hs-cTn assays with Class I recommendations since 2011 using a 0- to 3-h protocol (4), with iterations in 2015 and 2020 evolving to advocate algorithms capable to rule-in and rule-out MI within 1 to 2 h (5,6).

European data on hs-cTn implementation indicate that the introduction of these assays into clinical practice is associated with an improved MI rule-out process, including a reduction in the time to discharge, and a higher incidence of MI (7–11), only a modest increase in coronary angiographies (8,9), and no significant impact on downstream resource utilization (7).

The Roche 5th generation (Gen) cardiac troponin T (cTnT) assay, referred to as hs-cTnT, received U.S. Food and Drug Administration clearance in January 2017 (12). Several other hs-cardiac troponin I (cTnI) assays have since received 510k clearance. However, limited real-life U.S. data exist, especially in regard to the frequency of MI diagnoses and resource utilization following hs-cTn implementation (13–15). The latter information will have important clinical, logistic, and financial implications as wider implementation of these assays occurs. Furthermore, U.S. practices tend to use cTn more broadly than those in Europe (16,17), which has led to concerns about these critical issues (18).

Our goals were to assess the impact of transitioning from 4th to 5th Gen cTnT on the incidence of myocardial injury and MI diagnoses following the Fourth Universal Definition of Myocardial Infarction (UDMI) and resource utilization in a U.S. regional health care system.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The ACTION (MAyo Southwest WisConsin 5th Gen Troponin T ImplementatiON) study is a retrospective, multicenter (n = 2), observational cohort study evaluating the transition from 4th Gen cTnT (6 months pre-implementation period from March 12, 2018, to September 11, 2018) to 5th Gen cTnT (6 months post-implementation period from September 12, 2018, to March 11, 2019) across the Southwest Wisconsin Mayo Clinic Health System (MCHS) hospitals at La Crosse and Sparta in Wisconsin. Following Institutional Review Board approval, we evaluated consecutive encounters of adult patients presenting to these emergency departments (EDs) in whom at least 1 cTnT measurement was obtained for clinical purposes. Data were abstracted and reviewed from the electronic health records by trained study staff following a standardized data collection process and entered in REDCap (Research Electronic Data Capture). Patients who did not present through the ED, were <18 years old, or had both 4th and 5th Gen cTnT measurements at transition were excluded.

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Southwest Wisconsin MCHS is a regional health care system constituted by 8 clinics and 2 hospitals with 24 h/7 days EDs (MCHS La Crosse and MCHS Sparta) addressing a population of ~331,000 individuals (2017 estimate). MCHS La Crosse is the higher acuity, 142-bed hospital, and regional referral hub with 24 h/7 days cardiac services, including a percutaneous coronary intervention and a ST-segment elevation MI program, that has approximately 18,000 annual ED visits. MCHS Sparta is a 25-bed community hospital with approximately 5,300 annual ED visits. Most, but not all, patients presenting to MCHS Sparta who require higher level care are transferred to MCHS La Crosse.

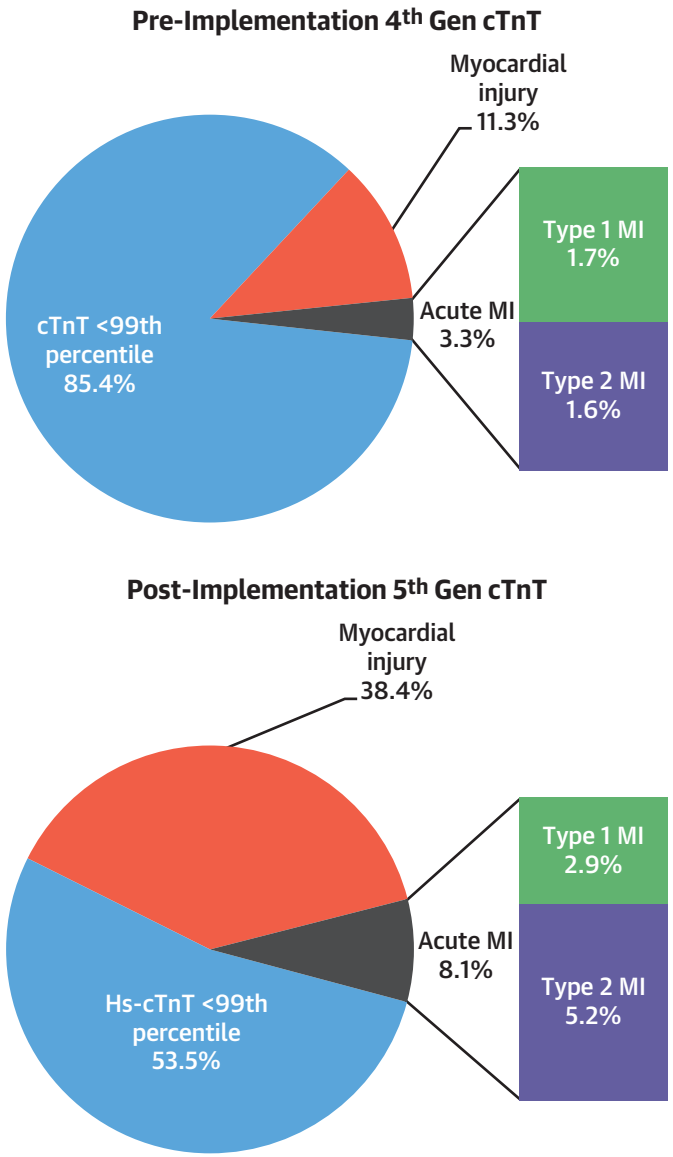
cTnT MEASUREMENTS. During the pre-implementation period, cTnT was measured using the contemporary 4th Gen cTnT assay (Roche Diagnostics, Indianapolis, Indiana) on the Cobas e 601 (MCHS La Crosse) and Cobas e 411 (MCHS Sparta). Both the lowest reportable concentration and overall 99th percentile upper-reference limit (URL) are <0.01 ng/ml. A concentration of 0.01 ng/ml or higher is indicative of myocardial injury. Results are reported as decimals in ng/ml. Institutional guidelines recommended a 0-, 3-, and 6-h protocol to rule-in and rule-out acute MI, with an overall 99th percentile URL used to determine the presence of myocardial injury and support the diagnosis of acute MI.

