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Clinical research

# Creatine kinase-MB elevation after percutaneous coronary intervention predicts adverse outcomes in patients with acute coronary syndromes

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## KEYWORDS

Acute coronary syndromes;  
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Biomarkers;  
Percutaneous coronary  
interventions

**Aim** To study the relationship between outcomes and peak creatine kinase (CK)-MB levels after percutaneous coronary intervention (PCI) in patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS).

**Methods and results** Peak CK-MB ratios (peak CK-MB level/upper limit of normal [ULN]) after PCI were analysed in 6164 patients with NSTEMI ACS from four randomized trials who underwent in-hospital PCI. We excluded 696 patients with elevated CK or CK-MB levels <24 h before PCI; the primary analysis included 2384 of the remaining 5468 patients (43.6%) with CK-MB levels measured ≤24 h after PCI. The incidence of in-hospital heart failure (0.1%, 0.8%, 3.4%, 4.1%, and 6.1%;  $P<0.001$ ), arrhythmias (0.8%, 1.9%, 6.9%, 4.1%, and 7.9%;  $P<0.001$ ), cardiogenic shock (0.1%, 1.3%, 2.0%, 2.3%, and 2.6%;  $P=0.004$ ), and mortality through 6 months (2.1%, 2.4%, 4.9%, 4.1%, and 5.7%,  $P=0.005$ ) was increased with peak CK-MB ratios of 0–1, 1–3, 3–5, 5–10, and >10×ULN, respectively. The continuous peak CK-MB ratio after PCI significantly predicted adjusted 6-month mortality (risk ratio, 1.06 per unit increase above ULN; 95% confidence interval, 1.01–1.11;  $P=0.017$ ).

**Conclusions** Greater CK-MB elevation after PCI is independently associated with adverse outcomes in NSTEMI ACS. These results underscore the adverse implications of elevated CK-MB levels after PCI in this high-risk population.

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## Introduction

Elevated cardiac enzyme levels can be detected in 10–20% of patients undergoing percutaneous coronary intervention (PCI), but the clinical significance of myocardial

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necrosis after PCI and the definition of periprocedural myocardial infarction (MI) remain controversial.<sup>1–3</sup> Multiple studies have shown an increased risk of mortality with elevated levels of creatine kinase (CK) and CK-MB isoenzymes after PCI.<sup>4–7</sup> Although patients with acute coronary syndromes (ACS) have a higher risk of procedural complications during PCI than patients undergoing elective coronary intervention, the incidence, definition, and prognostic implications of periprocedural cardiac enzyme elevations in patients with ACS have not been well-studied.<sup>8,9</sup> Because almost one-fourth of patients with ACS undergo PCI during their initial hospitalization, and non-fatal ischaemic events are often incorporated into definitions for clinical trial end-points, cardiac enzyme elevations after PCI could significantly influence individual outcomes and the results of trials that include patients with ACS.<sup>10–13</sup>

The Global Use of Strategies To Open occluded coronary arteries in acute coronary syndromes (GUSTO-IIb), Platelet glycoprotein in Unstable angina Receptor Suppression Using Integrilin Therapy (PURSUIT), Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON-A), and PARAGON-B trials evaluated new antithrombotic and antiplatelet therapies for patients with non-ST segment elevation (NSTEMI) ACS. We evaluated patients from these trials who underwent PCI during the initial hospitalization to assess the impact of periprocedural CK-MB elevations on clinical outcomes.

## Methods

### Study population

The enrolment criteria for these trials were similar across trials.<sup>10–12,14</sup> Patients with NSTEMI ACS were enrolled if they had ischaemic chest pain within 12–24 h before presentation with electrocardiographic (ECG) signs of ischaemia or elevated serum cardiac markers, including troponin I or T or CK-MB. The subgroup of patients in the GUSTO-IIb trial with persistent ST-segment elevation was not evaluated. The institutional review committees of all participating hospitals approved the study protocols, and all subjects gave informed consent.

