Association Between Minor Elevations of Creatine Kinase-MB Level and Mortality in Patients With Acute Coronary Syndromes Without ST-Segment Elevation

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Context Controversy surrounds the diagnostic and prognostic importance of slightly elevated cardiac markers in patients with acute coronary syndromes without ST-segment elevation.

Objectives To investigate the relationship between peak creatine kinase (CK)-MB level and outcome and to determine whether a threshold CK-MB level exists below which risk is not increased.

Design and Setting Retrospective observational analysis of data from the international Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, conducted from November 1995 to January 1997.

Patients A total of 8250 patients with acute coronary sydromes without ST-segment elevation who had at least 1 CK-MB sample collected during their index hospitalization.

Main Outcome Measure Mortality at 30 days and 6 months, was assessed by category of index-hospitalization peak CK-MB level (0-1, >1-2, >2-3, >3-5, >5-10, or >10 times the upper limit of normal). Multivariable logistic regression was used to determine the independent prognostic significance of peak CK-MB level after adjustment for baseline predictors of 30-day and 6-month mortality.

Results Mortality at 30 days and 6 months increased from 1.8% and 4.0%, respectively, in patients with normal peak CK-MB levels, to 3.3% and 6.2% at peak CK-MB levels 1 to 2 times normal, to 5.1% and 7.5% at peak CK-MB levels 3 to 5 times normal, and to 8.3% and 11.0% at peak CK-MB levels greater than 10 times normal. Log-transformed peak CK-MB levels were predictive of adjusted 30-day and 6-month mortality ($P<.001$ for both).

Conclusions Our data show that elevation of CK-MB level is strongly related to mortality in patients with acute coronary syndromes without ST-segment elevation, and that the increased risk begins with CK-MB levels just above normal. In the appropriate clinical context, even minor CK-MB elevations should be considered indicative of myocardial infarction.

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THE CRITERIA USED TO DIAGnose myocardial infarction (MI) are important both clinically and in clinical trials. The most widely accepted diagnostic criteria for MI are those of the World Health Organization, first proposed almost 20 years ago. These criteria require presence of at least 2 of the following 3 elements to diagnose MI: (1) a history of ischemic-type chest discomfort, (2) evolutionary changes on serial electrocardiograms, and (3) a rise and fall in serum cardiac enzymes.[1]

Today, the cornerstone of these diagnostic criteria is evaluation of serial cardiac markers. The most commonly used markers, both clinically and in clinical research, are creatine kinase (CK) and

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its more myocardium-specific MB isoenzyme, CK-MB.[2,3] While many physicians consider even small elevations in CK-MB levels to represent evidence of MI, the diagnostic and prognostic importance of these small elevations remains controversial both in patients with acute coronary syndromes (ACSs) and in those who undergo coronary intervention.[4-10] Due to evolving cardiac-marker technology and the vagueness of the World Health Organization criteria regarding what constitutes adequate evidence of "a rise and fall in serum enzymes," the definitions of MI used both clinically and in clinical trials have varied widely.

The large, multicenter Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial presents a unique opportunity to investigate the prognostic significance of CK-MB elevations in patients with ACSs without persistent ST-segment elevation.[11] We evaluated the relationship between peak CK-MB level (as an estimate of infarct size) and outcome to determine whether a threshold of CK-MB elevation exists below which there is no increased risk. In addition, we examined the relationship between MI at the time of admission to the hospital (admission infarction) and after admission (postadmission infarction) and subsequent mortality.