During the post-implementation period, cTnT was measured using the Elecsys Troponin T Gen 5 STAT assay (Roche Diagnostics) on the Cobas e 601 (MCHS La Crosse) and Cobas e 411 (MCHS Sparta). Per U.S. Food and Drug Administration guidance, concentrations were reported down to the limit of quantitation of <6 ng/l. Sex-specific 99th percentile URLs of 10 ng/l for women and 15 ng/l for men were used (12). Concentrations >10 ng/l for women and >15 ng/l for

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
cTn = cardiac troponin
cTnI = cardiac troponin I
cTnT = cardiac troponin T
ED = emergency department
Gen = generation
hs = high-sensitivity
LOS = length of stay
MCHS = Mayo Clinic Health System
MI = myocardial infarction
OR = odds ratio
UDMI = Universal Definition of Myocardial Infarction
URL = upper-reference limit

FIGURE 1 Distribution of Diagnoses



Frequency of cardiac troponin T (cTnT) concentrations ≤99th percentile, myocardial injury, and acute myocardial infarction (MI) including type 1 and 2 MIs during the pre- and post-implementation periods. Gen = generation; hs-cTnT = high-sensitivity cardiac troponin T.

men are considered indicative of myocardial injury. Results are reported as whole units (no decimals) in ng/l. The Mayo Clinic protocol and rationale for the rule-in and rule-out of MI using 5th Gen cTnT has been described (12,14). In brief, patients with suspected MI are evaluated using a 0- and 2-h hs-cTnT protocol that uses sex-specific 99th percentile URLs and an absolute delta (serial change) of >10 ng/l to identify patients with acute myocardial injury. Those with 0- and 2-h deltas of ≤3 ng/l are classified as having no significant change, and those with deltas of 4 to 9 ng/l as indeterminate. For the indeterminate group, a 6-h sample is automatically ordered by the laboratory and an empirical change ≥12 ng/l over 6 h is considered indicative of acute myocardial injury. Prior to hs-cTnT implementation, a multidisciplinary advisory group developed and monitored educational processes across the enterprise, which in addition to designating "champions" at each region included extensive educational resources such as in-person and online lectures, dissemination of forms, peer-reviewed material (12), pocket cards, slide presentations, online courses, and podcasts (14). At Southwest Wisconsin MCHS there were in-person educational sessions with the ED, hospitalists, cardiologists, and residents.

MYOCARDIAL INJURY AND INFARCTION ADJUDICATION. All available data from the clinical presentation, including 12-lead electrocardiogram, echocardiography, stress test, and angiograms, were reviewed. All encounters with at least 1 cTnT >99th percentile URL were adjudicated using the Fourth UDMI criteria by trained physicians. Cases with challenging adjudication were reviewed by the principal investigator (Y.S.), and if needed, by a member of the Task Force for the Fourth UDMI (A.S.J.).

Following the Fourth UDMI (1), patients with at least 1 cTnT concentration >99th percentile URL were classified as having either myocardial injury (acute or chronic) or acute MI if there were clinical features of acute myocardial ischemia, such as ischemic symptoms, new ischemic electrocardiogram changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, and/or identification of a culprit lesion on coronary angiography. Those with overt evidence of myocardial ischemia were classified as having MI and further subclassified into 1 of 5 MI subtypes. Type 1 MI is an atherothrombotic MI and type 2 MI is due to nonatherothrombotic supply-demand myocardial ischemia (1,19) (see Supplemental Methods). In this document we use the term "myocardial injury" when patients were adjudicated to have cTnT increases (acute or chronic) without overt clinical evidence of acute myocardial ischemia.

