

Frequency and Clinical Implications of Discordant Creatine Kinase-MB and Troponin Measurements in Acute Coronary Syndromes

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- OBJECTIVES** We sought to evaluate the association between discordant cardiac marker results and in-hospital mortality and treatment patterns in patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS).
- BACKGROUND** Creatine kinase-MB (CK-MB) and cardiac troponins (cTn) are often measured concurrently in patients with NSTEMI ACS. The significance of discordant CK-MB and cTn results is unknown.
- METHODS** Among 29,357 ACS patients in the CRUSADE initiative who had both CK-MB and cTn measured during the first 36 hours, we examined relationships of four marker combinations (CK-MB-/cTn-, CK-MB+/cTn-, CK-MB-/cTn+, and CK-MB+/cTn+) with mortality and American College of Cardiology/American Heart Association guidelines-recommended acute care.
- RESULTS** The CK-MB and cTn results were discordant in 28% of patients (CK-MB+/cTn-, 10%; CK-MB-/cTn+, 18%). In-hospital mortality was 2.7% among CK-MB-/cTn- patients; 3.0%, CK-MB+/cTn-; 4.5%, CK-MB-/cTn+; and 5.9%, CK-MB+/cTn+. After adjustment for other presenting risk factors, patients with CK-MB+/cTn- had a mortality odds ratio (OR) of 1.02 (95% confidence interval [CI] 0.75 to 1.38), those with CK-MB-/cTn+ had an OR of 1.15 (95% CI 0.86 to 1.54), and those with CK-MB+/cTn+ had an OR of 1.53 (95% CI 1.18 to 1.98). Despite variable risk, patients with CK-MB+/cTn- and CK-MB-/cTn+ were treated similarly with early antithrombotic agents and catheter-based interventions.
- CONCLUSIONS** Among patients with NSTEMI ACS, an elevated troponin level identifies patients at increased acute risk regardless of CK-MB status, but an isolated CK-MB+ status has limited prognostic value. Recognition of these risk differences may contribute to more appropriate early use of antithrombotic therapy and invasive management for all cTn+ patients. (J Am Coll Cardiol 2006;47:312-8) © 2006 by the American College of Cardiology Foundation

Cardiac marker testing is a fundamental component of both diagnosis and risk stratification in patients presenting with symptoms suggestive of an acute coronary syndrome (ACS). The recent European Society of Cardiology/American College of Cardiology recommendation for redefinition of myocardial infarction established cardiac troponin (cTn)

testing as the “gold standard” for diagnosis (1), and its superiority over other biomarkers for risk stratification has been demonstrated in numerous studies using core laboratories (2-6). In addition, several studies using core laboratory cTn testing have defined treatment benefit for several therapies based on a positive ($>1\times$ upper limit of normal [ULN]) or negative ($\leq 1\times$ ULN) result (7-14). Despite these data, use of creatine kinase-MB (CK-MB) testing in clinical practice remains commonplace, and often cTn and CK-MB levels are both tested.

Although dual testing is often performed, physicians have concerns about false positive cTn results and often question the prognostic value of cTn in the absence of a positive CK-MB result. Similarly, studies examining the risks associated with an “isolated elevated CK-MB” result have been conflicting, in part because of limited study size and methodology (15,16). Thus, a better understanding of the risks associated with concordant and discordant cardiac markers could lead to improved application of American College of Cardiology (ACC)/American Heart Association

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Abbreviations and Acronyms

ACC	= American College of Cardiology/
ACS	= acute coronary syndrome
AHA	= American Heart Association
CI	= confidence interval
CK-MB	= creatine kinase-MB
CRUSADE	= Can Rapid Risk stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines
cTn	= cardiac troponin
NSTEMI	= non-ST-segment elevation
OR	= odds ratio
ULN	= upper limit of normal

(AHA) guidelines-recommended management of patients with non-ST-segment elevation (NSTEMI) ACS (17,18).

We investigated the use of dual cardiac marker testing in clinical practice, including the frequency of discordant results and the association of the results with in-hospital mortality and ACC/AHA guidelines-recommended acute medication and invasive procedure use among NSTEMI ACS patients who were enrolled in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) Quality Improvement Initiative.