METHODS

Study Population

This study involved the 9461 patients included in the primary analysis of the PURSUIT trial. The PURSUIT trial has been described in detail.[11] Briefly, patients with ACSs without persistent ST-elevation were randomly assigned to receive either a 180-µg/kg bolus and 2.0-µg/kg per minute infusion of the glycoprotein IIb/IIIa inhibitor eptifibatide (Integrilin, COR Therapeutics Inc, San Francisco, Calif) or placebo for up to 72 to 96 hours. Inclusion criteria were ischemic symptoms within 24 hours of randomization accompanied by (1) ST-segment depression, transient ST-segment elevation, or T-wave inversion, or (2) an elevated CK-MB level. Major exclusion criteria were persistent ST-segment elevation, history of bleeding diathesis, recent gastrointestinal tract or genitourinary bleeding, severe hypertension, recent major surgery, prior hemorrhagic stroke, stroke of any type in the past 30 days, pregnancy, renal failure (serum creatinine level $\geq$2.0 mg/dL), and planned or recent administration of a glycoprotein IIb/IIIa inhibitor or thrombolytic agent. Patients were followed up for a primary end point of death or nonfatal MI at 30 days.

The protocol specified that 3 CK-MB samples be collected from all patients every 8 hours after enrollment, with another 3 samples (at 8-hour intervals) after any suspected MI, percutaneous coronary intervention, or coronary artery bypass grafting. Additional samples were collected at the discretion of the treating physician. Sites that could not perform CK-MB assays performed total CK assays. The CK-MB and CK samples were analyzed in each hospital's clinical laboratory. The results, along with the upper limit of normal (ULN) for that laboratory, were collected on the case report form and verified against original source documents. Baseline characteristics, enrollment variables, and clinical outcomes also were collected on the case report form.

The primary use of the CK and CK-MB data was to diagnose MI. A diagnosis of MI on admission was made if there was elevation of CK-MB above the ULN prior to or within 16 hours of admission. Postadmission MI was diagnosed if there was new ischemic chest pain and new ST-segment elevation lasting at least 30 minutes within 18 hours of admission. After 18 hours, MI was diagnosed if there was a new or repeated elevation of CK-MB above the ULN or if there were new Q waves in 2 electrocardiographic leads. For patients undergoing percutaneous coronary intervention, an MI after the procedure was diagnosed if there was elevation of CK-MB to 3 or more times the ULN or new Q waves in 2 electrocardiographic leads. The diagnosis of MI following coronary artery bypass graft surgery required an elevation of CK-MB to 5 or more times the ULN or new Q waves in 2 electrocardiographic leads.[11] A blinded clinical events committee adjudicated all suspected infarctions that occurred after admission to 30 days according to prespecified criteria.[11]

Comparison Groups

The 8250 patients (87.2%) who had at least 1 CK-MB sample collected during the index admission were stratified by the peak CK-MB level during this admission: 0 to 1 times ULN (or normal), greater than 1 to 2 times ULN, greater than 2 to 3 times ULN, greater than 3 to 5 times ULN, greater than 5 to 10 times ULN, or greater than 10 times ULN. Patients also were stratified into these categories after excluding enzymes associated with an admission infarction. To exclude these enzymes, patients who had either an admission infarction or an elevated CK-MB level within 12 hours of admission had CK-MB samples excluded for 48 hours or until they had a CK-MB level of less than the ULN. To eliminate the potentially confounding effect of percutaneous coronary intervention and coronary artery bypass surgery on CK-MB levels, analyses were repeated after excluding patients who had these procedures during their first admission. Patients also were stratified into the categories of admission infarction only, postadmission infarction only, neither, or both.

Statistical Methods

Continuous variables are expressed as medians, and categorical variables are expressed as percentages. Baseline variables, 30-day and 6-month mortality, and other clinical outcomes were determined by peak CK-MB category. The continuous relationships between peak CK-MB level and both 30-day and 6-month mortality also were determined. Hypothesis testing was performed using a logistic-proportional odds regression model for continuous variables and the Cochran-Mantel-Haenszel general association and correlation statistics for nominal and ordinal variables, respectively. Mortality rates were then determined for patients in each

infarction category (admission infarction, postadmission infarction, neither, and both). Odds ratios and 95% confidence intervals were calculated for 30-day and 6-month mortality for each category vs the no infarction category.