STUDY ENDPOINTS. The primary diagnostic endpoints were the incidence of cTnT increases >99th percentile URL and the adjudicated diagnoses of myocardial injury and acute MI, including both type 1 and 2 MI, among all encounters during the pre- and

TABLE 1 Baseline Characteristics for Unique Patients Based on Their First ED Presentation During the Study Period

	Total Unique Patients (N = 3,536)	Pre-Implementation, 4th Gen cTnT (n = 1,738)	Post-Implementation, 5th Gen cTnT (n = 1,798)	p Value
Age, yrs	62 ± 18	62 ± 18	61 ± 18	0.08
Women	1,817 (51)	880 (51)	937 (52)	0.38
Chest discomfort	1,609 (46)	724 (42)	885 (49)	<0.0001
Dyspnea	1,422 (40)	685 (39)	737 (41)	0.34
Hypertension	2,045 (58)	1,050 (60)	995 (55)	0.002
Obesity	1,488 (42)	732 (42)	756 (42)	0.97
Current or prior tobacco use	2,002 (57)	1,026 (59)	976 (54)	0.004
CAD	725 (21)	388 (22)	337 (19)	0.008
Prior MI	325(9.2)	170 (9.8)	155 (8.6)	0.23
Prior coronary revascularization	482 (14)	247 (14)	235 (13)	0.32
Cerebrovascular disease	325 (9.2)	162 (9.3)	163 (9.1)	0.79
History of atrial dysrhythmias	649 (18)	339 (20)	310 (17)	0.08
Heart failure	681 (19)	383 (22)	298 (17)	<0.0001
Diabetes mellitus	874 (25)	460 (27)	414 (23)	0.02
Chronic kidney disease	730 (21)	380 (22)	350 (20)	0.08
Family history of CAD	1,100 (31)	561 (32)	539 (30)	0.14
Peripheral arterial disease	357 (10)	185 (11)	172 (9.6)	0.29
Dyslipidemia	1,870 (53)	968 (56)	902 (50)	0.001

Values are mean ± SD or n (%).
CAD = coronary artery disease; cTnT = cardiac troponin T; ED = emergency department; Gen = generation; MI = myocardial infarction.

post-implementation periods. The primary resource utilization endpoints were length of stay (LOS), proportion of direct ED discharges, and cardiac testing including echocardiography, stress testing (exercise electrocardiogram, nuclear myocardial perfusion imaging, and stress echocardiography), coronary computed tomography angiography, and invasive coronary angiography.

STATISTICAL ANALYSIS. Baseline characteristics were based on the first ED presentation for unique patients using median (interquartile range) and compared using the Kruskal-Wallis test for continuous variables. All other analyses address all encounters during both periods. Categorical variables are presented as numbers (percentages) and compared using the chi-square test. Odds ratio (ORs) and corresponding 95% confidence intervals (CIs) are presented. For resource utilization, multivariable models were developed including age, sex, chest discomfort, history of hypertension, coronary artery disease, heart failure, diabetes mellitus, chronic kidney disease, dyslipidemia, and current or prior tobacco use. LOS was evaluated as median (interquartile range) hours, with sensitivity analyses used to exclude transferred patients. A p value of <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and R version 4.0.2 (R Foundation, Vienna, Austria).

RESULTS

A total of 3,536 unique patients were evaluated. During the pre-implementation period there were 1,738 patients with 2,069 ED encounters, including 222 (13%) with more than 1 presentation. During the post-implementation period there were 2,082 patients with 2,491 ED encounters, including 294 (14%) with more than 1 presentation. There were 284 patients that had at least 1 encounter during both periods. Baseline characteristics based on the first presentation during the study period are summarized in Table 1. The mean age of the population was 62 ± 18 years and 51% were women. Chest discomfort was present in 46% of patients. Those presenting during the post-implementation period had a higher frequency of chest discomfort and had fewer comorbidities, with less hypertension, current or prior tobacco use, coronary artery disease, heart failure, diabetes mellitus, and dyslipidemia.

IMPACT ON MYOCARDIAL INJURY AND ACUTE MI DIAGNOSES. The incidence of cTnT increases, myocardial injury, and acute MI, including MI subtypes, across encounters are shown in Table 2 and Figure 1 for both periods. Compared with the 4th Gen cTnT assay, encounters with ≥1 cTnT >99th percentile increased significantly using 5th Gen cTnT (15% vs. 47%; p < 0.0001; OR: 5.1; 95% CI: 4.4 to 5.9). Increases were observed in both men (20% vs. 48%;

TABLE 2 Myocardial Injury and Infarction Diagnoses Pre- and Post-Implementation Across Encounters

	Pre-Implementation, 4th Gen cTnT	Post-Implementation, 5th Gen cTnT	p Value
Overall			
Encounters	2,069	2,491	–
At least 1 cTnT >99th percentile	302 (15)	1,159 (47)	<0.0001
Myocardial injury	236 (11)	957 (38)	<0.0001
Acute MI	68 (3.3)	202 (8.1)	<0.0001
Type 1 MI	35 (1.7)	71 (2.9)	0.0097
Type 2 MI	33 (1.6)	130 (5.2)	<0.0001
Men			
Encounters	1,011	1,221	–
At least 1 cTnT >99th percentile	199 (20)	582 (48)	<0.0001
Myocardial injury	157 (16)	478 (39)	<0.0001
Acute MI	44 (4.4)	104 (8.5)	<0.0001
Type 1 MI	27 (2.7)	42 (3.4)	0.30
Type 2 MI	17 (1.7)	62 (5.1)	<0.0001
Women			
Encounters	1,058	1,270	–
At least 1 cTnT >99th percentile	103 (9.7)	577 (45)	<0.0001
Myocardial injury	79 (7.5)	479 (38)	<0.0001
Acute MI	24 (2.3)	98 (7.7)	<0.0001
Type 1 MI	8 (0.8)	29 (2.3)	0.003
Type 2 MI	16 (1.5)	68 (5.4)	<0.0001

Values are n or n (%).
Abbreviations as in Table 1.