METHODS

Study population. The study population for our analysis comprised 29,357 patients with high-risk NSTEMI ACS who presented directly to one of 396 U.S. hospitals participating in the CRUSADE Initiative. We excluded patients who transferred in from another hospital (because of difficulty in timing cardiac marker assessment) and those who transferred out to another hospital (as their outcomes could not be tracked because of U.S. privacy laws). The inclusion criteria and data collection methods for the CRUSADE Initiative have been described in detail elsewhere (19). Briefly, patients with symptoms of ACS for at least 10 min who presented within 24 h of onset and who had either electrocardiographic changes consistent with a diagnosis of ischemia (transient ST-segment elevation 0.5 to 1.0 mm [lasting for <10 min], ST-segment depression ≥ 0.5 mm) or elevation of either cTn or CK-MB to greater than the value reported by a site's local laboratory to designate definite myocardial necrosis or a positive bedside cardiac marker assay were included in the CRUSADE Initiative. A data collection form was used to gather information on baseline demographic and clinical characteristics, cardiac marker results, medication and procedure use, and in-hospital outcomes for all enrolled patients. Only baseline and peak cardiac marker results (including time of peak measurement) were recorded on the CRUSADE data collection form. All patients in the present analysis had both baseline and peak cTn and CK-MB values recorded. Data were collected anonymously during the initial hospitaliza-

tion, and because no patient identifiers are collected, individual informed consent was not required. The institutional review board of each institution approved participation in the CRUSADE Initiative.

Marker status and outcomes of interest. We determined the frequency of discordant cTn and CK-MB results among patients with peak measurements within 36 h of patient presentation. Creatine kinase-MB and cTn were considered positive when any reported value (baseline or peak) exceeded the ULN for the assays used in the site's local laboratory. Patients were partitioned into four groups on the basis of these results: both markers negative (CK-MB-/cTn-), CK-MB positive and cTn negative (CK-MB+/cTn-), CK-MB negative and cTn positive (CK-MB-/cTn+), and both markers positive (CK-MB+/cTn+). We then investigated the relationship of each marker category with in-hospital mortality and with acute use of ACC/AHA guidelines-recommended medical therapies (<24 h of presentation) and an early invasive management strategy (within 24 to 48 h of presentation).

Statistical methods. Baseline characteristics, medical treatment, procedure use, and in-hospital outcomes were compared across the four CK-MB/cTn categories. Continuous variables were reported as medians with 25th and 75th percentiles, and categorical variables were reported as frequencies. Continuous variables were compared using the Kruskal-Wallis test, and categorical variables were compared using the chi-square test.

In examining the relationship between the CK-MB/cTn categories and care patterns and outcomes, we initially performed unadjusted comparisons. We then adjusted for a broad range of patient and hospital characteristics, including demographic, clinical, and hospital variables, using generalized estimating equation models to account for correlations among clustered responses (e.g., within-hospital correlations) (20, 21). All odds ratios (ORs) were reported with CK-MB-/cTn- as the reference group.

Finally, as troponin results can also be elevated among those with renal failure, which could inflate their prognostic value, we performed a sensitivity analysis by repeating all analyses after excluding patients with renal insufficiency or for whom data on renal insufficiency were missing ($n = 4,821$). A p value of <0.05 was established as the level of statistical significance for all tests. All analyses were performed using SAS software (versions 8.2, SAS Institute, Cary, North Carolina).

RESULTS

Patient population. Among 29,357 patients with NSTEMI ACS, 22,867 were cTn+ and 20,506 were CK-MB+. The majority of patients had concordant cardiac marker results as 3,502 (11.9%) were CK-MB-/cTn- and 17,518 (59.7%) were CK-MB+/cTn+. In 28% of patients, CK-MB and cTn results were discordant ($n = 2,988$ [10.2%] CK-MB+/cTn- and $n = 5,349$ [18.2%] CK-MB-/cTn+).