### Randomization and treatment

In GUSTO-IIb, patients were randomized to receive intravenous unfractionated heparin or recombinant hirudin for 3–5 days.<sup>10</sup> In PURSUIT, patients were randomized in a double-blind fashion to receive placebo or one of two doses of the platelet glycoprotein IIb/IIIa inhibitor eptifibatid for 3–4 days.<sup>11</sup> In PARAGON-A, patients were randomized in a 2×2 factorial design to receive low-dose lamifiban (a glycoprotein IIb/IIIa inhibitor), high-dose lamifiban with intravenous heparin, or placebo with intravenous heparin for 3–5 days.<sup>12</sup> In PARAGON-B, patients were randomized to receive lamifiban or placebo for 3–5 days, and study drug was adjusted for renal function.<sup>14</sup>

### Concomitant treatment

Aspirin (80–325 mg daily) was recommended for all trial patients. Heparin was recommended for all patients in PURSUIT and PARAGON-B but was not required.<sup>11,14</sup> Heparin use was

determined by randomized treatment assignment in GUSTO-IIb and PARAGON-A. Other medications were given at the discretion of the treating physicians. Decisions about coronary angiography, PCI, and bypass surgery were not protocol-mandated and were made by the treating physician. Routine surveillance of CK-MB levels was strongly recommended at enrolment, after recurrent ischaemic events, and after revascularization (PCI or bypass surgery) but was not mandated by the study protocols. CK-MB levels were analysed locally at participating sites and in a central core laboratory in a portion of patients from PARAGON-B.

### Patient selection

The study group included all patients with NSTEMI ACS from the respective trials who underwent PCI during the initial hospitalization. Patients who did not have CK-MB levels measured <24 h after PCI and those who had a measured total CK or CK-MB level >1 times the upper limit of normal (×ULN) in the 24 h before PCI were excluded from the primary analysis. Patients with measured CK-MB levels had ≥1 CK-MB level recorded on the case report form within 24 h after PCI.

### End-points

The primary end-point of this analysis was all-cause mortality through 6 months, the longest common follow-up period among the trials. Additional in-hospital outcomes evaluated after PCI included congestive heart failure (new onset of dyspnoea with evidence of heart failure on physical examination), shock (persistent hypotension, diminished cardiac output, and evidence of end-organ hypoperfusion), and arrhythmias (ventricular fibrillation or tachycardia, atrial fibrillation or flutter, or advanced atrioventricular block). The incidence of (re)infarction after PCI was not evaluated, because repeat infarctions were not consistently collected and recorded among the trials when patients had multiple recurrent ischaemic events. Events occurring before PCI were not evaluated.

### Comparison groups

Patients with ≥1 CK-MB level measured <24 h after PCI were stratified into categories by peak CK-MB ratios of 0–1, 1–3, 3–5, 5–10, and >10×ULN for statistical comparisons. The absolute peak CK-MB values for each patient were transformed into peak CK-MB ratios with the following formula: peak CK-MB ratio=actual peak CK-MB value divided by the ULN for CK-MB from the local institution, according to expert recommendations.<sup>1,15</sup> The clinical characteristics and outcomes of patients excluded from the primary analysis were not directly compared but were recorded to describe differences between excluded patients and the primary analysis group. Baseline characteristics of patients undergoing PCI from the different trials also were compared to assess differences across the populations.

### Statistical analysis

Baseline, angiographic, and procedural characteristics are presented as numbers and percentages for categorical variables and as medians with 25th and 75th percentiles for continuous variables. Likelihood ratio chi-square, Mantel–Haenszel chi-square, Kruskal–Wallis, and Wilcoxon rank-sum tests were used to compare baseline categorical and continuous variables, respectively, among the comparison groups.