$p < 0.0001$; OR: 3.7; 95% CI: 3.1 to 4.5) and women (9.7% vs. 45%; $p < 0.0001$; OR: 7.7; 95% CI: 6.1 to 9.7).

Adjudication following the Fourth UDMI of cases with ≥1 cTnT >99th percentile demonstrated both acute MI (3.3% vs. 8.1%; $p < 0.0001$; OR: 2.60; 95% CI: 1.96 to 3.44) and myocardial injury (11% vs. 38%; $p < 0.0001$; OR: 4.85; 95% CI: 4.14 to 5.67) increased using 5th Gen cTnT (**Central Illustration**). Type 1 MIs increased (1.7% vs. 2.9%; $p = 0.0097$; OR: 1.71; 95% CI: 1.13 to 2.57) but the overall MI increase was largely due to more type 2 MIs (1.6% vs. 5.2%; $p < 0.0001$; OR: 3.40; 95% CI: 2.31 to 4.99).

Acute MI increased from 4.4% to 8.5% ($p < 0.0001$; OR: 2.05; 95% CI: 1.42 to 2.94) in men and from 2.3% to 7.7% in women ($p < 0.0001$; OR: 3.60; 95% CI: 2.29 to 5.67) using 5th Gen cTnT. Likewise, myocardial injury increased from 16% to 39% ($p < 0.0001$; OR: 3.50; 95% CI: 2.85 to 4.30) in men and from 7.5% to 38% ($p < 0.0001$; OR: 7.50; 95% CI: 5.81 to 9.69) in women. Similar increases were observed for type 2 MI in men (1.7% vs. 5.1%; $p < 0.0001$; OR: 3.13; 95% CI: 1.82 to 5.38) and women (1.5% vs. 5.4%; $p < 0.0001$; OR: 3.68; 95% CI: 2.12 to 6.39), but not type 1 MI, where increases were observed in women (0.8% vs. 2.3%; $p = 0.003$; OR: 3.07; 95% CI: 1.40 to 6.74) but not men (2.7% vs. 3.4%; $p = 0.3$; OR: 1.30, 95% CI: 0.80 to 2.12).

Women were less likely than men to have cTnT concentrations >99th percentile (9.7% vs. 20%; $p < 0.0001$), myocardial injury (7.5% vs. 16%; $p < 0.0001$) and acute MI (2.3% vs. 4.4%; $p = 0.008$) during the pre-implementation period using 4th Gen cTnT (**Figure 2**). They were also less likely to have type 1 MI (0.8% vs. 2.7%; $p = 0.0007$) but not type 2 MI (1.5% vs. 1.7%; $p = 0.76$). In contrast, using 5th Gen cTnT, there were no differences between men and women in the proportion of cases with cTnT concentrations >99th percentile, myocardial injury, and acute MI, including MI subtypes.

IMPACT ON RESOURCE UTILIZATION AND LOS. Resource utilization results are summarized in **Table 3**. Overall, including encounters with and without cTnT increases, there was a reduction in stress testing (6.5% vs. 4.9%; $p = 0.02$) (Supplemental Table 1) and an increase in invasive coronary angiography (2.3% vs. 3.5%; $p = 0.02$) post-implementation. There was no overall difference in the proportion of patients directly discharged from the ED or in the use of echocardiography. Sex-specific analyses are presented in Supplemental Tables 2 and 3. Men had a reduction in stress testing (8.6% vs. 5.5%; $p = 0.004$) and women had an increase invasive coronary angiography (1.2% vs. 2.5%; $p = 0.02$). There were otherwise no differences between pre- and post-implementation periods in resource utilization in men and women.