Table 1. Baseline Characteristics by Cardiac Marker Category

	CK-MB-/ <i>c</i> Tn- (n = 3,502)	CK-MB+/ <i>c</i> Tn- (n = 2,988)	CK-MB-/ <i>c</i> Tn+ (n = 5,349)	CK-MB+/ <i>c</i> Tn+ (n = 17,518)
Demographics				
Age, yrs	66 (55, 77)	66 (55, 77)	70 (57, 79)	70 (57, 80)
Female gender	47.9	34.0	44.6	39.9
Race				
White	77.0	74.5	75.6	80.4
Black	15.6	16.5	15.3	11.7
Asian	1.5	2.0	1.3	1.2
Hispanic	3.2	3.1	4.1	3.3
Other	1.9	2.8	2.6	2.2
Body mass index, kg/m ²	28 (24, 32)	28 (25, 32)	27 (24, 31)	27 (24, 31)
Insurance status				
HMO/private	44.5	44.3	39.5	43.8
Medicare/Medicaid	48.2	47.3	53.5	48.4
Self/none	6.2	7.3	6.2	6.7
Medical history and risk factors				
Family history of CAD	42.0	35.6	33.6	34.7
Hypertension	74.8	69.9	70.8	67.5
Diabetes mellitus	32.4	31.5	37.1	32.5
Current/recent smoker	25.4	25.6	22.9	26.7
Hypercholesterolemia	50.5	47.0	45.5	43.8
Prior myocardial infarction	34.1	31.6	34.1	29.9
Prior PCI	32.6	24.3	23.4	18.6
Prior CABG	25.6	21.5	22.1	19.1
Heart failure	17.0	19.1	22.3	19.5
Stroke	9.8	9.4	12.6	11.4
Renal insufficiency	10.5	11.0	18.3	14.1
Clinical presentation				
Electrocardiogram				
ST-segment depression	76.2	33.3	31.9	26.1
Transient ST-segment elevation	14.6	9.4	6.0	9.4
Type of troponin				
Baseline				
Troponin I	84.2	68.5	86.2	82.1
Troponin T	13.8	28.6	12.7	16.6
Peak				
Troponin I	70.9	56.9	83.2	78.6
Troponin T	11.6	23.7	12.4	15.3
Signs of heart failure	15.0	18.4	27.1	25.4
Heart rate, beats/min	79 (68, 94)	81 (69, 96)	84 (71, 100)	86 (72, 102)
Systolic blood pressure, mm Hg	148 (128, 168)	148 (129, 168)	146 (125, 167)	146 (125, 167)
Time from symptom onset, h	2.9 (1.3, 7.0)	2.6 (1.2, 6.2)	2.9 (1.3, 7.3)	2.8 (1.3, 7.2)
Care patterns				
Cardiology care primary	56.9	51.4	53.2	53.9
Hospital features				
Academic hospital	24.3	29.5	29.6	26.1
Total hospital beds	350 (245, 490)	365 (241, 475)	377 (264, 532)	374 (260, 492)
Cath laboratory only	8.1	5.8	8.4	8.3
PCI, no bypass surgery	7.3	5.4	7.6	5.0
CABG	79.8	85.2	79.0	82.8

Values are % or median (25th, 75th percentile).

CABG = coronary artery bypass grafting; CAD = coronary artery disease; Cath = catheterization; CK-MB = creatine kinase-MB; *c*Tn = cardiac troponin; HMO = health maintenance organization; PCI = percutaneous coronary intervention.

Table 1 displays the baseline characteristics of the study population by cardiac marker category. Patients in the *c*Tn+ groups were older regardless of CK-MB status; more often had prior stroke and renal insufficiency; and had higher heart rate, lower blood pressure, and, more frequently, signs of heart failure at presentation. They were also more likely to receive cardiology consultation during their hospitalization and be enrolled at larger hospitals. The

CK-MB+ patients were more often male and less often had prior myocardial infarction regardless of *c*Tn status. Groups with discordant cardiac markers had a greater proportion of racial/ethnic minorities. All marker-positive groups had lower proportions of patients with a history of coronary artery disease and hypertension than patients in the group that was negative for both markers. The use of a troponin I assay predominated in all groups, but troponin T was used

more frequently among patients in the CK-MB+/cTn- group compared with other groups.

