Relationship Between Risk Stratification by Cardiac Troponin Level and Adherence to Guidelines for Non–ST-Segment Elevation Acute Coronary Syndromes

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Background: The threshold of troponin elevation that stimulates changes in clinical decision making for patients with non–ST-segment elevation acute coronary syndromes (NSTE ACSs) has not been previously evaluated.

Methods: A total of 23 298 patients with NSTE ACSs from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) initiative were separated into categories of maximum troponin ratios (ratio of the highest recorded troponin value in the first 24 hours to the local laboratory troponin assay upper limit of normalization [ULN]).

Results: Unadjusted rates of in-hospital mortality increased from the group with troponin levels below the reference limit (maximum troponin ratio 0-1×ULN; n=5291) to those with minor (1-2×ULN; n=2499), intermediate (2-5×ULN; n=3825), and major (>5×ULN; n=11 683) elevations (–2.8% vs 4.6% vs 4.7% vs 6.0%). The use of early (<24 hours) aspirin, heparin, glycoprotein IIb/IIIa inhibitors, and β-blockers was similar for the group with troponin levels below the reference limit compared with those with minor troponin elevations, and greater use of medications was demonstrated in patients with intermediate and major troponin elevations. Use of cardiac catheterization and percutaneous coronary intervention was higher in patients with troponin levels below the reference limit compared with those with minor troponin elevations, and procedures were used most frequently in patients with major troponin elevations. Similar patterns of care were demonstrated after excluding patients with chronic renal insufficiency.

Conclusions: Any degree of troponin elevation is associated with a higher risk of mortality for patients with NSTE ACSs, but guideline-recommended medical therapies are used more commonly only in patients with intermediate and major troponin elevations, whereas patients with troponin levels below the reference limit underwent invasive procedures more frequently than those with mild troponin elevations.

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CARDIAC TROPONINS ARE SENsitive and specific markers of myocardial necrosis used to evaluate patients with suspected acute coronary syndromes (ACSs).[1-3] Elevated troponin levels identify patients with non–ST-segment elevation (NSTE) ACSs, who have a higher risk of mortality and who derive particular benefit from therapies such as platelet glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparin, and early invasive management strategies.[1,2,4-11] These findings may be due to the strong correlation between the presence of intracoronary thrombus and troponin elevation.[12,13] Thus, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of NSTE ACSs recommend early troponin testing for all patients with suspected ACSs and advocate targeting aggressive therapies for patients with elevated troponin levels.[14,15] However, the reliability of currently available troponin assays remains controversial, and the threshold of troponin elevation that should be used to make treatment decisions is not clearly specified by the ACC/AHA guidelines.[16-18]

We evaluated troponin levels obtained within 24 hours of hospital presentation in patients from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With

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Early Implementation of the ACC/AHA Guidelines) quality improvement initiative[19] (see also www.crusadeqi.com) to characterize the relationship between the degree of troponin elevation and adherence to the ACC/AHA NSTE ACS guidelines and to investigate how the degree of troponin elevation relates to adverse clinical outcomes in routine clinical practice.

METHODS

Patients included in the CRUSADE initiative have ischemic symptoms at rest (for ≥10 minutes) within 24 hours before hospital presentation and at least 1 of the following high-risk features designated by the ACC/AHA guidelines: ST-segment depression of 0.5 mm or greater, transient ST-segment elevation of 0.5 to 1.0 mm (for <10 minutes), and positive cardiac markers (elevated troponin I or T levels or creatine kinase–MB levels greater than the upper limit of normalization [ULN] for the local laboratory assay used at each institution).[14,15] Patients without elevated troponin levels were included in CRUSADE if they were found to have elevated creatine kinase–MB levels or ischemic electrocardiographic changes as indicated previously herein. Patients who transferred from another institution were included if they arrived at the institution participating in CRUSADE within 24 hours of their latest episode of ischemic symptoms.