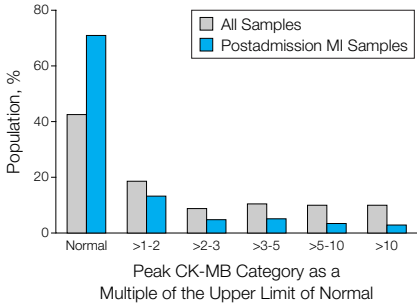
A multivariable regression model that predicts 30-day mortality in the PURSUIT population has been developed.[12] Variables in this model are age, sex, weight, weight squared, height, region of enrollment, prior hypertension, diabetes mellitus, smoking status, worst Canadian Heart Classification in the past 6 weeks, prior congestive heart failure, prior angioplasty, prior coronary artery bypass surgery, prior β-blocker use, prior calcium-antagonist use, prior nitrate use, admission MI, systolic blood pressure, heart rate, rales, ST-segment depression, time from onset of symptoms, eptifibatide use, and the interaction terms of age by admission infarction, heart rate by admission infarction, and eptifibatide by admission infarction.

For the purpose of our analyses, variables pertaining to admission infarction were removed from the model because of their confounding effect with CK-MB data. A single variable describing peak CK-MB level was then added to the model to determine whether overall peak CK-MB level had independent prognostic significance for 30-day and 6-month mortality, after adjustment. Log transformation was performed because of the nonlinear relationship between peak CK-MB level and mortality. This single-peak CK-MB variable was then removed and each individual peak CK-MB category was added to the model to determine its independent prognostic significance after adjusting for other baseline predictors of mortality.

RESULTS

Of 8250 patients with CK-MB data, 42% did not have CK-MB levels above the ULN, 18% had peak CK-MB levels of greater than 1 to 2 times the ULN, and approximately 10% had peak CK-MB

Figure 1. Distribution of Peak Creatine Kinase (CK)-MB Levels by Category



Includes all enzymes and only enzymes associated with postadmission infarctions.

Table 1. Baseline Patient Characteristics by Peak Creatine Kinase (CK)-MB Category*

	Peak CK-MB†						
	Normal (n = 3500)	>1-2 (n = 1524)	>2-3 (n = 732)	>3-5 (n = 848)	>5-10 (n = 820)	>10 (n = 826)	*P* Value
Median age, y	62.1	63.1	63.1	63.9	63.5	63.2	<.001
Sex							
Men	58.4	64.2	71.9	69.3	71.5	74.2	<.001
Women	41.6	35.8	28.1	30.7	28.5	25.8	
Race‡							
White (n = 7351)	86.6	92.4	91.4	90.8	91.0	89.5	<.001
Black (n = 410)	6.4	3.0	3.4	3.7	4.8	5.4	
Other (n = 242)	6.9	4.7	5.2	5.6	4.3	5.1	
Median weight, kg	78.7	78.8	79.8	79.5	81.3	80.5	<.001
Median height, cm	168.7	168.9	170.0	169.8	170.4	171.1	<.001
Median systolic blood pressure, mm Hg	133.1	131.1	131.3	129.8	131.3	129.3	<.001
Median heart rate, beats/min	72.8	73.8	74.5	73.4	72.8	73.4	.38
Hypertension	57.3	57.8	50.8	52.2	54.4	52.4	<.001
Diabetes	22.7	26.0	23.4	22.5	22.9	20.6	.22
Hypercholesterolemia	42.8	42.3	41.2	43.1	37.9	41.8	.12
Smoking status§							
Current (n = 2365)	26.7	27.5	31.5	30.1	31.9	33.7	<.001
Former (n = 2661)	33.0	31.7	31.6	32.1	29.7	35.1	
Never (n = 3176)	40.3	40.8	36.9	37.7	38.3	31.2	
Family history of coronary artery disease	37.2	30.6	34.5	33.1	34.8	35.5	.19
Prior myocardial infarction	31.8	34.4	33.8	30.6	30.4	30.0	.15
History of congestive heart failure	10.7	12.5	10.9	12.4	10.5	9.7	.55
Prior stroke	2.9	3.7	3.6	3.4	3.8	4.7	.02
Peripheral vascular disease	7.6	9.4	7.8	9.2	10.1	8.6	.06
Prior angioplasty	13.2	11.1	9.3	10.3	12.5	12.4	.21
Prior coronary artery bypass surgery	12.5	9.3	10.4	11.3	10.2	14.0	.90
Prior angina	84.9	83.3	78.6	76.4	76.7	72.8	<.001
ST-segment depression	33.9	38.6	39.9	41.3	43.4	47.8	<.001