After excluding 2,506 patients (8.5%) whose only positive cTn was after a percutaneous coronary intervention, results were similar: 29.9% of patients had discordant marker results; 11.1% CK-MB+/cTn- and 18.8% CK-MB-/cTn+. Baseline characteristics by marker category were also similar to those for the overall population.

Clinical outcomes. Considering only single-marker status, in-hospital mortality among cTn+ patients was 5.5% compared with 2.8% among cTn- patients. In-hospital mortality was 5.4% among CK-MB+ patients and 3.8% among CK-MB- patients. In-hospital mortality was 2.7% among CK-MB-/cTn- patients, 3.0% among CK-MB+/cTn- patients, 4.5% among CK-MB-/cTn+ patients, and 5.9% among CK-MB+/cTn+ patients. After eliminating the 2,506 patients whose only positive troponin occurred after a percutaneous coronary intervention, mortality rates were similar in the cTn- groups (CK-MB-/cTn-, 2.7% and CK-MB+/cTn-, 3.0%) and were only slightly higher in the cTn+ groups (CK-MB-/cTn+, 4.6% and CK-MB+/cTn+, 6.3%).

In multivariable analysis, after accounting for other baseline clinical and electrocardiographic factors (ST-segment depression [chi square 8.0]) and within hospital clustering, both CK-MB and cTn, tested as continuous variables, added incremental information regarding patients' risk for in-hospital mortality. However, cTn was more strongly associated with mortality than CK-MB (chi square 23.2 for cTn vs. 7.6 for CK-MB). When we limited our analyses to only the 23,794 patients who had troponin I testing, the results were consistent with those in the overall population. Further, when type of cTn (I or T) was tested in the model, it was nonsignificant, suggesting that there was no difference in association with mortality based on the type of troponin assayed.

Similarly, there was a clear gradient of risk among our four categorical groupings. Relative to patients who were negative for both markers (CK-MB-/cTn-), those who were CK-MB+/cTn- had a mortality OR of 1.02 (95% confidence interval [CI] 0.75 to 1.38); patients who were CK-MB-/cTn+ had an OR of 1.15 (95% CI 0.86 to 1.54); and those who were CK-MB+/cTn+ had an OR of 1.53 (95% CI 1.18 to 1.98). After excluding patients with renal insufficiency or missing information on renal insufficiency, the pattern of in-hospital mortality was similar: CK-MB-/cTn-, 2.3%; CK-MB+/cTn-, 2.5%; CK-MB-/cTn+, 3.4%; and CK-MB+/cTn+, 5.1%.

Among patients with discordant cardiac marker results, we repeated the analysis of the continuous relationship of cTn elevation with mortality among CK-MB- patients and the continuous relationship of CK-MB elevation with mortality among cTn- patients. Among patients with negative cTn, in-hospital mortality was not elevated above baseline until CK-MB exceeded four times ULN (12.8% of all CK-MB+/cTn- patients). In contrast, among CK-

MB- patients, in-hospital mortality was in the 4% to 5% range (two- to three-fold increased risk) for all elevations of cTn >1× ULN even in the presence of a negative CK-MB assay.

Acute use of medications and invasive management. Rates of adherence to guidelines-recommended acute medications and invasive procedures are shown in Table 2, along with adjusted ORs with 95% CIs for each marker category relative to the CK-MB-/cTn- group. After adjustment for patient and hospital characteristics, the odds of use of all guidelines-recommended acute medical therapies were consistently greatest among patients with both cardiac markers positive. However, patients with discordant CK-MB and cTn results received acute antithrombotic therapy in nearly identical patterns, with both groups being treated only slightly more aggressively than those with CK-MB-/cTn- panels. For example, use of acute glycoprotein IIb/IIIa inhibitors was 18.4% for patients with CK-MB-/cTn-, 23.7% in the CK-MB+/cTn- group, and 22.9% among the CK-MB-/cTn+ group. Paradoxically, an early interventional strategy was actually more commonly applied to patients with CK-MB-/cTn- panels relative to those with discordant positive cardiac marker panels. Rates of diagnostic cardiac catheterization within 48 h ranged from 40% to 44.5% for the three groups (Table 2). These patterns of care remained similar after adjustment for patient and hospital characteristics (Fig. 1).