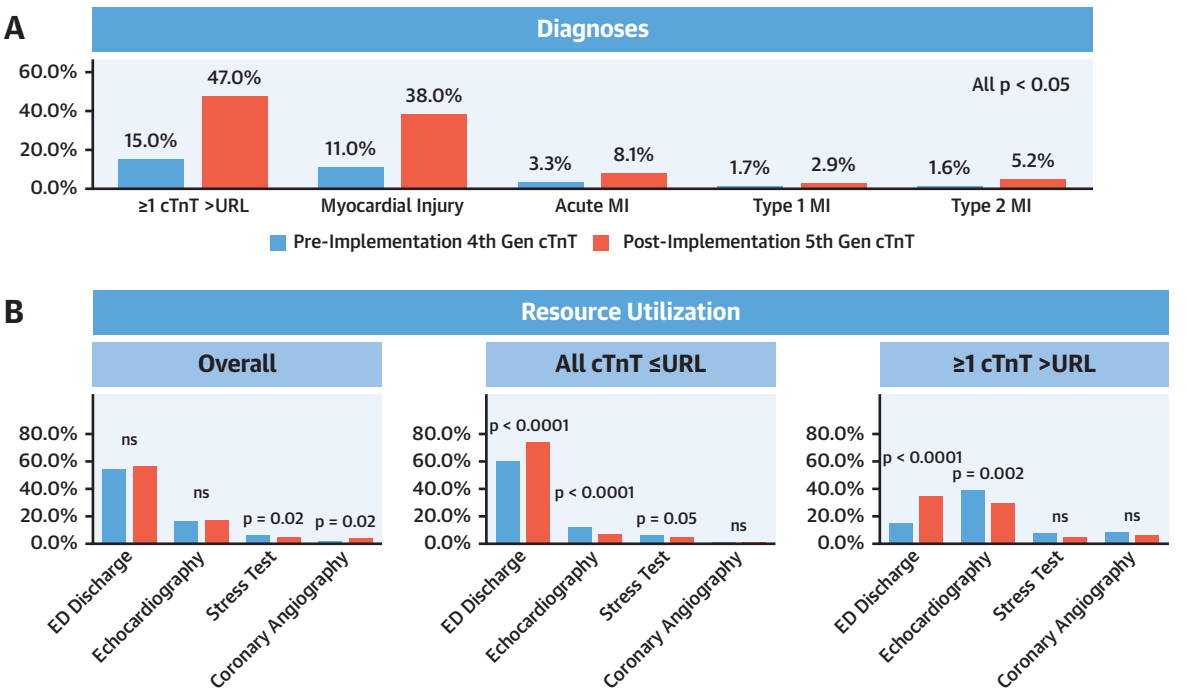
Among patients without cTnT increases, there was a significant increase in the proportion of patients directly discharged from the ED (60% vs. 74%; $p < 0.0001$) post-implementation. There was also a reduction in echocardiography (12% vs. 6.5%; $p < 0.0001$) and stress tests (6.5% vs. 4.8%; $p = 0.05$). Similar findings were observed for direct ED discharges and echocardiography use among men and women without cTnT increases, but not stress testing, which was reduced in men (8.5% vs. 5.9%; $p = 0.07$) but not women.

Among patients with cTnT increases, there was also a significant increase in the proportion of patients directly discharged from the ED (15% vs. 34%; $p < 0.0001$) and a reduction in echocardiography (39% vs. 29%; $p = 0.002$) post-implementation. Similar findings were observed for direct ED discharges among men and women with cTnT increases. Men with cTnT increases underwent fewer stress tests post-implementation (9.0% vs. 5.0%; $p = 0.04$), whereas women with cTnT increases had a reduction in echocardiography (46% vs. 29%; $p = 0.001$).

Post-implementation there was a significant reduction in overall (with and without myocardial

CENTRAL ILLUSTRATION **Impact of hs-cTnT Implementation of MI Diagnoses and Resource Utilization**

Implementing High-Sensitivity Cardiac Troponin T in a U.S. Regional Health Care System		
	4th Gen cTnT Assay	5th Gen cTnT Assay
Assay	Contemporary	High-sensitivity
Units	ng/mL (decimals)	ng/L (whole numbers)
99th percentile URL	Single, overall threshold of <0.01 ng/mL	Sex-specific thresholds: Women: 10 ng/L, Men: 15 ng/L
Sampling protocol	0/3/6-h sampling	0/2-h sampling; indeterminate delta undergoes 6-h sample



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(A) Diagnoses and **(B)** resource utilization across the 4th generation (Gen) cardiac troponin T (cTnT) pre-implementation period **(blue bars)** compared with the 5th Gen cTnT post-implementation period **(red bars).** ED = emergency department; hs-cTnT = high-sensitivity cardiac troponin T; MI = myocardial infarction; ns = not significant; URL = upper-reference limit.