Data were collected only during the initial hospitalization in an anonymous manner without informed consent, and the institutional review board of each institution approved participation in the CRUSADE initiative. Participating hospitals were encouraged to submit data on consecutive patients who met the inclusion criteria for CRUSADE, and common screening methods used by the data collectors included evaluating hospital discharge diagnoses, reviewing troponin data from patients admitted to the hospital on a daily basis, and reviewing admission logs from the emergency department and the coronary care unit. Data collected included the early use of medications (<24 hours of presentation), the use and timing of invasive cardiac procedures, laboratory results, and clinical outcomes. Contraindications to therapies given class IA or IB recommendations by the ACC/AHA guidelines were recorded, and early medication adherence rates were determined only for patients without listed contraindications to each medication class.[14,15]

TROPONIN DATA COLLECTION

Baseline and the highest recorded (maximum) troponin results, the ULN for each local laboratory troponin assay, and the timing of troponin sampling were recorded. Baseline troponin values were recorded in the first sample drawn after hospital admission. The maximum troponin value was the highest value recorded during the entire hospitalization (including the baseline value, when applicable). The ULN was reported as the reference limit or cutoff value used clinically to designate definite myocardial necrosis per the specifications of the local laboratory troponin assay used at each institution. All serial troponin values were not recorded.

Patients in the CRUSADE database between January 1, 2001, and December 31, 2002, were evaluated in this analysis if they met the following criteria: (1) the baseline troponin value was recorded, (2) the maximum troponin value was recorded after the baseline sample, and (3) the ULN was recorded. We excluded patients who did not meet these criteria and those transferred to another institution because clinical outcomes could not be collected after transfer to another institution owing to privacy regulations that prevented the tracking of patients after transfer without obtaining informed consent.

Troponin I or T values were categorized according to multiples of the local laboratory assay ULN defined by the maximum troponin ratio (equal to the highest recorded troponin value divided by the ULN). Maximum troponin ratios were determined only from troponin values collected during the first 24 hours after hospital presentation to evaluate how troponin levels affected early care delivery (<24 hours of presentation). For patients in whom the highest recorded troponin level occurred more than 24 hours after hospital presentation, the baseline troponin value was used to determine the maximum troponin ratio because maximum troponin results would not have been available to the treating physician during the early care period. Furthermore, our group showed in a separate analysis[20] that maximum troponin values were recorded within 20 hours of hospitalization in more than 90% of patients from the CRUSADE population with elevated troponin levels. Maximum troponin ratios were categorized as follows: 0 to 1 × ULN (below the reference limit), 1 to 2 × ULN (minor elevation), 2 to 5 × ULN (intermediate elevation), and greater than 5 × ULN (major elevation).

STATISTICAL ANALYSIS

The use of early medications and interventions given class IA or IB recommendations by the ACC/AHA guidelines was compared across maximum troponin ratio categories (in relation to patients with maximum troponin levels below the reference limit) using Cochran-Armitage trend and Kruskal-Wallis tests.[14,15] Similar comparisons were made after excluding patients with a history of chronic renal insufficiency (reported by sites as a creatinine level >2.0 mg/dL [>177 μmol/L], a calculated creatinine clearance <30 mL/min [<0.50 mL/s], or the need for long-term renal dialysis).

Troponin elevation categories were also compared among categories of risk determined by the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) risk model, which is acknowledged by the ACC/AHA guidelines as a useful tool for risk stratification of patients with suspected ACSs.[14,15,21] The PURSUIT 30-day mortality risk model for NSTE ACSs was modified for this analysis to predict the risk of in-hospital mortality (categorized as low, moderate, and high risk) in the CRUSADE population from initial clinical characteristics.

Generalized estimating equation models were used to examine the association between maximum troponin ratio categories and the use of diagnostic cardiac catheterization and early catheterization (<48 hours of presentation). This method adjusted for differences in baseline and presenting characteristics, hospital features, and availability of invasive cardiac procedures, and it accounted for the clustering of patients within hospitals.[22]

Separate multivariable generalized estimating equation modeling was used to compare the adjusted risk of in-hospital mortality according to maximum troponin ratio categories. The modified PURSUIT risk model was used for this analysis as well.[21] Variables in the mortality regression model included age, female sex, signs of congestive heart failure on presentation, ST-segment depression, presenting systolic blood pressure, presenting heart rate, chronic renal insufficiency, previous percutaneous coronary intervention (PCI), previous coronary artery bypass grafting, and categorical values for maximum troponin ratios. We also analyzed the continuous relationship between maximum troponin ratios and unadjusted in-hospital mortality rates after transforming the continuous distribution of maximum troponin ratios into splines.[23]