Kaplan–Meier event rates through 6 months were determined by peak CK-MB categories. Log-rank statistics were used to compare unadjusted clinical event rates among patients in the different peak CK-MB categories. We also determined the

**Table 1** Baseline clinical characteristics by trial enrolment for all patients undergoing PCI

	GUSTO-IIb (n=1594)	PURSUIT (n=2226)	PARAGON-A (n=334)	PARAGON-B (n=1314)	P value <sup>a</sup>
Age (years)	62 (54, 70)	62 (53, 69)	64 (55, 70)	61 (52, 70)	0.07
Male sex	71.0%	69.3%	72.2%	72.1%	0.30
Heart rate (bpm)	72 (63, 81)	70 (61, 80)	74 (64, 84)	73 (64, 85)	<0.001
Systolic BP (mmHg)	137 (120, 150)	130 (115, 142)	144 (130, 160)	140 (125, 160)	<0.001
Diabetes	18.6%	20.2%	13.2%	21.7%	0.002
Enrolment infarction	47.7%	37.7%	28.0%	40.9%	<0.001
Prior infarction	26.9%	29.1%	30.5%	28.2%	0.37
Prior PCI	17.4%	20.3%	17.1%	21.9%	0.01
Prior bypass surgery	12.8%	14.7%	12.6%	15.4%	0.15
Prior CHF	3.3%	6.7%	3.9%	8.1%	<0.001
ECG findings					
ST depression	54.0%	30.6%	60.7%	42.9%	<0.001
Transient ST elevation	17.0%	10.6%	22.8%	17.3%	<0.001
T-wave inversion	53.2%	53.6%	56.3%	45.9%	<0.001

<sup>a</sup>Across trials. BP=blood pressure; PCI=percutaneous coronary intervention; CHF=congestive heart failure; ECG=electrocardiographic.

unadjusted continuous relationship between peak CK-MB levels after PCI and 6-month mortality after transforming continuous peak CK-MB levels into splines.<sup>16</sup>

A multivariable regression model was developed from the PURSUIT database that reliably predicts 30-day mortality among patients with NSTEMI ACS from eight baseline clinical characteristics (age, systolic blood pressure, heart rate, previous angina, male sex, ST-segment depression, enrolment infarction, and signs of congestive heart failure) that were shown to be the strongest predictors of mortality in a larger, expanded regression model.<sup>17</sup> The variable 'signs of congestive heart failure' from the model was denoted as physical examination findings consistent with congestive heart failure upon hospital presentation. Variables added to the established model for this analysis included angiographic characteristics (two- and three-vessel coronary disease), unsuccessful PCI (stenosis >50% or Thrombolysis In Myocardial Infarction [TIMI] grade <3 flow after PCI), experimental treatment (hirudin, eptifibatide, or lamifiban) as a dichotomous variable that denotes experimental treatment versus non-experimental treatment, time to PCI, and peak CK-MB ratio as a continuous variable (per one unit increase above ULN). Left ventricular ejection fraction could not be included in the multivariable model because it was not recorded on data-collection forms in 2470 of 5468 patients analysed (45.2%). The continuous form of peak CK-MB levels was transformed into splines for incorporation into the model.<sup>16</sup> Testing for linearity using the independent splines yielded non-significant results, hence the linearity assumption was satisfied and peak CK-MB ratio as a continuous variable was incorporated into the model in its true state with no transformations.

Based on Cox proportional-hazards modelling, Wald chi-square analyses were used to determine significant predictors of 6-month mortality and to test the statistical significance of the relationship of the continuous peak CK-MB ratio variable to 6-month mortality. Linear hypothesis testing was used to evaluate the relation of peak CK-MB ratio categories with 6-month mortality in a separately fitted version of the regression model rather than peak CK-MB ratio as a continuous variable. Interactions between the different categories of peak CK-MB ratios and time to death were tested to verify the proportional hazards assumption. Based upon non-significant *P*-values for these interactions, the assumption was considered to be valid.

An interaction term between experimental treatment and peak CK-MB ratio was incorporated into the regression model

to evaluate the impact of the assigned treatments (hirudin, eptifibatide, or lamifiban) on the predictive capabilities of peak CK-MB ratios. Experimental treatment was considered to be a dichotomous variable that denotes experimental treatment versus non-experimental treatment. Trial enrolment was not included in the final regression model because this variable depends linearly on experimental treatment, but a separately fitted version of the model that did not include experimental treatment showed no interaction between trial enrolment (using GUSTO-IIb as the reference) and peak CK-MB ratio categories (using the group with peak CK-MB ratios 0–1×ULN as the reference) with linear hypothesis testing (Wald chi square, 0.86, *df*=3, *P*=0.83).

