Stratified Reporting of High Sensitivity Troponin I Assay Is Associated With Suboptimal Management of Patients With Acute Coronary Syndrome and Intermediate Troponin Elevation

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Background: Newer troponin assays provide high sensitivity and precision and are reported in a stratified manner by some laboratories. We sought to investigate the clinical impact of such reporting in the treatment of patients with suspected acute coronary syndrome (ACS). **Methods:** We identified patients presenting with suspected ACS over a one-year period. Patients were stratified based on their peak troponin I values within 24 hours of admission into the following categories as reported by our laboratory: troponin value ≤ 0.03 ng/ml, which is reported as normal (negative troponin group), troponin value 0.04–0.29 ng/ml, which is reported as suggestive of myocardial damage (intermediate troponin group), and troponin value ≥ 0.3 ng/ml which is reported as indicative of myocardial necrosis (high troponin group). **Results:** Plasma

troponin concentrations were ≤ 0.03 ng/ml in 77 patients (68.7%), 0.04–0.29 ng/ml in 18 patients (16.1%), and ≥ 0.30 ng/ml in 17 patients (15.2%). Patients in the intermediate troponin group had thrombolysis in myocardial infarction (TIMI) risk scores that were similar to that of the high troponin group. Despite this, patients in the intermediate troponin group were almost 50% less likely to receive coronary angiography, anticoagulation, and clopidogrel when compared to the high troponin group. **Conclusion:** Patients in the intermediate troponin group that meet the guideline definition of acute myocardial infarction are less likely to receive optimal medical and invasive therapy as compared to the high troponin group even though TIMI risk scores were similar in the two groups. *J. Clin. Lab. Anal.* 27:402–406, 2013. © 2013 Wiley Periodicals, Inc.

Key words: acute coronary syndrome; myocardial infarction; biological markers; troponin; sensitive troponin assay

INTRODUCTION

The latest generation of sensitive troponin assays has been shown to improve the early diagnosis of myocardial infarction due to its high accuracy at lowered thresholds for detecting myocardial necrosis (1, 2). The clinical use of high sensitivity troponin assay has thus far been limited by the lack of standardization of optimal cut-off and reporting values (3–5). The Global Task Force for the Universal Definition of Myocardial Infarction and the National Academy of Clinical Biochemistry recommends that to diagnose an acute myocardial infarction (AMI), an elevation in cTn concentrations above the 99th percentile of a healthy population should be used as the target cut-off as long as the assay used for this measurement has a coefficient variation (CV) of $\leq 10\%$ (6, 7). Newer genera-

tion of troponin assays are able to meet these precision criteria at the diagnostic threshold. Despite this, a wide

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range of upper reference limits are currently in use in clinical practice and thus complicating the diagnosis of AMI for clinicians (8). We examine the practice patterns of a facility where a stratified troponin reporting is utilized using the values for diagnostic cut-off value recommended by the manufacturer (≥ 0.3 ng/ml) and the target cut-off based on the recommendations by the Global Task Force (6–9). In this institution, troponin values are reported with values under 0.03 ng/ml as normal, between 0.03 and 0.3 ng/ml reported as *suggestive* of myocardial damage, and values above 0.3 ng/ml reported as *indicative* of myocardial necrosis. The clinical impact of such stratified reporting patterns remains unknown.

METHODS

This was a retrospective cohort study by chart review using electronic medical record system at the Providence Veterans Affairs Medical Center.

Patient Population

All patients with suspected acute coronary syndrome (ACS) evaluated in the Providence Veterans Affairs Medical Center between the adoption date of the new sensitive troponin assay and up to 12 months after (August 2010 to August 2011) were screened using ICD 9 codes, which included AMI. Patients were included in the analysis if they presented with chest pain and had a troponin drawn within two hours of evaluation. We applied the same exclusion criteria used in the clinical trials of new sensitive troponin assays (10), which included stage IV chronic kidney disease with glomerular filtration rate (GFR) <30 ml/min, poorly controlled tachyarrhythmia, anemia with hematocrit <24 , severe valvular disease, hypertrophic cardiomyopathy, pericarditis, or cocaine use.