Table 1. Baseline Clinical Characteristics of 30 295 High-Risk Patients With NSTE ACSs

Characteristic	Excluded Patients (n = 6997)	Overall Study Cohort (n = 23 298)	Maximum Troponin Ratio				*P* Value*
			0-1 × ULN (n = 5291)	1-2 × ULN (n = 2499)	2-5 × ULN (n = 3825)	>5 × ULN (n = 11 683)	
Age, median (25th-75th percentiles), y	67 (55-76)	68 (56-78)	67 (56-77)	69 (56-79)	69 (57-79)	69 (57-79)	<.001
Female sex, %	38.8	40.8	40.4	42.6	44.1	39.6	.06
Hypertension, %	67.8	68.6	71.9	69.1	69.5	66.8	<.001
Diabetes mellitus, %	31.9	32.7	32.9	34.7	34.9	31.5	.009
Current/recent smoking, %	28.1	27.2	25.9	25.9	26.1	28.4	.001
Renal insufficiency, %†	10.2	14.0	12.2	16.2	15.7	13.7	.06
Hypercholesterolemia, %	46.2	45.5	50.0	41.9	44.1	44.7	<.001
Previous MI, %	28.9	31.4	34.8	32.6	31.5	29.7	<.001
Previous CHF, %	14.8	19.3	18.8	22.7	22.6	17.8	.002
Previous PCI, %	21.5	21.5	28.7	22.2	20.7	18.4	<.001
Previous CABG, %	18.2	20.5	24.8	20.4	19.3	18.9	<.001
Presenting features, %							
ST-segment depression	50.4	40.6	53.0	34.9	33.4	38.4	<.001
Transient ST-segment elevation	14.0	9.5	11.0	5.8	6.8	10.5	.19
Signs of CHF	18.8	23.1	18.8	25.2	26.2	23.6	<.001
Transferred in	13.3	18.5	14.9	14.8	17.5	21.2	<.001
Risk score, %‡							
Low	24.8	22.1	25.4	22.0	20.8	21.1	<.001
Medium	26.1	23.3	27.3	22.2	21.4	22.3	<.001
High	44.9	50.5	43.7	51.4	53.1	52.6	<.001

Abbreviations: CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; NSTE ACSs, non–ST-segment elevation acute coronary syndromes; PCI, percutaneous coronary intervention; ULN, upper limit of normalization.

**P* values compare trends across the 4 categories of troponin elevation.

†Serum creatinine level greater than 2.0 mg/dL (>177 μmol/L), estimated creatinine clearance less than 30 mL/min (<0.50 mL/s), or need for dialysis.

‡Predicted risk of in-hospital mortality from presenting clinical characteristics (as described in the "Methods" section).

For all tests, $P<.05$ was established as the level of statistical significance. All analyses were performed using a statistical software program (SAS version 8.2; SAS Institute Inc, Cary, NC).

RESULTS

A total of 30 295 high-risk patients with NSTE ACSs were included in the CRUSADE database during the analysis period. We excluded 3730 patients (12%) who were transferred from the presenting hospital to another institution and another 3267 patients (11%) for whom adequate troponin data were not recorded on the data collection form, resulting in a total of 23 298 patients in the analysis cohort. Excluded patients had clinical characteristics similar to those of patients included in the overall study cohort (**Table 1**).

Most patients (88%) were evaluated using troponin I assays, and the remainder (12%) were evaluated using troponin T assays. When patients were divided into maximum troponin ratio categories determined by the local laboratory troponin assay ULN, 22.7% (n=5291) had troponin levels below the reference limit (maximum troponin ratio 0-1×ULN), 10.7% (n=2499) had minor troponin elevations (1-2×ULN), 16.4% (n=3825) had intermediate troponin elevations (2-5×ULN), and 50.2% (n=11 683) had major troponin elevations (>5×ULN). Patients with higher maximum troponin ratios were older but less commonly underwent previous revascularization procedures (Table 1).