DISCUSSION

We have shown that among patients with high-risk NSTEMI ACS managed under conditions of clinical practice, in-hospital mortality in cTn+ patients is increased regardless of CK-MB status. Although both markers contribute independent information in multivariable modeling, the overall contribution of troponin is stronger, and there is variability within the relationship such that there is little increase in risk at low-level CK-MB elevation. We also found that current patterns of use of acute antithrombotic therapies and an early invasive management strategy in community-based practice fail to reflect these risk profiles. Given higher risk among cTn+ patients and previous evidence for preferential benefit from the use of these treatments on the basis of cTn status, we should be wary of treating CK-MB+/cTn- patients aggressively and focus on improving delivery of these treatment strategies to cTn+ patients regardless of CK-MB results.

Marker status and outcome. Patients with both markers positive within 36 h of presentation were at highest risk for in-hospital events, and those with both markers negative were at lowest risk. Among patients with discordant results (28%), any degree of isolated troponin elevation was more consistently associated with increased mortality than isolated CK-MB elevation, for which mortality was similar to that with both markers negative until CK-MB exceeded three to four times the ULN.

Table 2. Use of Guideline-Recommended Acute Medications* and Procedures†

	CK-MB-/cTn- (n = 3,502)	CK-MB+/cTn- (n = 2,988)	CK-MB-/cTn+ (n = 5,349)	CK-MB+/cTn+ (n = 17,518)
Medications (first 24 h)				
Aspirin, %	88.8	90.6	90.5	91.8
Adjusted OR (95% CI)	—	1.15 (0.96–1.38)	1.24 (1.06–1.45)	1.41 (1.22–1.63)
Beta-blocker, %	69.7	69.9	75.7	79.3
Adjusted OR (95% CI)	—	1.02 (0.89–1.17)	1.34 (1.20–1.51)	1.62 (1.45–1.80)
Heparin, any, %	70.9	72.8	75.9	86.8
Adjusted OR (95% CI)	—	1.31 (1.14–1.51)	1.56 (1.40–1.74)	2.87 (2.57–3.20)
Unfractionated heparin, %	41.7	45.5	42.6	55.2
Adjusted OR (95% CI)	—	1.31 (1.14–1.50)	1.30 (1.17–1.44)	2.01 (1.80–2.24)
Low molecular weight heparin, %	33.7	31.3	38.2	38.5
Adjusted OR (95% CI)	—	0.92 (0.83–1.03)	1.05 (0.95–1.15)	1.06 (0.97–1.16)
Clopidogrel, %	32.5	33.5	33.9	40.3
Adjusted OR (95% CI)	—	1.22 (1.09–1.37)	1.26 (1.15–1.37)	1.59 (1.45–1.75)
GP IIb/IIIa inhibitor, %	18.4	23.7	22.9	38.3
Adjusted OR (95% CI)	—	1.88 (1.58–2.22)	1.89 (1.63–2.18)	3.73 (3.26–4.26)
Procedures				
Diagnostic cardiac cath				
<24 h, %	26.2	26.5	21.7	32.5
Adjusted OR (95% CI)	—	1.37 (1.13–1.66)	1.22 (1.06–1.40)	1.94 (1.68–2.23)
<48 h, %	44.5	39.8	40.0	50.1
Adjusted OR (95% CI)	—	1.09 (0.92–1.30)	1.28 (1.12–1.48)	1.79 (1.55–2.06)
PCI				
Any, %	36.3	34.6	33.1	41.4
Adjusted OR (95% CI)	—	1.15 (0.95–1.39)	1.22 (1.03–1.45)	1.62 (1.39–1.89)
<24 h, %	11.8	16.8	10.8	20.0
Adjusted OR (95% CI)	—	2.11 (1.65–2.68)	1.47 (1.21–1.79)	2.73 (2.27–3.27)
CABG surgery, %				
Adjusted OR (95% CI)	—	0.80 (0.66–0.98)	1.06 (0.89–1.25)	1.10 (0.95–1.28)

*Among patients without contraindications to a given medication. †Among patients enrolled at hospitals with coronary bypass surgery capability. CI = confidence interval; GP = glycoprotein; OR = odds ratio; Other abbreviations as in Table 1.

