Impact on Patient Management and Outcome of Switching between 2 Contemporary Sensitive Cardiac Troponin Assays

Craig B. Wilen,1 Jeffrey J. Szymanski,1 Steven Hung,2 Anand Rajan,1 Paul M. Lavigne,3 Douglas M. Char,2 Edward M. Geltman,3 and Mitchell G. Scott1*

BACKGROUND: Myocardial infarction is characterized by an increase of cardiac troponin I (cTnI) above the 99th percentile of a reference population. Our hospital switched from 1 contemporary cTnI assay to another and observed a doubling of cTnI results above the assays’ respective 99th percentile cutoffs. We investigated the potential impact on inpatient management and outcomes.

METHODS: We performed a retrospective cohort study of 45,498 individuals with ≥1 cTnI result between January 2013 and June 2014. The Dimension cTnI assay was used in 2013; the Abbott Architect cTnI assay was used in 2014.

RESULTS: Before switching cTnI assays, 19.2% (4742/24,428) of patients had at least 1 of the first 3 cTnI above the 99th percentile (0.07 µg/L). After switching to the Architect cTnI assay, 31.4% (4034/14,626) of patients had at least 1 cTnI above the 99th percentile (0.03 µg/L). This increase was due to the difference in the assays’ 99th percentile cutoffs. Having an increased cTnI reported on the Architect assay that would not have been reported as such on the Dimension assay (0.03–0.06 µg/L) correlated with increased inpatient mortality, length of stay, non-ST elevation myocardial infarction diagnosis, therapeutic heparin use, and percutaneous coronary intervention, relative to individuals with cTnI <0.03 µg/L.

CONCLUSIONS: The changes observed in patient outcomes and management were likely due to the increased sensitivity and lower 99th percentile cutoff of the Architect assay. It is important to recognize the potential impact that differences in sensitivity and assay configuration may have on patient management.

© 2015 American Association for Clinical Chemistry

Myocardial infarction (MI)4 is characterized by a rise and/or fall in a cardiac troponin biomarker with ≥1 value above the 99th percentile of a reference population (1, 2). Both cardiac troponin I (cTnI) and cTnT assays are widely used and are considered diagnostically equivalent (1). In addition to diagnostic utility, cardiac troponin has prognostic value in both cardiac and noncardiac settings, including individuals with exacerbation of chronic obstructive pulmonary disease, sepsis, pulmonary embolism, and major noncardiac surgery (3–6).

Despite their proven clinical utility, cardiac troponin assays have several limitations. First, analytical variation at the 99th percentile cutoff concentration varies among assays, thus confounding the interpretation of small cardiac troponin concentration changes at low cardiac troponin values (7). Second, because cTnI assays are not standardized (8), each assay manufacturer must determine its own 99th percentile cutoff. This variability is confounded by the lack of a consensus definition regarding appropriate sample size and specific composition of a reference population (7, 9). Small changes in assay sensitivity and resulting changes in the 99th percentile cutoff may have significant implications on patient management and outcomes. For example, increased cardiac troponin may determine whether a patient undergoes a stress test or cardiac catheterization (1).

Most contemporary sensitive cardiac troponin assays have an analytical sensitivity below the 99th percentile of a healthy reference population, whereas high-sensitivity assays, by definition, detect cardiac troponin above the limit of detection in at least half of the reference population (10). Although high-sensitivity cardiac troponin assays are in wide use in Europe and elsewhere, they are not yet available in the US, and therefore contemporary sensitive cardiac troponin assays remain the standard of care.

1 Department of Pathology and Immunology, 2 Department of Emergency Medicine, and 3 Cardiovascular Division, Department of Medicine, Washington University School of Medicine, St. Louis, MO.
* Address correspondence to this author at: 6605 Euclid Ave, Campus Box 8118, St. Louis, MO 63110. E-mail: mscott@path.wustl.edu.
Received January 6, 2015; accepted March 23, 2015.
Previously published online at DOI: 10.1373/clinchem.2015.238089

Disclaimer: The contents of this paper are solely the responsibility of the authors.

4 Nonstandard abbreviations: MI, myocardial infarction; cTnI, cardiac troponin I; cTnT, cardiac troponin T; BJH, Barnes-Jewish Hospital; LOD, limit of detection; LOS, length of stay; ICD9, International Classification of Diseases, Ninth Revision; ACS, acute coronary syndrome; STEMI, ST-elevation MI; NSTEMI, non-ST elevation MI; ICS/UA, intermediate coronary syndrome/unstable angina; ED, emergency department; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention.