The frequency of unadjusted in-hospital outcomes increased across maximum troponin ratio categories (**Table 2**). After excluding patients with chronic renal insufficiency, similar findings were demonstrated for unadjusted in-hospital mortality across increasing troponin ratio categories (2.1% vs 3.9% vs 4.2% vs 5.0%). The continuous relationship of maximum troponin ratios with in-hospital mortality rates showed that higher maximum troponin ratios were associated with a continuous increase in unadjusted in-hospital mortality rates (**Figure**).

Compared with patients with troponin levels below the reference limit, the adjusted risk of in-hospital mortality was higher with minor troponin elevations (odds ratio [OR], 1.49; 95% confidence interval [CI], 1.11-2.01; $P=.009$), intermediate troponin elevations (OR, 1.53; 95% CI, 1.18-2.00; $P=.002$), and major troponin elevations (OR, 1.83; 95% CI, 1.47-2.28; $P<.001$).

The use of early therapies (<24 hours) was similar in patients with minor troponin elevations compared with those with troponin levels below the reference limit. Significant increases in the use of guideline-recommended medications were demonstrated in patients with larger troponin elevations (**Table 3**). After excluding patients with renal insufficiency, similar findings across maximum troponin categories were demonstrated for the early use of aspirin (troponin levels below the reference limit vs minor elevation vs intermediate elevation vs major elevation: 89.9% vs 91.3% vs 90.5% vs 92.4%), heparin (77.5% vs 79.5% vs 82.8% vs 88.7%), glycoprotein IIb/IIIa inhibitors (23.2% vs 24.6% vs 28.9% vs 40.8%), and β-blockers (72.8% vs 76.3% vs 77.4% vs 79.5%).

Overall and early (<24-48 hours) use of diagnostic cardiac catheterization and PCI were lower in patients with

Table 2. Unadjusted In-Hospital Outcomes*

Outcome	Overall Study Cohort (n = 23 298)	Maximum Troponin Ratio			
		0-1 × ULN (n = 5291)	1-2 × ULN (n = 2499)	2-5 × ULN (n = 3825)	>5 × ULN (n = 11 683)
Death, %	4.9	2.8	4.6	4.7	6.0
Death or (re-)infarction, %	8.1	6.4	7.0	7.4	9.4
Congestive heart failure, %	10.9	8.5	11.1	11.5	11.7
Cardiogenic shock, %	2.8	1.8	2.3	2.0	3.5
RBC transfusion, %	15.0	12.5	13.8	14.8	16.5

Abbreviations: RBC, red blood cell; ULN, upper limit of normalization.
*$P<.001$ for all outcomes comparing trends across the 4 categories of troponin elevation.

minor troponin elevations and similar in patients with intermediate troponin elevations compared with patients with troponin levels below the reference limit (**Table 4**). After excluding patients with chronic renal insufficiency, similar utilization patterns for cardiac catheterization (65.7% vs 61.6% vs 66.4% vs 74.7%) and PCI (35.3% vs 31.5% vs 34.8% vs 43.8%) were demonstrated across the categories of maximum troponin ratios.

Of 19 273 patients with elevated troponin levels (minor, intermediate, or major troponin elevations), 4025 (20.9%) underwent PCI within 24 hours of presentation. Of these 4025 patients, the maximum troponin level recorded within 24 hours was after the time of PCI in 1934 patients (10.0% of the total population of patients with elevated troponin levels).

The adjusted likelihood of overall use of catheterization was similar in patients with minor troponin elevations compared with patients with troponin levels below the reference limit (OR, 1.01; 95% CI, 0.90-1.14; $P=.80$). Patients with intermediate (OR, 1.19; 95% CI, 1.05-1.35; $P<.001$) and major (OR, 1.65; 95% CI, 1.45-1.88; $P<.001$) troponin elevations underwent catheterization more frequently. Similar findings were demonstrated for the use of catheterization within 48 hours with minor (OR, 1.06; 95% CI, 0.96-1.18; $P=.26$), intermediate (OR, 1.27; 95% CI, 1.15-1.41; $P<.001$), and major (OR, 1.59; 95% CI, 1.44-1.77; $P<.001$) troponin elevations.