This may represent more biological “noise” with CK-MB since there is normally some present in the blood, whereas cTn is not normally detectable, making the specificity of small elevations of cTn greater. As cTn assays become more sensitive, it is likely that CK-MB-/cTn+ results will become more frequent. Regardless, our results suggest that in clinical practice there is little advantage of simultaneous CK-MB and cTn testing for risk stratification in patients with high-risk ACS presentations, although a role may still remain for use of

CK-MB in timing of infarction or defining re-infarction or infarction associated with percutaneous coronary intervention or coronary artery bypass graft surgery. The stronger association of cardiac troponins than CK-MB with adverse clinical outcomes most likely reflects their greater sensitivity and specificity for minor myocardial necrosis resulting from microembolization from active plaques, which predispose to subsequent major clinical events, but whose activity may not be detectable by less sensitive or specific markers such as CK-MB until a larger event occurs. The explanation for the CK-MB+/cTn- discordance is more challenging. These could reflect timing of marker testing relative to symptom onset or discordance in timing of sampling, or simply false negative troponin tests. It is interesting that troponin T use was more frequent among the CK-MB+/cTn- group than in the three other marker categories. This may reflect the previously recommended use of a higher ROC-determined ULN for this assay relative to using a cutoff at the 99th percentile of a reference control population as occurs for some troponin I assays. Recently, the package insert for this assay was changed to reflect a recommended ULN of 0.03 ng/ml based on the 99th percentile of a reference control population and 10% CV level compared with the previous 0.1 ng/ml recommended ULN based on ROC analysis. It will be inter-

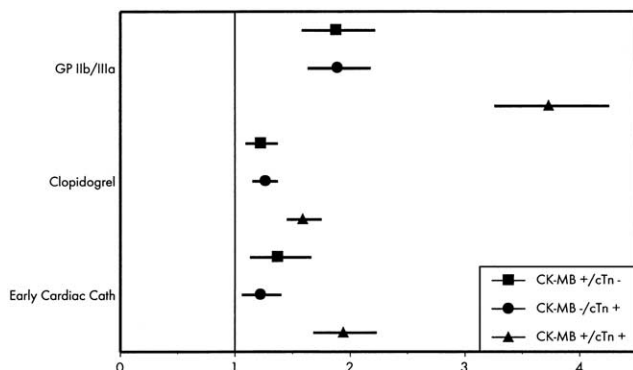


Figure 1. Odds ratios with 95% confidence intervals for acute use of glycoprotein (GP) IIb/IIIa inhibitors, clopidogrel, and an early invasive management strategy. CK-MB = creatine kinase-MB; cTn = cardiac troponin.

esting to see whether increased use of the 0.03 ng/ml cutoff for patients tested with this assay results in a change in this pattern as more patients accrue in the database.

Our results among high-risk patients in clinical practice are similar to a previous analysis of high-risk ACS patients enrolled in clinical trials, in which baseline cTn elevation with or without CK-MB elevation was associated with increased risk for 30-day death or myocardial infarction, and patients with CK-MB elevation without cTn elevation had 30-day risk that was similar to patients with both markers negative (16). However, a single-center study of 542 troponin-negative patients who were followed for six months for the composite endpoint of death, cardiac rehospitalization, stroke, or myocardial infarction, revealed an OR for CK-MB+/cTn- relative to CK-MB-/cTn- of 1.86 (95% CI 1.14 to 3.03) (15). The differences between these studies possibly reflect the timing of the end point assessment, with elevations of CK-MB in the absence of cTn elevation being more sensitive for risk over the long term rather than acutely.