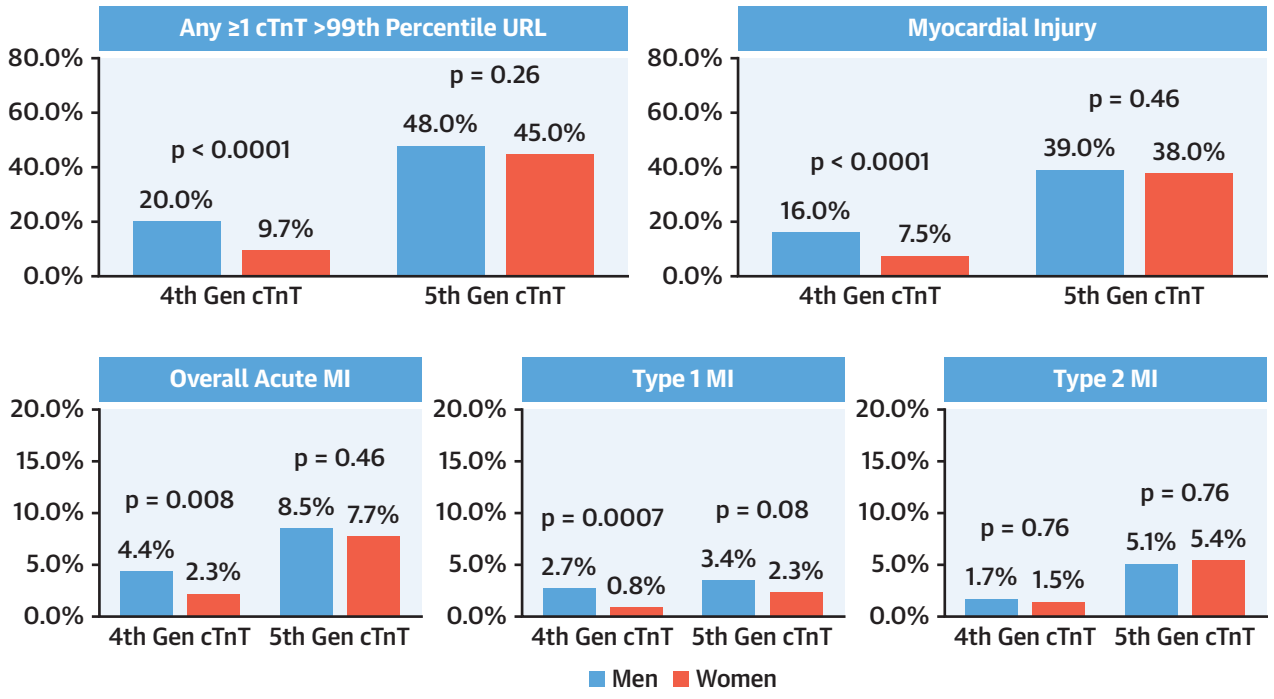
injury) median LOS (4.3 vs. 4.2 h; p = 0.01) (Supplemental Tables 4 and 5). Similar findings were observed for those without (3.6 vs. 3.0 h; p < 0.0001) and with (56.0 vs. 33.4 h; p < 0.0001) cTnT increases. Sensitivity analyses excluding patients who were transferred showed similar findings. Among those directly discharged from the ED, overall LOS increased (2.4 vs. 2.9 h; p < 0.0001), primarily because of longer LOSs in those with cTnT increases (2.9 vs. 3.6 h; p = 0.0001).

DISCUSSION

The present is the first comprehensive U.S.-based study addressing the impact of the transition from a contemporary cTnT assay using an overall 99th percentile to a hs-cTnT assay with sex-specific 99th percentiles on myocardial injury and infarction diagnoses determined using the Fourth UDMI and resource utilization. Previous U.S. studies have been limited to assessing hs-cTn at single-center and larger urban sites. Frequently, sex-specific 99th percentiles and the application of the Fourth UDMI (13) have not been employed. Furthermore, many such studies have been smaller in size and based on comparisons with a contemporary cTnI assay rather than cTnT (15).

Several findings are unique. First, we report a marked absolute increase of 32% in the proportion of patients with at least 1 cTnT increase >99th percentile URL following implementation of an hs-cTnT

FIGURE 2 Diagnoses Among Men and Women for Both 4th and 5th Gen cTnT Assays



Diagnoses among men **(blue bars)** and women **(red bars)** comparing the proportion of cases with any cTnT increase >99th percentile, myocardial injury, and acute MI including type 1 and 2 MIs using 4th and 5th Gen cTnT. URL = upper-reference limit; other abbreviations as in **Figure 1**.

assay using sex-specific thresholds. With the use of the hs-cTnT assay, almost one-half of the patients evaluated during the post-implementation period had an increase >99th percentile URL. These findings are critical to institutions transitioning from 4th to 5th Gen cTnT. They underscore the need for adequate education and preparation along with multidisciplinary collaboration to successfully incorporate these assays into clinical care. The successful implementation of hs-cTnT across our entire health system was possible due to our extensive educational program and multidisciplinary collaboration that focused on the more rapid and efficient evaluation of patients with suspected MI, while explaining how to successfully handle the marked increase in abnormal results.

Our results align with previous data showing that hs-cTnT identifies many more patients with increased concentrations than the contemporary cTnT assay does (10,20). Data from the APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation) study addressing baseline samples reported cTnT increases >99th percentile in 22% of cases using the contemporary assay as compared to 36% with hs-cTnT using an overall 99th percentile URL of 14 ng/l (20). These observations are specific to Roche's cTnT to hs-cTnT comparisons and are explained in large part by the poor analytical sensitivity of the older 4th Gen cTnT assay. Comparisons addressing cTnI to hs-cTnI across the Abbott (Chicago, Illinois) (21), Beckman (Brea, California) (22), and Siemens (Munich, Germany) (23) assays have shown no such difference in the proportion of patients with concentrations >99th percentile. Thus, it appears that the frequency of increased concentrations with transition to hs-cTn is dependent on the analytical sensitivity of the prior assay and cutoffs used rather than the novel hs-cTn assay itself. Critically, the transition from cTnT to hs-cTnT improves detection of high-risk patients that were under-recognized using the previous insensitive assay (20).