Troponin Testing

Troponin I concentrations were measured using the Abbott ARCHITECT assay, which was revised in November 2009 (Abbott Laboratories, Abbott Park, IL). The 99% percentile of a reference population is reported by the manufacturer to be 0.028 ng/ml with a 10% coefficient of variation of 0.032 ng/ml (9). As per manufacturer's guidelines, the diagnostic threshold for AMI of the assay is 0.3 ng/ml (9). Following these guidelines, the hospital lab reports troponin values as follows: troponin values 0.03 ng/ml or below, which is reported as normal, between 0.04 and 0.29 ng/ml, which is reported as *suggestive* of myocardial damage, and values 0.3 ng/ml or above, which is reported as *indicative* of myocardial necrosis.

End Points

The primary end point for this analysis was clinical management during index hospitalization including rates

of optimal medical therapy for AMI including dual antiplatelet therapy, statin, beta blocker and anticoagulation use, and coronary angiography. Secondary end points included revascularization rates on index admission and frequency of rehospitalization, revascularization, and death at follow-up.

Data Collection

Baseline clinical characteristics, cardiac risk factors, and medications on admission were reviewed. Thrombolysis in myocardial infarction (TIMI) risk scores (range 0–7) were calculated using the sum of seven variables with one point for each variable if present: age ≥ 65 years, ≥ 3 risk factors for coronary artery disease, use of aspirin within past seven days, known coronary artery stenosis $\geq 50\%$, ≥ 2 episodes of angina within the past 24 hours, ST-segment deviation, and elevated cardiac biomarker (11). For elevated cardiac biomarker, troponin values >0.03 ng/ml was used as the diagnostic threshold per 99% percentile cut-off suggested by the manufacturer. Information regarding clinical management during index admission including referral to cardiology, coronary angiography, and coronary revascularization as well as medications on discharge was abstracted. At a median follow-up of 479 ± 119 days, information regarding readmission, stress testing, and revascularization was collected.

Statistical Analysis

Patients were stratified into three categories based on their peak troponin levels within 24 hours of admission: less than or equal to 0.03 ng/ml (negative troponin group), troponin assay concentrations of 0.04 to 0.29 ng/ml (intermediate troponin group), and plasma troponin concentrations of 0.3 ng/ml or more (high troponin group). Baseline characteristics were compared across the three categories using ANOVA for continuous and chi-square analyses for discrete variables. Similar testing strategy was used for the comparison of the management of patients and medication upon discharge as described in the outcome section mentioned above. Data were analyzed using STATA version 10. A 2-sided P value of <0.05 was considered significant.

RESULTS

We identified 451 patients who met the inclusion criteria. Among these, 339 patients had at least one of the pre-specified exclusion criteria and were thus excluded from the study. In all, 112 patients with suspected ACS were included in the study. Within the study population, 77 patients (68.7%) had plasma troponin assay concentration less than or equal to 0.03 ng/ml, 18 patients (16.1%)