## Results

### Patients

A total of 26,465 patients with NSTEMI ACS were enrolled in the four trials. About one-fourth of the patients (23.3%) underwent PCI during the initial hospitalization (*n*=6164). CK or CK-MB levels <24 h before PCI were elevated in 696 patients, who were excluded. The primary analysis cohort included 2384 of the remaining 5468 patients (43.6%) who had ≥1 CK-MB level measured <24 h after PCI. A total of 3084 patients (56.4%) without CK-MB elevation before PCI did not have CK-MB levels measured after PCI. The breakdown of patients with measured CK-MB levels after PCI from each trial included: 390 of 1594 patients from GUSTO-IIb (24.5%), 1280 of 2226 patients from PURSUIT (57.5%), 63 of 334 patients from PARAGON-A (18.9%), and 651 of 1314 patients from PARAGON-B (49.5%).

### Clinical, treatment, and procedural characteristics

Clinical characteristics differed significantly across the trials among patients undergoing PCI (after excluding those with pre-procedural CK-MB elevations) (Table 1). In the combined dataset, the incidence of hypercholesterolemia, prior PCI, previous angina, and T-wave inversions

**Table 2** Baseline clinical characteristics by peak creatine kinase (CK)-MB ratio category

	Not measured after PCI (n=3084)	>1×ULN, 24 h Pre-PCI (n=696)	Peak CK-MB elevation after PCI, ×ULN					P <sup>a</sup>
			0–1 (n=1335)	1–3 (n=508)	3–5 (n=144)	5–10 (n=170)	>10 (n=227)	
Age (years)	62 (53, 70)	59 (51, 69)	61 (52, 68)	62 (53, 69)	62 (54, 69)	62 (53, 70)	62 (50, 72)	0.46
Male sex	71.5%	73.6%	67.9%	69.7%	70.1%	72.9%	70.9%	0.46
Heart rate (per min)	72 (62, 80)	71 (62, 82)	71 (62, 82)	70 (62, 80)	73 (64, 82)	70 (64, 80)	70 (64, 82)	0.85
Systolic BP (mmHg)	136 (120, 150)	130 (115, 148)	132 (120, 150)	130 (120, 150)	130 (118, 146)	134 (115, 150)	130 (116, 148)	0.05
Hypertension	50.1%	50.9%	57.4%	51.0%	58.3%	52.9%	49.3%	0.04
Diabetes	18.7%	18.7%	21.9%	18.3%	22.9%	21.8%	20.7%	0.53
Current smoking	37.0%	36.7%	32.5%	37.5%	33.9%	32.9%	36.3%	0.36
Hypercholesterolaemia	48.0%	47.0%	51.4%	48.5%	50.4%	47.1%	37.2%	0.003
Enrolment infarction	39.6%	84.0%	31.1%	47.3%	59.0%	57.5%	72.8%	<0.001
Prior infarction	28.1%	26.7%	29.4%	30.1%	25.2%	24.3%	23.9%	0.22
Prior PCI	18.3%	19.1%	22.2%	22.3%	20.8%	29.2%	15.9%	0.04
Prior bypass surgery	13.1%	13.4%	16.0%	15.4%	18.1%	17.1%	12.8%	0.67
Prior CHF	5.5%	6.2%	6.4%	6.5%	4.2%	6.5%	7.9%	0.72
Previous angina	74.8%	65.8%	83.3%	83.1%	76.4%	77.7%	70.0%	<0.001
ECG findings								
ST depression	45.8%	36.9%	33.0%	39.2%	37.1%	40.6%	46.5%	0.001
Transient ST elevation	15.2%	17.3%	12.5%	12.9%	15.6%	21.9%	21.0%	<0.001
T-wave inversion	51.9%	46.0%	54.7%	50.7%	48.6%	41.6	44.3%	<0.001

<sup>a</sup>Across peak CK-MB ratio categories of 0–1, 1–3, 3–5, 5–10, and >10×ULN. ULN=upper limit of normal; BP=blood pressure; PCI=percutaneous coronary intervention; CHF=congestive heart failure; ECG=electrocardiographic.