Second, based on criteria from the Fourth UDMI, there is a substantial increase in myocardial injury and acute MI following hs-cTnT implementation. The proportion of cases classified as myocardial injury (acute or chronic) increased significantly using hs-cTnT and explained most cases with increased hs-cTnT concentrations. The transition from 4th to 5th Gen cTnT was also associated with an increase in MI

TABLE 3 Overall Resource Utilization Pre- and Post-Implementation

	Pre-Implementation, 4th Gen cTnT	Post-Implementation, 5th Gen cTnT	Unadjusted OR (95% CI), p Value	Adjusted OR (95% CI), p Value
Overall				
Encounters	2,069	2,491	–	–
Direct ED discharge	1,109 (54)	1,386 (56)	1.09 (0.99–1.22), 0.17	1.04 (0.92–1.18), 0.55
Echocardiography	327 (16)	426 (17)	1.09 (0.94–1.29), 0.24	1.14 (0.97–1.34), 0.12
Stress test	135 (6.5)	123 (4.9)	0.74 (0.58–0.96), 0.02	0.67 (0.51–0.86), 0.002
Invasive coronary angiography	48 (2.3)	88 (3.5)	1.54 (1.08–2.20), 0.02	1.42 (0.99–2.04), 0.06
Coronary computed tomography angiography	3 (0.1)	5 (0.2)	p = 0.65*	*
All cTnT ≤99th percentile URL				
Encounters	1,767	1,332	–	–
Direct ED discharge	1,065 (60)	991 (74)	1.92 (1.64–2.24), <0.0001	1.37 (1.15–1.62), 0.0003
Echocardiography	210 (12)	87 (6.5)	0.52 (0.40–0.67), <0.0001	0.69 (0.53–0.91), 0.008
Stress test	114 (6.5)	64 (4.8)	0.73 (0.53–1.00), 0.05	0.67 (0.48–0.93), 0.02
Invasive coronary angiography	23 (1.3)	17 (1.3)	0.98 (0.52–1.84), 0.95	*
Coronary computed tomography angiography	2 (0.1)	2 (0.2)	p = 0.78*	*
At least 1 cTnT >99th percentile URL				
Encounters	302	1,159	–	–
Direct ED discharge	44 (15)	395 (34)	3.03 (2.15–4.27), <0.0001	2.89 (2.03–4.10), <0.0001
Echocardiography	117 (39)	339 (29)	0.65 (0.50–0.85), 0.002	0.63 (0.48–0.83), 0.001
Stress test	21 (7.0)	59 (5.1)	0.72 (0.43–1.20), 0.21	0.68 (0.39–1.17), 0.16
Invasive coronary angiography	25 (8.3)	71 (6.1)	0.72 (0.45–1.16), 0.18	0.57 (0.34–0.96), 0.03
Coronary computed tomography angiography	1 (0.3)	3 (0.3)	p = 0.83*	*

Values are n or n (%), unless otherwise indicated. *Additional analyses not performed due to limited statistical power (small numbers).
CI = confidence interval; OR = odds ratio; URL = upper-reference limit; other abbreviations as in Table 1.

diagnoses. Similar increases in MI with hs-cTnT implementation have been reported in the APACE (20) and SWEDEHEART (Swedish Web-based System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies) (8) studies. Studies using a contemporary cTnI assays as the comparator rather than cTnT (15) or using higher decision thresholds (i.e., 10% coefficient of variation concentration) other than the 99th percentile URL for the contemporary cTnT assay (10) have shown no difference in acute MI.

Third, while both type 1 and 2 MIs increased significantly post-implementation, the increase in MI was primarily due to more type 2 MIs. An epidemiological shift in MI subtypes has been reported using the contemporary 4th Gen cTnT assay (24), with the incidence of type 2 MI becoming similar to the incidence of type 1 MI. It has been expected that the transition to hs-cTn assays will further increase the incidence of type 2 MI. Data from the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome) trial showed that the implementation of hs-cTnI increased the diagnosis of type 1 and 2 MI and, like our findings, demonstrated a disproportionate increase in type 2 MI and myocardial injury (25). Our data showing a notable increase in type 2 MI with hs-cTnT implementation further underscores the urgent need for more data, in particular therapeutic interventions, to improve outcomes in this frequently encountered high-risk patient subset (19). Our study validates similar observations regarding increases in type 2 MI diagnoses previously reported using International Classification of Diseases-10th Revision codes across the entire MCHS system (14). Those analyses differ from the present study with regard to study design, including the use of hospital-level rather than patient-level data specific to those presenting to the ED, analysis of resource utilization across total patients rather than just those undergoing cTnT, and use of International Classification of Diseases-10th Revision codes rather than adjudicated diagnoses. Thus, the present study used more robust methods and analyses based on cTn results and adjudicated diagnoses per the Fourth UDMI.