TABLE 1. Baseline Characteristics

	(≤ 0.03 ng/ml) Negative troponin group; $n = 77$	(0.04–0.29 ng/ml) Intermediate troponin group; $n = 18$	(≥ 0.30 ng/ml) High troponin group; $n = 17$	<i>P</i> value
Age	68.5 $\pm$ 12.5	72.7 $\pm$ 10.9	68.7 $\pm$ 15.1	0.401
Men	76 (98.7%)	18 (100%)	17 (100.0%)	0.795
History of PCI	19 (24.7%)	5 (27.8%)	8 (47.1%)	0.180
History of CABG	18 (23.4%)	9 (50.0%)	2 (11.2%)	0.024
History of heart failure	9 (11.7%)	5 (27.8%)	3 (17.6%)	0.220
History of stroke	4 (5.2%)	1 (5.6%)	0 (0.0%)	0.625
Hypertension	66 (85.7%)	15 (83.3%)	13 (76.5%)	0.642
Hyperlipidemia	58 (75.3%)	13 (72.2%)	12 (70.1%)	0.904
Diabetes Mellitus	23 (30.0%)	10 (55.6%)	6 (35.3%)	0.120
Current smoker	17 (22.1%)	8 (44.4%)	7 (41.2%)	0.077
Former smoker	36 (46.8%)	6 (33.3%)	4 (23.5%)	0.163
ST segment depression on presenting ECG	2 (2.6%)	3 (16.7%)	3 (17.7%)	0.021
T wave inversion on presenting ECG	15 (19.5%)	4 (22.2%)	7 (41.2%)	0.158
Bundle branch block	2 (2.6%)	1 (5.6%)	0	0.594
Mean TIMI score	2.1 $\pm$ 1.1	3.8 $\pm$ 0.9	3.5 $\pm$ 1.5	0.160
Medications on admission				
Aspirin	50 (65.0%)	14 (77.8%)	12 (70.6%)	0.557
Clopidogrel	9 (11.7%)	2 (11.1%)	3 (17.6%)	0.783
Beta blocker	46 (60.0%)	9 (50.0%)	12 (70.6%)	0.462
ACE/ARB	40 (51.9%)	9 (50.0%)	6 (35.3%)	0.460
Statins	54 (70.1%)	12 (66.7%)	10 (58.8%)	0.660

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ECG, electrocardiogram; TIMI, thrombolysis in myocardial infarction; ACE/ARB, angiotensin converting-enzyme inhibitor/angiotensin II receptor blocker.

had plasma troponin assay concentrations of 0.04–0.29 ng/ml and plasma troponin concentrations of 0.3 ng/ml or more.

Baseline Characteristics

The majority of patients in the study were men with one woman in the entire cohort. Baseline characteristics of the patients in the three troponin groups are presented in Table 1. Patients in the intermediate troponin group had the highest rates of prior coronary artery bypass grafting (CABG; 24.7% in the negative troponin group versus 50.0% in the intermediate troponin group and 11.2% in the high troponin group; $P = 0.024$). Baseline cardiac medication profile at admission among the three groups was similar. The intermediate troponin group had TIMI risk scores that were similar to those of the high troponin group (3.8 $\pm$ 0.9 in the intermediate group versus 3.5 $\pm$ 1.5 in the high troponin group and 2.1 $\pm$ 1.1 in the normal troponin group; $P = 0.160$).

Hospital Management

There were significant differences in the clinical management of patients among the three troponin groups (Table 2). The frequency of cardiology referrals was significantly different among the three groups with the low-

est frequency of referrals in the negative troponin group (33.8%), followed by the intermediate troponin group (72.2%), and highest frequency seen in the high troponin group (88.2%; $P < 0.001$). Similarly, rates of anticoagulation use were significantly different among the three groups. The lowest rates of anticoagulation were observed in the negative troponin group (9.1%), followed by the intermediate troponin group (38.9%), and highest rates were observed in the high troponin group (76.5%; $P < 0.001$). Coronary angiography was less frequently performed in the negative troponin group (5.2%), followed by the intermediate group (33.3%), and highest rates were observed in the high troponin group (64.7%; $P < 0.001$ between the groups). Also, revascularization rates were significantly different among the three groups, with the highest rates of percutaneous coronary intervention (PCI) in the high troponin group (29.4% versus 16.7% in the intermediate group and 0% in the negative troponin group; P value < 0.001). Similarly, CABG was also performed most frequently among patients in the high troponin group (23.5% versus 5.6% in the intermediate group and 0% in the negative troponin group; $P < 0.001$). In contrast, the negative troponin group had the highest rates of stress testing (39.0% versus 11.1% in the intermediate troponin group and 5.9% in the high troponin group; $P = 0.004$). At discharge, clopidogrel was prescribed more frequently in the high troponin group (70.6% versus 33.3%