*Data presented are percentages within each CK-MB category unless otherwise noted. *P* values refer to overall relationship between the characteristic and peak CK-MB category.
†Categories are multiples of the upper limit of normal.
‡Data missing for 247 subjects.
§Data missing for 48 subjects.

levels in each of the other categories (FIGURE 1). Baseline patient characteristics by peak CK-MB category are shown in TABLE 1. Patients with higher peak CK-MB levels were older, and more often were male, white, and current smokers. These patients also had lower systolic blood pressure on admission, tended to weigh more and be taller, had more prior strokes and peripheral vascular disease, were less likely to have had prior angina, and were more likely to have ST-segment depression on their admission electrocardiogram.

Figure 2. Mortality at 30 Days and 6 Months by Peak Creatine Kinase (CK)-MB Category, All CK-MB Samples

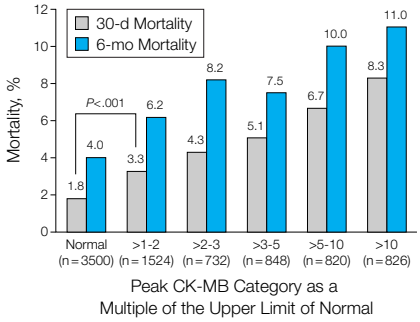
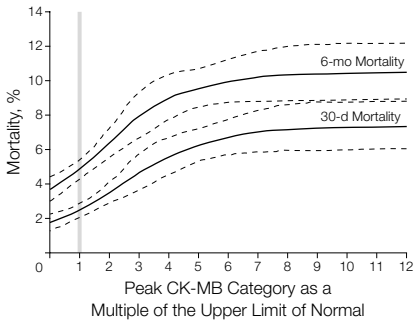


Figure 3. Continuous Relationship Between Peak Creatine Kinase (CK)-MB as a Multiple of the Upper Limit of Normal and Mortality at 30 Days and 6 Months



Dotted lines represent 95% confidence intervals. Gray line represents the upper limit of the normal range.

The relationship between peak CK-MB level and mortality at 30 days and 6 months is shown in FIGURE 2 and FIGURE 3. There was a statistically significant overall relationship between peak CK-MB level and both 30-day and 6-month mortality ($P<.001$ for both). This higher risk of 30-day mortality began with the peak CK-MB category just above the ULN ($P<.001$). The relationship between peak CK-MB level and other clinical outcomes is shown in TABLE 2. Patients with higher peak CK-MB levels had higher in-hospital rates of stroke, shock, congestive heart failure, ventricular tachycardia or fibrillation, atrioventricular block, moderate or severe bleeding, and coronary artery bypass surgery and percutaneous coronary artery intervention at 30 days, than patients with lower peak CK-MB levels.

When only CK-MB samples not associated with admission infarctions were considered, 71% of patients did not have CK-MB levels above the ULN, 13% had peak CK-MB levels of greater than 1 to 2 times the ULN, and between 3% and 5% had peak CK-MB levels in each of the other categories (Figure 1). The relationship between postadmission infarction peak CK-MB level and mortality is shown in FIGURE 4. There was a statistically significant relationship overall between postadmission infarction peak CK-MB level and 30-day and 6-month mortality ($P<.001$ for each), similar to the relationship observed when all CK-MB samples were included. This higher risk of 30-day mortality began with the postadmission infarction peak CK-MB category just above the ULN ($P<.001$).