Copyright (C) 2015 by The American Association for Clinical Chemistry
Recently, to consolidate testing platforms, our hospital laboratory switched from 1 contemporary sensitive cTnI assay to another. Despite using the 99th percentile cutoffs from the respective package inserts, we noticed a significant increase in the frequency of cTnI values above the 99th percentile cutoff at patient presentation after switching cTnI platforms. Both the limits of detection and the 99th percentile cutoffs were considerably lower for the newer assay. In this article, we investigate the impact of the higher incidence of increased cTnI values on inpatient care and management.

Methods

StUDY DeSIGN
This retrospective cohort study of adults (>18 years old) examined 45,498 unique patient visits with ≥1 cTnI test performed at Barnes-Jewish Hospital (BJH) laboratories between January 2013 and June 2014. Samples from unidentifiable individuals, including those from clinical trials and John/Jane Does, were excluded. Individuals were classified based on the assay used for their first cTnI measurement. There were no significant changes in order sets or clinical protocols during the study period. This study was approved by the Washington University Institutional Review Board.

SiEMENS DIMENSION Rxl cTnI ASSAy
Our laboratory used the Siemens Dimension RxL cTnI assay from 1999 to January 2014. We used the 99th percentile cutoff of 0.07 μg/L from the package insert (11). The reported CV at the 99th percentile was 20%, the 10% CV concentration was 0.14 μg/L, and the limit of detection (LOD) was 0.04 μg/L (10, 12). Any value <0.07 μg/L was reported as “<0.07 μg/L.” Any value >0.24 μg/L was flagged as a critical value and triggered a call to the ordering clinician. Values between 0.07 and 0.24 μg/L were flagged as abnormal but not called back as critical values. Sex-specific cutoffs were not used.

ABBOTT ARCHITECT STAT cTnI ASSAy
In January 2014, our laboratory switched to the Abbott Architect STAT cTnI assay. A 99th percentile cutoff of <0.03 μg/L was used. According to the manufacturer, the CV at the package insert 99th percentile (0.028 μg/L) was 14%, the 10% CV concentration was 0.032 μg/L, and the LOD was 0.009 μg/L (10, 13). Values <0.03 μg/L were reported as “<0.03 μg/L.” All values >0.03 μg/L were flagged as abnormal, and values ≥0.20 μg/L triggered a critical alert call from the laboratory to the clinician. Sex-specific cutoffs were not used.

cTnI METHODS COMPARISON AND CV DETERMINATION
As part of the clinical validation before switching from the Dimension to the Architect cTnI assay, 209 samples with a cTnI range from undetectable to 34 μg/L on the Dimension were split and simultaneously run on both platforms. To determine CVs for both assays, we assessed the analytical variation of 4 Bio-Rad QC samples across a range of cTnI concentrations for a period of 1 month during clinical use of each method (December 2013 for Dimension and May 2014 for Architect). The QC samples were analyzed 3–4 times throughout the day.

PREPARATIONS FOR ASSAY SWITCH
Four months before the cTnI assay switch, key clinicians were notified, including the directors of the BJH heart failure program, cardiac care unit, and emergency department chest pain program. Two months before the assay switch, direct comparison data was generated and reviewed with the same clinicians. One month before the assay switch, a hospital-wide newsletter was disseminated explaining the new cTnI assay and its performance characteristics.

CLINICAL DATA COLLECTION
Data including cTnI results, patient age, and sex were collected from the laboratory information system (Cerner Millennium). All-cause inpatient mortality, length of stay (LOS), discharge diagnosis (International Classification of Diseases, Ninth Revision (ICD9) codes), therapeutic heparin administration, and whether an individual had an inpatient stress test or nonsurgical cardiac procedure were obtained from the individual’s billing records. LOS data was only available rounded down to the nearest integer of days. Therapeutic heparin administration was determined by whether an individual received heparin as part of an acute coronary syndrome (ACS) order set.