TABLE 2. Management of Patients

	(≤ 0.03 ng/ml) Negative troponin group; $n = 77$	(0.04–0.29 ng/ml) Intermediate troponin group; $n = 18$	(≥ 0.30 ng/ml) High troponin group; $n = 17$	<i>P</i> value
Cardiology referral	26 (33.8%)	13 (72.2%)	15 (88.2%)	0.000
Anticoagulation during hospitalization	7 (9.1%)	7 (38.9%)	13 (76.5%)	0.000
Stress test	30 (39.0%)	2 (11.1%)	1 (5.9%)	0.004
Coronary angiography	4 (5.2%)	6 (33.3%)	11 (64.7%)	0.000
PCI	0	3 (16.7%)	5 (29.4%)	0.000
CABG	0	1 (5.6%)	4 (23.5%)	0.000
Medications on discharge				
Aspirin	60 (77.9%)	17 (94.4%)	15 (88.2%)	0.200
Clopidogrel	10 (13.0%)	6 (33.3%)	12 (70.6%)	0.000
Beta blockers	48 (62.3%)	17 (94.4%)	16 (94.1%)	0.002
ACEI/ARB	42 (54.5%)	11 (61.1%)	9 (52.9%)	0.860
Statins	56 (72.7%)	16 (88.9%)	13 (76.5%)	0.352

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEI/ARB, angiotensin converting-enzyme inhibitor/angiotensin II receptor blocker.

in the intermediate troponin group followed by 13.0% in the negative troponin group; $P < 0.001$).

Long-Term Follow-Up

The secondary outcome data are presented in Table 3. After a median follow-up of 479 days, there was no significant difference in the mortality outcome of patients in the three troponin groups. Four patients (5.2%) died at follow-up in the negative troponin group versus one patient (5.6%) in the intermediate troponin group, and two patients (11.8%) in the high troponin group ($P = 0.593$). In addition, we found no significant differences in the rehospitalization rates of patients across the three troponin groups.

DISCUSSION

To the best of our knowledge, this is the first study to examine practice patterns of clinicians in the treatment of AMI patients with the utilization of the new sensitive troponin assays in the United States. The main findings of our study are as follows: (1) Patients with troponin values in the intermediate range had the highest rates of prior CABG and had TIMI risk scores that were similar to that of the high troponin group. (2) Despite the intermediate troponin elevation group meeting AMI criteria as defined by the American College of Cardiology/American Heart Association (ACC/AHA), these patients were less likely to receive optimal diagnostic testing and therapies for AMI. Specifically, patients with intermediate troponin values had lower rates of coronary angiography and revascularization and were less likely to receive treatment with optimal cardiac medications including anticoagula-

tion and clopidogrel. Fewer cardiology referrals were also noted in this group.

We speculate that the above differences in the management of patients in the three troponin groups could be due to the stratified nature of the reporting of troponin values. By reporting an intermediate troponin threshold as well as a higher troponin threshold, clinicians are more likely to under-treat patients with these intermediate troponin values, as compared to their counterparts with a higher troponin cut-off. This is despite the fact that the intermediate troponin threshold of 0.03 ng/ml is 99th percentile of the upper reference limit and 10% CV as recommended by guidelines definition for AMI. Similar differences in practice patterns with under-utilization were noted in a prior study in Scotland where lowered levels of troponin values were undisclosed to clinicians (10). Interestingly in this Scottish study, when lowered level troponin values were subsequently disclosed to clinicians as being abnormal, practice patterns changed and patients with low level positive troponin elevations were subsequently treated similarly to those patients with higher positive troponin elevations. Prospective studies are needed to assess whether practice patterns could change based on modification of reporting patterns, such as the elimination of the intermediate range. Another possibility for these differences in practice patterns could be related to clinicians being accustomed to the reporting of higher troponin thresholds before the adaptation of the new generation of sensitive troponin assays. Clinicians maybe adhering to the practice patterns of treating only patients with higher level troponin releases as AMI based on the reporting of the older generation troponin assays.