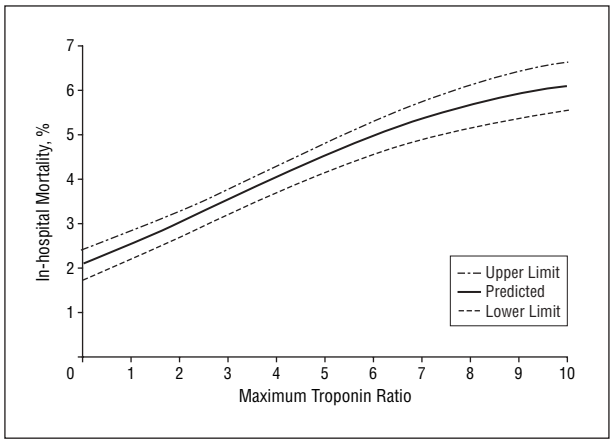

Figure. Continuous relationship between unadjusted in-hospital mortality rates and maximum troponin ratios according to multiples of the upper limit of normalization (ULN). Dashed lines indicate 95% confidence intervals. Data were truncated at a cutoff point of maximum troponin ratios greater than 10 × ULN.

COMMENT

We showed that elevated troponin levels identified by local laboratory troponin assays are associated with a higher risk of mortality for patients with NSTE ACSs. Paradoxically, patients with minor troponin elevations had a higher risk of mortality but were treated no more aggressively than patients with troponin levels below the reference limit. These disparities in care persisted after excluding patients with chronic renal insufficiency. Thus, these results demonstrate dissociation between the risk stratification and early care treatment recommendations from the ACC/AHA guidelines in routine clinical practice.

GUIDELINE ADHERENCE BASED ON TROPONIN LEVELS

Although the ACC/AHA guidelines recommend integrating early risk stratification by troponin levels with subsequent therapy selection, previous analyses[14,15] have not evaluated how the degree of troponin elevation affects the delivery of early care for NSTE ACSs. We observed that a threshold of intermediate troponin elevation necessary to stimulate significant increases in the use of evidence-based medications and invasive procedures seems to exist in routine practice. However, early treatments that selectively benefit troponin-positive patients, such as low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and early invasive management strategies, were still used in fewer than half of the patients with major troponin elevations and were underused to an even greater extent in patients with minor and intermediate troponin elevations, although all troponin elevation categories were associated with a higher risk of in-hospital mortality.[7-11] Therefore, adoption of ACC/AHA early care guideline recommendations remains suboptimal for patients with elevated troponin levels despite the previously demonstrated relationship between troponin elevation and mortality.[1,2,4,6]

RISK STRATIFICATION BY DEGREE OF TROPONIN ELEVATION

Previous studies have demonstrated that elevated troponin levels predict a higher risk of mortality in patients with ACSs, but the quantitative relationship between the

Table 3. Early Therapies*

Medication	Overall Study Cohort (n = 23 298)	Maximum Troponin Ratio			
		0-1 × ULN (n = 5291)	1-2 × ULN (n = 2499)	2-5 × ULN (n = 3825)	>5 × ULN (n = 11 683)
Aspirin, %	90.8	89.5	90.3	90.1	91.7
Heparin, %					
All	83.2	76.4	78.1	81.5	87.8
Unfractionated	53.6	47.8	48.0	50.2	58.4
Low molecular weight	36.4	34.2	35.7	37.2	37.3
Glycoprotein IIb/IIIa inhibitors, %	31.6	22.4	22.8	26.6	39.1
β-Blockers, %	76.9	73.0	75.3	76.8	79.0
Clopidogrel bisulfate, %	37.8	33.3	32.0	36.3	41.6

Abbreviation: ULN, upper limit of normalization.
*Therapies delivered within 24 hours to eligible patients without listed contraindications.
†$P<.001$ for all medications comparing trends across the 4 categories of troponin elevation.