We used the top 15 ICD9 codes at discharge from each patient to classify the presence of ischemic heart disease (ICD9 410–414); ST-elevation MI (STEMI) (410 excluding 410.7); non–ST elevation MI (NSTEMI) (410.7); intermediate coronary syndrome (ICS/UA), which includes unstable angina, preinfarction angina, impending infarction, and preinfarction syndrome (411.1); or angina (413.9). Any individual with an ICD9 code corresponding to STEMI, NSTEMI, or ICS/UA was considered to have ACS. ICD9 codes were determined by the clinician at the time of discharge and were not evaluated further.

The results of stress tests and nonsurgical cardiac procedures were determined by manual chart review of the electronic medical record (Clinical Desktop 2). Stress tests and cardiac procedure results were extracted by 2 independent physicians, with discrepancies reconciled by a third physician when necessary. A subset (1977/728) of patients with cTnI <0.03 μg/L were selected for review with a random number generator. A positive exercise stress test was defined as ≥1 mm ST depression in ≥2
Consequences of Switching cTnl Assays

electrocardiogram leads or $\geq 1.5$ mm ST depression if the depression was upsloping (14). A stress test was deemed inconclusive if there was no evidence of ischemia and the test was stopped before achieving 85% of maximal predicted heart rate. Most stress tests were performed in conjunction with myocardial imaging, either stress echocardiography or stress myocardial perfusion imaging. When these tests were performed, the results of the imaging determined whether the test was indicative of ischemia. An echo stress test was considered positive when a new or worsening wall motion abnormality developed with stress. A myocardial perfusion study was considered positive when a new or worsening perfusion defect was detected.

Nonsurgical cardiac procedures included pacemaker or implantable cardioverter-defibrillator placements, ablations, pericardiocentesis, and cardiac catheterizations. A percutaneous coronary intervention (PCI) was defined as the successful placement of $\geq 1$ coronary artery stents.

LOCATION CLASSIFICATION

Although the vast majority of samples with a known location were from individuals in the emergency department (ED) or admitted to BJH, approximately 1% of individuals had an initial cardiac troponin in an affiliated clinic or peripheral facility. These individuals were included, since a positive cTnl would likely have resulted in further testing or admission to BJH. Patients were classified into 6 groups based on their location at the time of initial cTnl. ED individuals included those in the ED or 24-h observation unit. Intensive care unit (ICU) patients included those in any medical or surgical ICU. Patient classified as “inpatient floor” had their first cTnl as an inpatient, but outside of the ED or an ICU. “Outpatients” included those with a first cTnl during an office visit. Individuals with a classification of “other” included those who had their initial cTnl at an affiliated dialysis center, rehabilitation institute, or same-day procedure center. Individuals with an “unknown” classification were predominantly inpatients of an indiscernible location.

MISSING DATA

Unlike for the other variables available in our database in near-real time, there was a 2- to 3-month delay from actual discharge time until the availability of LOS data. All attempts were made to reconcile missing LOS data. Incidents with missing data were individually queried and combined with a concurrent or contiguous encounter of the same individual. However, there was a slight increase in missing LOS data from more recent individuals: 256 individuals (0.08%) had missing LOS data in the Dimension group and 231 individuals (0.16%) in the Architect group. These individuals were excluded only from analyses of LOS.

DATA ANALYSIS

Data cleanup and management was performed with Microsoft Excel and SPSS Statistics 22. A given admission or encounter was defined by a billing number specific to a single visit. Thus, repeat encounters by a single individual during the 18-month study period were analyzed as unique events. The chronological order of cTnl values was determined by ordering time, and when ordering time was identical, the time a sample was received for testing was used. Details on sample collection time were not available.

Statistical analysis was performed with SPSS Statistics 22 and GraphPad Prism 6. Categorical variables were compared with Pearson $\chi^2$ tests. Age and number of cTnl tests per visit were compared with a $t$-test, whereas LOS was compared with a Mann–Whitney test. To calculate the odds ratios (ORs) for age and LOS, both variables were dichotomized at the value corresponding to the inflection point in the ROC curve, 58.5 years and 1 day, respectively. Stress test results were analyzed by multinomial logistic regression. To assess the consequences of the increase in abnormal cTnl results, binomial logistic regression analysis was performed to compare patients analyzed on the Architect with maximum cTnl values of $<0.03$ µg/L to patients with maximum cTnl values of 0.03–0.06 µg/L. Age and sex were added as additional predictors. For each dependent variable analyzed, a test of the full model against a constant-only model was statistically significant ($P < 0.01$) unless otherwise noted. A $P$ value of $<0.05$ was considered significant.