**Table 3** Medication use by peak creatine kinase (CK)-MB ratio category

	Peak CK-MB Elevation After PCI, ×ULN					P <sup>a</sup>
	0–1 (n=1335)	1–3 (n=508)	3–5 (n=144)	5–10 (n=170)	>10 (n=227)	
In-hospital						
Aspirin	68.6%	72.6%	70.8%	71.8%	74.0%	0.30
Beta-blockers	52.7%	58.3%	56.3%	55.3%	58.1%	0.20
ACE-inhibitors	18.2%	23.4%	22.9%	27.1%	30.0%	<0.001
Anti-arrhythmics	4.2%	5.3%	7.6%	10.0%	14.1%	<0.001
Lipid lowering agents	21.4%	18.5%	19.4%	21.8%	18.9%	0.64
Discharge						
Aspirin	66.0%	68.0%	64.6%	68.2%	67.3%	0.89
Beta-blockers	44.7%	48.2%	43.1%	45.9%	46.3%	0.69
ACE-inhibitors	16.0%	20.1%	19.4%	22.4%	26.9%	0.001
Anti-arrhythmics	1.8%	1.2%	2.1%	4.1%	2.2%	0.19
Lipid lowering agents	23.0%	21.5%	22.9%	24.7%	18.1%	0.47

<sup>a</sup>Across peak CK-MB ratio categories of 0–1, 1–3, 3–5, 5–10, and >10×ULN. PCI=percutaneous coronary intervention; ULN=upper limit of normal; ACE=angiotensin converting enzyme.

on the presenting ECG decreased with higher peak CK-MB ratios (Table 2). The incidence of enrolment MI, ST-segment depression, and transient ST-segment elevation increased with higher peak CK-MB categories. In-hospital and discharge medication use was similar across the peak CK-MB categories except for greater use of angiotensin-converting enzyme (ACE) inhibitors and in-hospital anti-arrhythmic medications in patients with higher peak CK-MB ratios (Table 3)

Angiographic findings showed that patients with higher peak CK-MB ratios more commonly had multivessel coronary disease, impaired left ventricular func-

tion, and lower rates of procedural success (Table 4). The median time to PCI was shorter in patients with higher peak CK-MB ratios.

### Unadjusted clinical outcomes

The unadjusted frequencies of death, congestive heart failure, cardiogenic shock, and arrhythmias during the initial hospitalization were increased with higher peak CK-MB ratio categories, but the highest in-hospital mortality rate was seen in the group with peak CK-MB ratios

**Table 4** Angiographic and procedural characteristics by peak creatine kinase (CK)-MB ratio category

	Not measured after PCI (n=3084)	>1×ULN, 24 h Pre-PCI (n=696)	Peak CK-MB elevation after PCI, ×ULN					P <sup>a</sup>
			0–1 (n=1335)	1–3 (n=508)	3–5 (n=144)	5–10 (n=170)	>10 (n=227)	
No. diseased vessels								0.005
One	52.0%	47.7%	51.1%	47.5%	46.6%	45.9%	45.1%	
Two	30.4%	31.8%	30.2%	32.4%	27.8%	28.3%	30.9%	
Three	16.9%	20.1%	18.3%	20.1%	25.6%	25.2%	24.0%	
LV systolic function <sup>b</sup>								<0.001
Normal, EF >55%	56.0%	37.4%	57.2%	47.9%	52.3%	55.5%	30.8%	
Mild, EF 40–55%	31.8%	44.4%	31.3%	33.5%	36.1%	29.7%	44.6%	
Moderate, EF 30–40%	8.2%	13.8%	8.4%	11.3%	9.3%	9.9%	17.7%	
Severe, EF <30%	4.0%	4.4%	3.1%	7.4%	2.3%	5.0%	6.9%	
Median time to PCI, h	119 (69, 211)	29 (20, 29)	70 (26, 138)	57 (13, 120)	28 (4, 94)	20 (3, 91)	7 (2, 69)	<0.001
Devices used <sup>c</sup>								
Angioplasty only	57.6%	38.4%	42.0%	42.1%	43.1%	48.8%	48.5%	0.22
Stent	37.9%	59.2%	55.8%	54.1%	50.7%	50.0%	48.0%	0.15
Other device <sup>d</sup>	4.4%	5.0%	5.6%	5.3%	6.9%	5.3%	6.6%	0.91
Procedural success <sup>e</sup>	65.0%	95.0%	88.6%	81.7%	76.8%	76.7%	64.9%	<0.001