Patients receiving only medical treatment (no percutaneous or surgical revascularization) (n = 6512) showed the same significant relationship between peak CK-MB level and both 30-day and 6-month mortality ($P<.001$ for each). This higher risk of 30-day mortality also began with the peak CK-MB category just above the ULN ($P<.001$).

A total of 3545 patients had only an admission infarction, 529 had only a postadmission infarction, 681 had both, and 3791 patients had neither. Admission infarction was associated with modestly higher odds of death at 30 days and 6 months, whereas postadmission infarction was associated with markedly higher odds of death at both 30 days and 6 months compared with those with no infarction (FIGURE 5).

The log-transformed peak CK-MB level was highly predictive of both 30-day (Wald χ^2, 80.57; $P<.001$) and 6-month mortality (Wald χ^2, 74.46; $P<.001$) after adjustment for other

Table 2. Clinical Outcomes by Peak Creatine Kinase (CK)-MB Category*

	Peak CK-MB†						
	Normal (n = 3500)	>1-2 (n = 1524)	>2-3 (n = 732)	>3-5 (n = 848)	>5-10 (n = 820)	>10 (n = 826)	*P* Value
Stroke	0.5	0.9	1.2	0.7	1.1	1.6	.004
Shock	1.0	2.1	2.9	3.7	4.4	7.4	<.001
Congestive heart failure	2.9	5.9	6.1	7.2	10.5	13.5	<.001
Ventricular tachycardia or fibrillation	0.9	1.5	2.1	2.8	3.8	5.6	<.001
2nd- or 3rd-degree atrioventricular block	0.9	1.2	1.9	2.0	2.2	3.6	<.001
30-day coronary artery bypass surgery	8.9	15.5	20.5	23.6	28.0	24.1	<.001
30-day percutaneous coronary intervention	23.1	26.6	29.0	26.5	27.2	34.9	<.001
Moderate or severe bleeding	6.8	11.6	15.2	15.8	19.8	18.6	<.001

*Data presented are percentages within each CK-MB category. *P* values refer to overall relationship between outcome and peak CK-MB category.
†Categories are multiples of the upper limit of normal.

baseline predictors. When the individual peak CK-MB categories were included in the model, a strong stepwise association was found between peak CK-MB level and 30-day mortality (FIGURE 6). The relationship between peak CK-MB level and mortality was similar between patients who received eptifibatide and those who did not.

COMMENT

In this analysis of more than 8000 patients with ACSs, we found a strong relationship between a patient's peak CK-MB level during hospitalization and both 30-day and 6-month mortality. There was no threshold peak CK-MB elevation below which the risk of mortality was not increased. Even the peak CK-MB category of 1 to 2 times the ULN conferred a highly significant increase in the risk of death compared with a peak CK-MB level within the normal range. After adjustment for other baseline predictors of mortality, peak CK-MB level remained a strong independent predictor of mortality. Although the risk associated with a CK-MB level of just 1 to 2 times the ULN was not statistically significant after adjustment, there was a stepwise increase in risk with each higher peak CK-MB category. In addition to having higher mortality, patients with higher peak CK-MB levels also had higher rates of stroke, shock, congestive heart failure, ventricular arrhythmias, coronary procedures, and bleeding. This relationship between peak CK-MB level and mortality was observed both when all enzymes were included and when enzymes associated with admission infarctions were excluded. In addition, the same relationship between peak CK-MB level and mortality was observed when the potentially confounding effects of percutaneous intervention and bypass surgery were removed.

Patients who had an admission infarction (vs those with unstable angina) had a modestly increased risk of death at both 30 days and 6 months. In contrast, patients who had a postadmission infarction had a markedly increased risk of death, whether the patient was admitted with unstable angina or MI. Previous studies have shown that patients with positive cardiac markers at admission, whether CK-MB or troponin, have an increased risk of reinfarction[12-15] and that recurrent events are associated with an increased risk of death.[16-20] The reasons that recurrent coronary events carry such prognostic importance are not clear. These events may represent evidence of a refractory pathophysiological process that progresses despite ongoing medical therapy. Regardless of the mechanism, our findings reinforce the clinical importance of preventing, detecting, and treating even small reinfarctions in patients admitted with ACSs.