Results

PARTICIPANT DEMOGRAPHICS

There were 30 872 unique patient visits in the 12 months before the assay switch (Dimension), and 14 626 in the 6 months after the assay switch (Architect) (Table 1). No changes were made to ordering sets or ED protocols during this time. Compared with 4034 (27.6%) individuals with the Architect assay ($P < 0.0001$), 4472 (15.4%) individuals had an initial increased cTnl with the Dimension assay. Similarly, 19.2% of patients in the Dimension group had an increase in $\geq 1$ of the first 3 cTnl values compared with 31.4% in the Architect group ($P < 0.0001$). This increase in individuals with an increased cTnl was similar among subgroups with and without a diagnosis of ischemic heart disease: 69% for those without and 57% for those with ischemic heart disease. Between the Dimension and Architect groups, there was no change in number of visits over time ($P = 0.96$), mean age (59.5 vs 59.7 years; $P = 0.10$), or sex distribution (51.2% vs 51.4% female; $P = 0.65$). Both groups averaged 2.1 cTnls per visit. There was a statistically significant, albeit small, shift in patient location across the 2 groups ($P < 0.001$), with a slight increase ($<1.5\%$) in
patients with an initial cTnI collected in the ED, outpatient clinic, or unknown location and a concomitant decrease in cTnIs from inpatient floors, ICUs, and other affiliated facilities. In addition, there was a slight decrease in LOS (P < 0.001), although both groups had an identical median (2 days) and interquartile range (0–5 days).

Although there was no difference in the discharge diagnosis of ischemic heart disease, which included old MIs (27.2% vs 27.4%; P = 0.74), there was a significant increase in the diagnosis of ACS (5.6% vs 6.8%; P < 0.0001) after institution of the Architect method, owing to an increase in NSTEMI diagnoses (4.0% vs 5.3%; P < 0.0001). There were no significant differences in diagnosis of STEMI (0.46% vs 0.57%; P = 0.14), ICS/UA (1.2% vs 1.0%; P = 0.11), or angina (0.89% vs 0.92%; P = 0.76).

Between the 2 groups, there was no difference in frequency of nonsurgical cardiac procedures (7.9% vs 7.8%; 0.71), stress tests (6.6% vs 6.5%; P = 0.70), or heparin ordered as part of an ACS order set (4.8% vs 4.5%; P = 0.26). However, there was a slight but statistically significant decrease in inpatient mortality rate (3.9% vs 3.5%; P = 0.03). Similar trends were seen when analysis was limited to only ED patients (see Supplemental Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol61/issue6).

**DIRECT ASSAY COMPARISONS**

When 209 samples were analyzed by both methods, the best-fit line on the log2-transformed data set was y = 0.956x – 0.304, with an R² of 0.93 (Fig. 1A), whereas the best-fit line (on untransformed data) for only those values <0.25 µg/L (on both assays) was y = 0.834x + 0.005, with an R² of 0.65 (Fig. 1B). Notably, the intersection of the 2 reported 99th percentile cutoffs (0.07 µg/L for the Dimension and 0.03 µg/L for the Architect) fell outside the 95% CI for the best-fit lines calculated on
either a log2 transform or that of only samples with a cTnI $< 0.25 \mu g/L$ ($n = 99$). The regression predicted a measurement of $0.07 \mu g/L$ on the Dimension that was roughly equivalent to $0.06 \mu g/L$ on the Architect. Over a 1-month period, the observed cTnI concentration at which the CV was 10% was approximately $0.43 \mu g/L$ on the Dimension and approximately $0.061 \mu g/L$ on the Architect (Fig. 1C), in contrast to $0.14 \mu g/L$ and $0.032 \mu g/L$ reported for each assay respectively (10–13).

LOW-LEVEL TROPOININ INCREASES CORRELATE WITH POOR OUTCOMES

Of the 14626 Architect encounters, 10032 (68.6%) had a maximum cTnI (of the first 3 tests) of $< 0.03 \mu g/L$, 2067 (14.1%) had a maximum cTnI of $0.03–0.06 \mu g/L$, 1384 (9.5%) had a maximum cTnI of $0.07–0.24 \mu g/L$, and 1143 (7.8%) had a maximum cTnI of $0.24 \mu g/L$ (Table 2).