Use of guideline-recommended management and marker results. For aspirin, beta-blockers, and clopidogrel, no difference in relative benefit from therapy has been demonstrated by applying treatment based upon the results of cardiac marker testing. Despite this, there was a tendency to use aspirin and beta-blockers more frequently among patients who were both CK-MB+ and cTn+ or who were CK-MB-/cTn+; a difference that persisted even after accounting for differences in baseline patient characteristics and hospital-related factors. A tendency for more effective application of evidence-based medical therapy in patients with acute myocardial infarction compared with unstable angina has been demonstrated in other databases (22,23), but a differential in use in patients with discordant marker results (CK-MB+/cTn- and CK-MB-/cTn+) relative to both markers being negative has not been previously reported.

Conversely, several studies have shown that the results of troponin testing can define high-risk groups of patients who preferentially benefit from the use of low-molecular-weight heparin and glycoprotein IIb/IIIa inhibitors (with or without concomitant percutaneous coronary intervention) and an early invasive management strategy (7-14). Our observations suggest that this information is not applied consistently in clinical practice. Among patients with discordant results, there was no differential in glycoprotein IIb/IIIa use based on troponin status. Thus, it appears that treatment with glycoprotein IIb/IIIa inhibitors is biased by CK-MB status despite the evidence that favors use among cTn+ patients. Similarly, despite a previous analysis that showed no interaction of CK-MB status with benefit from an early invasive strategy, but when stratified by troponin status demonstrated evidence for benefit among CK-MB-/cTn+ patients (24), in our study, even after accounting for patient and hospital characteristics, CK-MB+/cTn+ patients were

most likely to undergo early diagnostic cardiac catheterization. Among those with discordant results, there was no difference in use of diagnostic catheterization within 24 h and only slightly more frequent use among CK-MB-/cTn+ patients than CK-MB+/cTn- patients in the <48-h time frame.

Study limitations. The ACC/AHA guidelines are in continual evolution as new evidence becomes available. Therefore, it is possible that some of the relationships we observed may be of more or less relevance over time. Independent of this, our findings highlight several areas for education about risk and the application of both marker testing and evidence-based therapies that could have a substantial impact on the outcomes of high-risk ACS patients in the present. In part, our observations may reflect issues of differences in clinical trials populations and clinical practice ACS populations, perhaps reflecting uncertainty among clinicians about the benefits and risks of using antiplatelet therapy and early invasive management strategies among older and sicker patients, who tended to be underrepresented in clinical trials. Continued efforts to enhance representation of these populations in future studies should help to better define treatment in these groups.

Since the CRUSADE population was selected on the basis of presence of high-risk characteristics, we cannot be sure that these findings would extend similarly to the entire spectrum of ACS, but there is no compelling reason to believe that they would not.

Marker-positive status was determined by using the site's own laboratory-reported ULN for comparison with baseline and peak values reported by the CRUSADE investigators. Troponin substudies of clinical trials have established the designation of positive troponins as any value above the ULN for the assay used, and it is at these levels that the mortality and treatment effect differences were observed and accepted (7-9). In an attempt to examine these findings in the context of clinical practice, we have applied the same paradigm to the best available marker data. Since a core laboratory was not used, there is unavoidable variation in the type, quality, and standardization of the individual troponin assays used across hospitals. However, we feel our observations fairly represent clinical practice and the integration of marker testing into clinical decision making. Despite this, and the fact that we adjusted for hospital characteristics in our modeling, it remains possible that concern among physicians about the reliability of a reported troponin result may have influenced clinical management decisions, since it appears from our results that a positive CK-MB was necessary in addition to a positive cTn before more aggressive care was applied.

Finally, we did not account for the timing of positive markers. It is possible that since we assigned patients to marker categories based upon the highest marker level attained, irrespective of when it occurred within the first 36 h, physicians were less aggressive in the management of

patients whose serial markers became minimally positive later in that period.

Conclusions. Short-term mortality in cTn+ patients is increased regardless of CK-MB status, but CK-MB elevation in the absence of elevated cTn does not necessarily carry the same implications. Paradoxically, some therapies that are equally effective across all levels of risk are used more frequently in cTn+ patients, whereas therapies demonstrated to be more effective among cTn+ patients are not used differentially based on marker status. Recognition of differences in risk based on the results of cardiac marker testing and the relationships of the effectiveness of available therapies with marker status and risk should contribute to more appropriate early use of evidence-based treatment for ACS, particularly antiplatelet therapy and early invasive management.

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