While we did not find a significant difference in clinical outcomes, we suspect that this was likely due to lack of

TABLE 3. Clinical Outcomes at Follow-Up^a

	(≤0.03 ng/ml) Negative troponin group; n = 77	(0.04–0.29 ng/ml) Intermediate troponin group; n = 18	(≥0.30 ng/ml) High troponin group; n = 17	P value
Death	4 (5.2%)	1 (5.6%)	2 (11.8%)	0.593
Revascularization	3 (3.9%)	1 (5.6%)	2 (11.8%)	0.427
Cardiac rehospitalization	17 (22.1%)	6 (33.3%)	4 (23.5%)	0.602
Rehospitalization from any cause	52 (42.9%)	31 (47.6%)	20 (39.2%)	0.650

^aMedian follow-up of 479 ± 119 days.

sufficient power to detect a difference. However, numerous studies have already demonstrated improved clinical outcomes with optimal medical therapy for AMI (12–14). A larger prospective study will be needed to definitively address the long-term impact of such practice patterns on clinical outcomes.

A major strength of our study is that our study population represents unselected patients who self-presented to our institution and thus is a “real world” representation of patients who present to the emergency room with chest pain of potential cardiac origin. Moreover, our study is the first in our knowledge to evaluate the impact of stratified troponin reporting on clinical management of patients with ACS. Our study does have several important limitations. First, these findings are from a retrospective analysis and hence are subject to confounding. Second, the sample size is small, from one institution of predominantly male patients, which potentially limit the generalizability of our results. In addition due to the same sample size restrictions, our study is underpowered to detect differences in event rates as a result of differences in clinical management. Lastly, because troponin elevations noted in this study were peak values within 24 hours of presentation, it is plausible that the actual peak value occurred prior to presentation and thus resulting in the misclassification of patients from higher to lower or negative troponin groups. The exact impact of this misclassification is unknown, but this does represent a widespread clinical issue, even in the absence of stratified troponin reporting, as there are patients who present late into their ACS, and peak troponin elevation occurs prior to admission. Further studies are needed to evaluate the impact of borderline or negative troponin peak in this group of patients; based on our study and the study by Mills et al. (10), we can speculate that these troponin peaks will affect practice patterns by clinicians.

In conclusion, this study suggests that patients with chest pain and suspected ACS with a peak troponin value within 24 hours in the intermediate range are a high-risk group who are less likely to receive optimal therapy for AMI than patients with troponin elevations of a higher magnitude. Further larger prospective studies are needed to determine whether changes in these practice patterns

would result in improved clinical outcomes for this group of high-risk patients.

REFERENCES

- Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;361:868–877.
- Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;361:858–867.
- Morrow DA, Antman EM. Evaluation of high sensitivity assays for cardiac troponin. *Clin Chem* 2009;55:5–8.
- Panteghini M. A critical appraisal of experimental factors in influencing the definition of the 99th percentile limit for cardiac troponins. *Clin Chem Lab Med* 2009;47:1179–1182.
- Panteghini M. Assay-related issues in the measurement of cardiac troponins. *Clin Chim Acta* 2009;402:88–93.
- Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined— a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959–969.
- Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Circulation* 2007;116:2634–2653.
- Cardinaels EP, Mingels AM, Jacobs LH, Meex SJ, Bekers O, van Dieijen-Visser MP. A comprehensive review of upper reference limits reported for (high) sensitivity cardiac troponin assays: The challenges that lie ahead. *Clin Chem Lab Med* 2012;50:791–806.
- ARCHITECT System STAT Troponin-I [package insert]. Abbott Park, IL: Abbott Laboratories; 2009.
- Mills NL, Churchhouse AM, Lee KK, et al. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA* 2011;305:1210–1216.
- Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–842.
- Fox KA, Steg PG, Egle KA, et al. Decline in rates of death and heart failure in acute coronary syndrome, 1999–2006. *J Am Med Assoc* 2007;297:1892–1900.
- Rogers AM, Ramanath VS, Grzybowski M, et al. The association between guideline-based treatment instructions at the point of discharge and lower 1 year mortality in Medicare patients after acute myocardial infarction: The American College of Cardiology's Guidelines Applied in Practice (GAP) initiative in Michigan. *Am Heart J* 2007;154:461–469.
- Mukherjee D, Fang J, Chetcuti S, Moscucci M, Kline-Roger E, Eagle KA. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation* 2004;109:745–749.