The relationship between the magnitude of CK increase and infarct size has been shown in patients with ST-segment elevation and acute MI.[21,22] In addition, prethrombolytic-era studies,

Figure 4. Mortality at 30 Days and 6 Months by Peak Creatine Kinase (CK)-MB Category, Postadmission Infarction CK-MB Samples Only

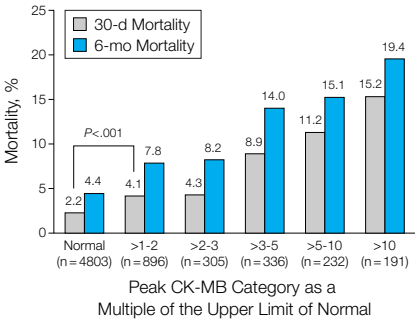
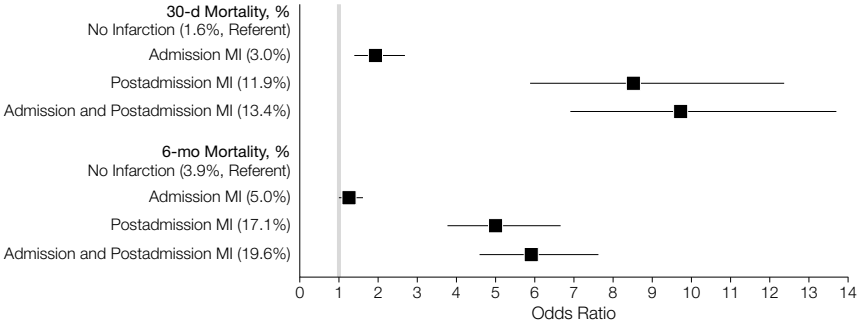
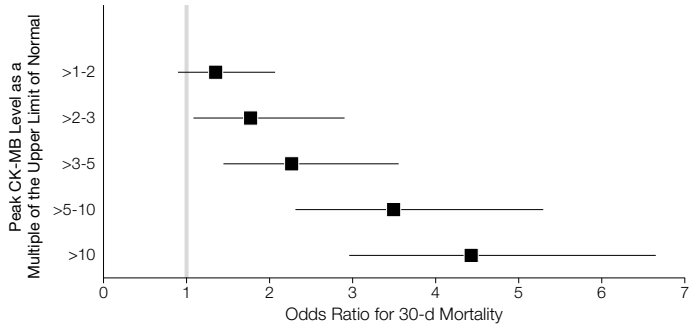


Figure 5. Odds Ratios and 95% Confidence Intervals for Risk of 30-Day and 6-Month Mortality



Values represent patients with admission infarction only, postadmission infarction only, and both compared with those with no infarction. MI indicates myocardial infarction. Gray line represents referent for 30-day and 6-month mortality for those patients with no infarction.

Figure 6. Odds Ratios and 95% Confidence Intervals for 30-Day Mortality for Each Peak Creatine Kinase (CK)-MB Category Relative to the Normal Range After Adjustment for Other Baseline Predictors



Gray line represents referent for 30-day mortality for normal peak CK-MB level.

primarily of patients with ST-segment elevation infarction, have reported associations between infarct size (as measured by CK or CK-MB) and prognosis, the incidence and severity of congestive heart failure, left ventricular dysfunction, the frequency and severity of ventricular arrhythmias, infarct size at autopsy, and angiographic estimates of infarct size.[22-30] Several studies in small numbers of patients with suspected infarction have shown that even mildly elevated CK-MB levels are associated with worse clinical outcomes.[5,7,8,31,32] Long-term mortality in these patients was found to be similar to that of patients without CK-MB elevation in one study[6] but was significantly higher in another.[8] Our analysis confirms, in a contemporary patient population presenting with ACSs without ST-segment elevation, that any elevation of CK-MB is associated with worse outcomes.