Compared with those with a maximum cTnI $< 0.03 \mu g/L$, individuals with a maximum cTnI of $0.03–0.06 \mu g/L$ were significantly older (OR 2.4, 95% CI 2.2–2.6), less likely to be female (OR 0.65, 95% CI 0.59–0.72), and more likely to have a discharge diagnosis of ischemic heart disease (OR 2.6, 95% CI 2.4–2.9), ACS (OR 3.1, 95% CI 2.4–4.1), or angina (OR 2.3, 95% CI 1.5–3.5). The increase in ACS was primarily due to an increase in NSTEMI diagnoses (OR 15.5, 95% CI 9.3–25.7), as there were no significant differences in the frequency of STEMI or ICS/UA (Table 2). In addition, patients with a cTnI of $0.03–0.06 \mu g/L$, compared to those with a maximum cTnI of $< 0.03 \mu g/L$, had a longer median LOS (OR 3.3, 95% CI 3.0–3.7) and were more likely to receive therapeutic heparin (OR 2.4, 95% CI 1.9–3.0) and undergo a left heart catheterization and angiogram (OR 2.5, 95% CI 1.9–3.1). Of those who underwent an angiogram, there was a similar frequency of those who had a PCI (29.46% vs 30.1%; $P = 0.90$).

Patients with a maximum cTnI of $0.03–0.06 \mu g/L$, compared with those with a maximum cTnI $< 0.03 \mu g/L$, were less likely to get a stress test (OR 0.71, 95% CI 0.57–0.87) but more likely to have a positive (OR 3.0, 95% CI 1.1–7.6) or inconclusive (OR 3.5, 95% CI 1.4–8.8) stress test. Finally, individuals with a maximum cTnI of $0.03–0.06 \mu g/L$ had significantly higher inpatient mortality (OR 3.0, 95% CI 2.2–3.9). The trends described were similar when the analysis was limited to only ED patients (see online Supplemental Table 2) or patients with a LOS $< 30$ days.

Across all 4 Architect groups, the cTnI value was associated with an increase in age, male sex, LOS, ACS diagnosis, cardiac procedures, PCIs, and therapeutic heparin administration. In addition, mortality increased concomitantly with the maximum cTnI from 1.3% ($< 0.03 \mu g/L$) to 3.9% ($0.03–0.06 \mu g/L$) to 8.5% ($0.07–0.24 \mu g/L$) to 15.1% ($> 0.24 \mu g/L$). A similar trend was seen across Dimension groups (see online Supplemental Table 3).

Whereas there were substantial differences in patient outcomes between the $< 0.03$ and $0.03–0.06 \mu g/L$ groups, there was a significant association between adverse outcomes, advanced age, and male sex. However, after adjusting for these significant covariates, all variables remained significantly associated with the maximum cTnI (Table 2).

Discussion

On switching from the Dimension to the Architect cTnI assay, we noticed a near 2-fold increase in the number of patients with a cTnI above the respective 99th percentile...
This corresponded to approximately 12% of all patients tested or 3800 patients annually at our institution. Individuals with a low-level cTnI increase (\(<\text{99th percentile}) on the Architect assay, who would have had a negative cTnI (\(<\text{99th percentile}) reported on the Dimension assay, had significantly different outcomes, including increased mortality, LOS, cardiac catheterizations, and therapeutic heparin administration. This increase in low-level cTnIs above the 99th percentile was associated with a gain of prognostic information and may have improved patient management and outcomes.

There are several potential explanations for the nearly 2-fold increase in patients with increased cTnI observed after switching assays. First, and quite likely, the increase could be due to differences in analytical sensitivity and differences in imprecision at the 99th percentile. The analytic sensitivity of the Architect is lower than that of the Dimension, which is likely due to detection of different cTnI fragments and assay design (antibodies, signal molecules, and instrumentation) (7, 10). Although the 99th percentile cutoff is relatively independent of the analytical variance (15), imprecision >20% CV at the 99th percentile (as observed for the Dimension) can artificially raise the 99th percentile (16). Second, differences in the composition or inclusion criteria of the reference population used to determine the 99th percentiles in the package inserts might result in the different reported cutoffs. The age ranges were 18 – 83 years for the Dimension and 18 – 63 years for the Architect, with an equal sex distribution; however, detailed demographics and inclusion criteria such as cardiac risk factors, renal disease, and electrocardiogram and stress test screening results, if any, were not described for either assay (11, 13). In addition, the sizes of the reference populations, 342 and 449 for the Dimension and Architect, respectively, were fewer than the proposed 650 individuals needed for an accurate determination of the 99th percentile range (16). Finally, it is possible that our patient demographics shifted to a sicker population over the study period. This is highly unlikely, given that the inner...