Fourth, for patients without cTnT increases, our study is among the first in the United States to indicate that hs-cTnT implementation is associated with a marked increase in the proportion of patients directly discharged from the ED. The latter is among the most important benefits of hs-cTn implementation in that it allows clinicians to more confidently identify low-risk patients that are eligible for discharge and avoid unnecessary hospitalizations. It was also associated with

a small but significant reduction in overall LOS, as well as more notable reduction in overall LOS in those without cTnT increases. Critically, whereas hs-cTnT implementation was associated with a significantly higher proportion of patients with cTnT increases, as well as more acute MI and myocardial injury, except for a small (2.3% to 3.5%) but statistically significant increase in coronary angiography use, there were no downstream increases in resource utilization. Increases in angiography likely occur because of the improved identification of high-risk patients and the expected shift from unstable angina to acute MI using hs-cTnT (20).

We demonstrate no increase in admissions or in cardiac tests such as echocardiography or stress testing. These observations should attenuate concerns about overdiagnosis and resource utilization on hs-cTnT implementation. It is critical to emphasize, however, that besides assay transition, implementation efforts also involved extensive educational efforts (14). The lack of increased resource utilization, particularly among those with cTnT increases, is notable. However, most increases were due to myocardial injury or type 2 MI; heterogeneous conditions without clear evidence-based actionable strategies, for which clinicians lack guidelines (19). These findings are similar to those observed in the High-STEACS trial (11), in which hs-cTnI reclassified patients but was not associated with improved outcomes, in large part because most events were due to type 2 MI or myocardial injury and only modest therapeutic changes occurred.

Last, whereas both men and women have more diagnoses post-implementation, sex-specific analyses demonstrate a greater incidence of cTnT increases, myocardial injury, and acute MI in women than in men. The latter findings are likely due to the transition from a contemporary assay using an overall threshold to an hs-cTnT assay with sex-specific 99th percentiles. These findings are consistent with those of Shah et al. (26) who suggested that the use of an overall threshold may contribute to the underdiagnosis of MI in women and showed that the use of an hs-cTnI assay with sex-specific thresholds doubled the diagnosis of acute MI in women as compared to the cTnI assay with an overall threshold. Whether the use of a lower sex-specific 99th percentile in women improves diagnosis, treatments, and outcomes remains uncertain, for which reason, the CODE-MI (hs-cTn-Optimizing the Diagnosis of Acute Myocardial Infarction/Injury in Women) study is testing such in a multicenter randomized controlled trial (27). Our data show that despite more diagnoses in women post-implementation, except for an overall increase in invasive coronary angiography, women with increased cTn concentrations did not undergo more noninvasive or invasive cardiac evaluations. These observations are consistent with those of Lee et al. (28) who reported women were more likely to have myocardial injury than men but were less likely to undergo additional evaluations and indicate that opportunities exist to improve care in women.

STUDY LIMITATIONS. First, the present is a retrospective, observational study, and residual confounding could exist. Results could be influenced by the pre-implementation educational efforts, as well as temporal changes in the characteristics and management of patients. Second, despite institutional recommendations for serial cTnT measurements, isolated measurements were frequent (76% using 4th Gen cTnT and 40% using 5th Gen cTnT), which likely reflect that testing is often performed in a population with a suspected lower pre-test probability for acute MI. The increased adherence to serial measurements using the recommended 0- and 2-h hs-cTnT protocol likely influenced by the educational efforts and implementation of a standardized serial sampling protocol likely contributed to the increased LOS in patients directly discharged from the ED. These findings are similar to those observed by Ford et al. (29). Third, the increase in ED discharges and reduction in LOS in those with increased cTnT during the post-implementation period may be partly related to the more rapid triage of patients but may also reflect that clinicians were educated about the fact that most cTnT increases are not due to acute MI using hs-cTnT. Thus, patients with hs-cTnT increases without acute changes on serial measurements that were clinically stable, such as those with chronic myocardial injury, do not always require hospital admission. Our study, however, did not differentiate acute from chronic injury. Fourth, diagnostic misclassification between myocardial injury and infarction is possible. Fifth, the p values and 95% CIs presented have not been adjusted for multiplicity, which is acceptable given the descriptive study design; however, inferences drawn from these statistics may not be reproducible. Sixth, even though one of the important strengths of our study is that it evaluates the transition to hs-cTnT in the community setting across 2 smaller community hospitals, larger multicenter studies are needed. Last, our findings are

based on the transition from 4th to 5th Gen cTnT, with more studies needed using other assays.

CONCLUSIONS

Hs-cTnT implementation resulted in a marked increase in myocardial injury and MI, particularly in women and patients with type 2 MI. Despite this, except for angiography, overall resource use did not increase. Among those without cTnT increases, there were more ED discharges and fewer cardiac tests.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The transition from cTnT to hs-cTnT increases myocardial injury and acute MI diagnoses, particularly in women and patients with type 2 MI. Despite this, implementation of hs-cTnT assays is not associated with significant increases in overall resource use except for a modest increase in referrals for coronary angiography.

TRANSLATIONAL OUTLOOK: Future studies should address whether implementation of hs-cTnT assays translates to improved outcomes for patients with suspected acute coronary syndromes, especially women.

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APPENDIX For supplemental methods and tables, please see the online version of this paper.