The most extensive work on the relationship between small-to-moderate CK-MB elevations and outcome has been done in patients undergoing coronary intervention.[9,10] After percutaneous intervention, CK-MB elevation occurs in 10% to 40% of patients, and in most studies has been associated with an increased risk of adverse outcomes.[9,10,33-39] Similar to our findings, the increased risk associated with CK-MB elevation in these studies began just above the ULN and was proportional to the degree of elevation.[9,37]

The exact mechanism of minor CK-MB elevation in patients with ACSs or in patients undergoing coronary intervention is not known. Most studies support that myocardial CK-MB is not released in the absence of irreversible myocardial necrosis; however, controversy does still exist.[9,40-42] Whether associated with pathologically demonstrable myocardial necrosis, however, even minor elevation of CK-MB is prognostically important. There is increasing evidence, predominantly from the interventional literature, that minor CK-MB elevation may be a marker of ongoing vascular instability resulting in recurrent platelet microemboli and microscopic infarction.[9,10,37,43] This vascular instability associated with recurrent platelet emboli may represent the refractory pathophysiology behind the worse outcomes observed in patients with ACSs who have evidence of recurrent myocardial necrosis. This hypothesis is supported by the effect of glycoprotein IIb/IIIa inhibitors on CK-MB elevations both after percutaneous intervention and in patients with ACSs, as well as the particularly robust effects of these agents in patients who present with evidence of myocardial necrosis.[44,45]

Almost 30% of the patients enrolled in the PURSUIT trial had an elevated CK-MB level after their admission event had resolved. This event rate is high compared with the 12.9% rate of MI reported in PURSUIT and the 6.0% rate in a similar subgroup within the Global Use of Strategies to Open Occluded Coronary Arteries-IIb (GUSTO-IIb) trial.[11,46] The difference between the rates of infarction and CK-MB elevation in PURSUIT probably reflects the application by the clinical events committee of protocol-specified criteria to define infarction.[11] Conversely, since GUSTO-IIb used the same definition of infarction, the difference in the infarction rates between PURSUIT and GUSTO-IIb likely results from a greater number of enzyme samples collected per patient in PURSUIT than in GUSTO-IIb (medians [25th, 75th percentiles], 3 [1, 4] vs 4.5 [3, 7]), respectively. Both the criteria for MI and the frequency of CK-MB sampling can have a profound effect on observed event rates. The accurate interpretation of trial results requires that these factors be reported in trial publications.

This analysis has several limitations. The study was retrospective and observational, and there may be unaccounted factors that could explain the observed differences in mortality. Although the PURSUIT inclusion criteria were broad, there are some patients with chest pain for whom these data do not apply. The 6-month follow-up period was relatively short; however, this should, if anything, reduce our ability to detect differences between groups. The CK-MB samples were analyzed in multiple laboratories using different assays. This variability also would reduce the ability to detect differences and we attempted to adjust for it by expressing the values as multiples of the laboratory's ULN. We used each patient's highest CK-MB level as an estimate of infarct size and did not take into account multiple infarctions. Finally, early deaths, which occurred before patients could reach their true peak CK-MB level, would be counted in a lower peak CK-MB category. This categorization would tend to bias the results in the direction of lower CK-MB categories being associated with worse outcomes, however, our primary findings were in the opposite direction.

In conclusion, this study demonstrates that in patients with ACSs without ST-segment elevation, a strong relationship exists between the magnitude of CK-MB elevation and mortality, and the risk begins just above the ULN. Small CK-MB elevations represent clinically important evidence of myocardial necrosis and, we believe, should be considered sufficient cardiac-marker criteria for a diagnosis of MI in patients with ACSs. Elevation of CK-MB above the ULN identifies a group of patients at higher risk of death. Whether these patients will benefit from aggressive medical or interventional therapy will require further study. Therapies that reduce the incidence or magnitude of CK-MB elevation may be clinically beneficial.

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