### Table 2. Outcomes of Architect subjects stratified by maximum cTnI.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;0.03</th>
<th>0.03-0.06</th>
<th>0.07-0.24</th>
<th>&gt;0.24</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)&lt;br&gt;a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient visits</td>
<td>10032 (68.6)</td>
<td>2067 (14.1)</td>
<td>1384 (09.5)</td>
<td>1143 (07.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>57.3 (16.1)</td>
<td>64.7 (15.4)</td>
<td>65.07 (16.02)</td>
<td>66.06 (15.20)</td>
<td>2.4 (2.2-2.6)&lt;br&gt;c NA&lt;br&gt;d</td>
<td>2.1 (1.8-2.3)</td>
</tr>
<tr>
<td>Female sex</td>
<td>5490 (54.7)</td>
<td>911 (44.1)</td>
<td>622 (44.9)</td>
<td>497 (43.48)</td>
<td>0.65 (0.59-0.72)</td>
<td>NA</td>
</tr>
<tr>
<td>Median length of stay (IQR)</td>
<td>1 (0-3)</td>
<td>3 (1-7)</td>
<td>4 (2-9)</td>
<td>5 (3-10.5)</td>
<td>3.3 (3.0-3.7)&lt;br&gt;e 2.9 (2.6-3.2)&lt;br&gt;e</td>
<td></td>
</tr>
<tr>
<td>ICD-9</td>
<td>1782 (17.8)</td>
<td>750 (36.3)</td>
<td>651 (47.0)</td>
<td>820 (71.7)</td>
<td>2.6 (2.4-2.9)</td>
<td>2.1 (1.8-2.3)</td>
</tr>
<tr>
<td>ACS</td>
<td>139 (1.4)</td>
<td>87 (4.2)</td>
<td>208 (15.0)</td>
<td>563 (49.3)</td>
<td>3.1 (2.4-4.1)</td>
<td>2.6 (1.9-3.4)</td>
</tr>
<tr>
<td>STEMI</td>
<td>6 (0.05)</td>
<td>3 (0.15)</td>
<td>7 (0.51)</td>
<td>67 (5.9)</td>
<td>2.4 (0.61-9.7)</td>
<td>2.0 (0.47-8.1)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>20 (0.20)</td>
<td>62 (3.0)</td>
<td>195 (14.1)</td>
<td>494 (43.2)</td>
<td>15.5 (9.3-25.7)</td>
<td>12.0 (7.1-20.1)</td>
</tr>
<tr>
<td>ICS/UA</td>
<td>115 (1.2)</td>
<td>22 (1.1)</td>
<td>7 (0.51)</td>
<td>5 (0.44)</td>
<td>0.93 (0.59-1.5)</td>
<td>0.78 (0.49-1.3)</td>
</tr>
<tr>
<td>Angina</td>
<td>69 (0.69)</td>
<td>32 (1.6)</td>
<td>24 (1.7)</td>
<td>9 (0.79)</td>
<td>2.3 (1.5-3.5)</td>
<td>2.1 (1.3-3.2)</td>
</tr>
<tr>
<td>Cardiac procedure</td>
<td>386 (3.9)</td>
<td>215 (10.4)</td>
<td>191 (13.8)</td>
<td>354 (31.0)</td>
<td>2.9 (2.4-3.5)</td>
<td>2.5 (2.1-3.0)</td>
</tr>
<tr>
<td>Left heart angiogram</td>
<td>229 (2.3)</td>
<td>112 (5.4)</td>
<td>123 (8.9)</td>
<td>277 (24.2)</td>
<td>2.5 (1.9-3.1)</td>
<td>0.74 (0.53-1.0)</td>
</tr>
<tr>
<td>PCI</td>
<td>69 (0.69)</td>
<td>33 (1.6)</td>
<td>36 (2.6)</td>
<td>159 (13.9)</td>
<td>2.3 (1.5-3.6)</td>
<td>0.79 (0.50-1.2)</td>
</tr>
<tr>
<td>Stress test</td>
<td>728 (7.3)</td>
<td>108 (5.2)</td>
<td>73 (5.3)</td>
<td>48 (4.2)</td>
<td>0.71 (0.57-0.87)</td>
<td>0.74 (0.60-0.91)</td>
</tr>
<tr>
<td>Positive</td>
<td>8 (4.1)&lt;br&gt;f</td>
<td>11 (10.2)</td>
<td>7 (9.6)</td>
<td>7 (14.6)</td>
<td>3.0 (1.1-7.6)</td>
<td>3.0 (1.1-8.1)</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>8 (4.1)&lt;br&gt;f</td>
<td>13 (12.0)</td>
<td>9 (12.3)</td>
<td>5 (10.4)</td>
<td>3.5 (1.4-8.8)</td>
<td>3.2 (1.3-8.4)</td>
</tr>
<tr>
<td>Therapeutic heparin</td>
<td>202 (2.0)</td>
<td>96 (4.6)</td>
<td>145 (10.5)</td>
<td>220 (19.3)</td>
<td>2.4 (1.9-3.0)</td>
<td>1.6 (1.2-2.0)</td>
</tr>
<tr>
<td>Mortality</td>
<td>134 (1.3)</td>
<td>80 (3.9)</td>
<td>117 (8.5)</td>
<td>173 (15.14)</td>
<td>3.0 (2.2-3.9)</td>
<td>2.5 (1.9-3.4)</td>
</tr>
</tbody>
</table>