Table 4. In-hospital Cardiac Procedures*

Procedure	Overall Study Cohort (n = 23 298)	Maximum Troponin Ratio			
		0-1 × ULN (n = 5291)	1-2 × ULN (n = 2499)	2-5 × ULN (n = 3825)	>5 × ULN (n = 11 683)
Diagnostic cardiac catheterization, %	66.1	63.1	57.4	62.1	70.7
<24 h	29.8	26.1	22.9	25.8	34.2
<48 h	44.9	40.7	36.9	41.4	49.6
PCI, %	36.3	33.6	28.8	32.1	40.6
<24 h	17.3	14.2	11.8	14.3	20.8
<48 h	25.4	22.2	19.5	22.2	29.2
CABG, %	11.2	9.1	10.4	11.5	12.2

Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; ULN, upper limit of normalization.
*$P<.001$ for all procedures comparing trends across the 4 categories of troponin elevation.

degree of troponin elevation and mortality risk has not been clearly defined.[1,2,4-6] Progressive troponin elevations were associated with an increased risk of intermediate-term mortality in patients with NSTE ACSs enrolled in clinical trials, but fewer than half of the patients had elevated troponin levels in these studies.[1,2] Similarly, 1-year mortality was shown to be progressively higher with greater degrees of troponin elevation in another selected clinical trial population,[24] but the mortality risk associated with low levels of troponin elevation was not specifically evaluated. In contrast, we demonstrated a continuous relationship between the degree of troponin elevation in the first 24 hours and in-hospital mortality rates in a large, diverse cohort of patients with NSTE ACSs from routine practice who commonly had elevated troponin levels identified using local laboratory troponin assays. Because patients with elevated troponin levels are more likely to have intracoronary thrombus and left ventricular dysfunction than patients without troponin elevations, the degree of troponin elevation may relate to mortality risk by reflecting the degree of distal thrombus embolization and subsequent infarct size and left ventricular dysfunction in patients with NSTE ACSs.[12,13,25,26] Nonetheless, the results of this study confirm the findings of previous studies[1,2,5] that demonstrated that any degree of troponin elevation above prespecified thresholds identifies patients with a higher risk of mortality.

LIMITATIONS

This study has several limitations. First, because 23% of patients were excluded owing to transfer to another hospital or inadequate troponin data, a selection bias was present. However, given current privacy regulations in the United States, patients could not be followed after transfer. We also reported clinical characteristics for excluded patients to demonstrate that these patients were similar to those analyzed. Second, all serial troponin results were not recorded, so we could not ascertain how the exact timing of troponin elevation affected care delivery, but elevated troponin levels at any point during the first 24 hours should have potentially affected early care delivery if appropriate notification systems were in place to inform treating physicians of the results. Also, because more than 90% of the patients in CRUSADE have the maximum troponin value recorded within 20 hours of presentation, our results are not likely to be confounded by maximum troponin elevations occurring more than 24 hours after hospital presentation.[20] Third, we could not verify whether sites submitted data on consecutive patients who met the inclusion criteria for

CRUSADE because data were collected anonymously without informed consent. Finally, we used the maximum troponin ratio to define categories of troponin elevation based on local laboratory troponin assay reference limits used by participating sites to guide clinical decision making, but this technique for normalizing results from disparate troponin assays has not been previously validated in ACS populations as have peak creatine kinase–MB ratios.[27] Consensus statements recommend that any elevation of cardiac troponin levels should be considered to be diagnostic of acute myocardial infarction in the appropriate clinical situation, and all patients included in this analysis had symptoms thought to be consistent with ischemia by the treating physician.[3,16-18] However, currently available troponin assays have many limitations because the use of different reference limits for defining positive troponin results can significantly impact the diagnosis of acute myocardial infarction.[28] We addressed these limitations by (1) adjusting for patient and hospital effects for the use of invasive procedures, (2) separately analyzing early treatments and outcomes after excluding patients with renal insufficiency because troponin results are difficult to interpret in this population, and (3) analyzing the relationship between mortality and maximum troponin ratios using categorical and continuous methods. Because it would be infeasible to analyze troponin results systematically in a core laboratory in a large, observational analysis such as CRUSADE, this study is based on the best available data from local laboratory troponin assays used in routine clinical practice, but categorical representation of troponin ratios may have different implications at various absolute troponin values and in different laboratories and assays.

In conclusion, although the ACC/AHA guidelines recommend using elevated troponin values for delineating treatment decisions for patients with NSTE ACSs, substantial gaps in guideline adherence based on these recommendations are present in clinical practice. Given the adverse consequences of any degree of troponin elevation demonstrated in this analysis and in recent studies[29,30] that have shown that comprehensive guideline adherence for NSTE ACSs is associated with lower mortality, quality improvement efforts are needed to improve the care of all patients with NSTE ACSs found to have elevated troponin levels.

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