| a Data are n (%) or mean (SD) unless noted otherwise.  
| b Adjusted for age and sex.  
| c An age cutoff of 58.5 years was used to determine the OR.  
| d NA, not applicable.  
| e A length-of-stay cutoff of 1 day was used to determine the OR.  
| f Of the 728 stress tests performed, 197 were randomly selected for review.  

crease in cTnI values correlated precisely with the time of assay switch. This study has several strengths. First, the broad inclusion criteria accurately reflect real-world cardiac troponin utilization. Second, it includes a large sample size, allowing for detection of significant differences among relatively rare outcomes. Third, it captures critical outcomes associated with increased cTnI, namely mortality, PCI, and ACS diagnosis.

This study also has several limitations. First, it is a retrospective review from a single academic tertiary-care center, which introduces potential reporting and selection bias. Second, the outcomes of death, cardiac catheterization, and stress tests are an underestimate, since if these occurred outside of the same admission as the cTnI result, they would not be captured. Also, the rate of therapeutic heparin use may also be an underestimate, as it reflects only heparin ordered through a specific ACS order set. Third, ICD9 codes, which may contain inaccuracies, were used to determine discharge diagnoses. Fourth, it is possible that unknown confounders influenced patient selection. We attempted to mitigate such bias by controlling for age and sex and performing subgroup analysis on individuals who presented to the ED and those with a LOS < 30 days.

The data presented here highlight the real-world consequences that can result from changing troponin methods that have differences in analytic sensitivity, imprecision, and 99th percentile cutoffs. These changes led to real changes in outcomes, patient management, and particularly, distinguishing individuals with NSTEMI from UA. As high-sensitivity cardiac troponin assays gain Food and Drug Administration approval in the US, many clinical laboratories will be switching cardiac troponin assays and will likely observe significant changes in the frequency of increased cTnI results that will have similar consequences on patient management, prognosis, and outcome.

**Author Contributions:** All authors contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors’ Disclosures or Potential Conflicts of Interest:** Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

**Employment or Leadership:** M.G. Scott, Clinical Chemistry, AACC.

**Consultant or Advisory Role:** None declared.

**Stock Ownership:** None declared.

**Honoraria:** None declared.

**Research Funding:** M.G. Scott, Abbott Laboratories and Siemens.

**Expert Testimony:** None declared.

**Patents:** None declared.

**Role of Sponsor:** The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

**Acknowledgments:** We thank Brenda Grossman, Vic Agarwal, Anne Marie-Greene, Adrain McClelland, Andrew Locke, and Nicholas Parish for data collection and helpful discussions. We also thank Sishewan Stulcliff of the Washington University Clinical and Translational Research Core for statistical review that was made possible by UL1 RR024992 from the National Center for Research Resources (NCRR) of the NIH.

References