<sup>a</sup>Across peak CK-MB ratio categories of 0–1, 1–3, 3–5, 5–10, and >10×ULN.

<sup>b</sup>Ejection fraction recorded in 2470 of 5468 patients.

<sup>c</sup>Not mutually exclusive.

<sup>d</sup>Includes atherectomy, rotablation, laser angioplasty, or extraction catheters. Does not include distal protection devices.

<sup>e</sup>Postintervention TIMI grade 3 flow or lesion stenosis <50%. PCI=percutaneous coronary intervention; ULN=upper limit of normal; LV=left ventricular; EF=ejection fraction.

**Table 5** Unadjusted clinical outcomes by peak creatine kinase (CK)-MB ratio category

	Not measured after PCI (n=3084)	>1×ULN, 24 h Pre-PCI (n=696)	Peak CK-MB elevation after PCI, ×ULN					P <sup>a</sup>
			0–1 (n=1335)	1–3 (n=508)	3–5 (n=144)	5–10 (n=170)	>10 (n=227)	
In-hospital								
Mortality	0.5%	0.9%	0.3%	1.0%	4.2%	2.4%	2.6%	0.001
Heart failure	0.4%	1.0%	0.1%	0.8%	3.4%	4.1%	6.1%	<0.001
Cardiogenic shock	0.2%	0.4%	0.1%	1.3%	2.0%	2.3%	2.6%	0.004
Arrhythmias <sup>b</sup>	1.0%	3.3%	0.8%	1.9%	6.9%	4.1%	7.9%	<0.001
30 Days								
Mortality	0.8%	1.4%	0.7%	1.2%	4.2%	2.9%	3.1%	<0.001
6 Months								
Mortality	1.3%	2.6%	2.1%	2.4%	4.9%	4.1%	5.7%	0.005
Repeat intervention	24.0%	8.3%	10.4%	15.6%	20.1%	12.9%	23.8%	<0.001
Bypass surgery	2.3%	5.6%	3.5%	6.9%	4.9%	8.8%	5.7%	0.02

<sup>a</sup>Across peak CK-MB ratio categories of 0–1, 1–3, 3–5, 5–10, and >10×ULN.

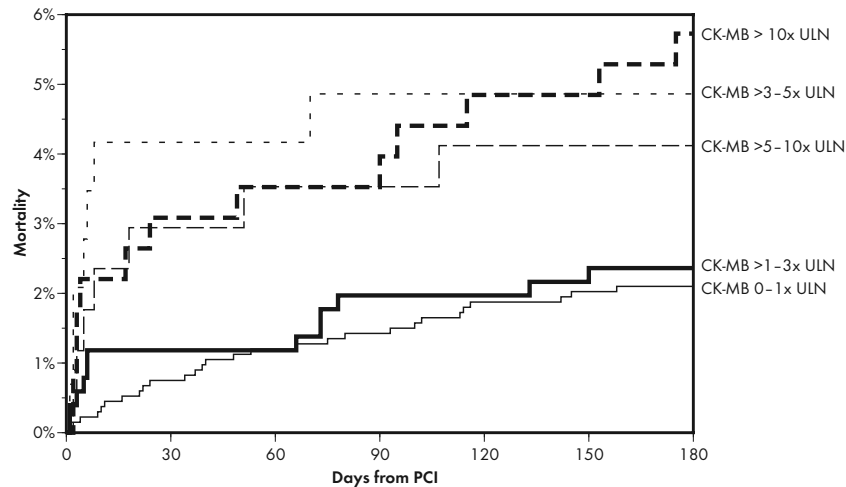
<sup>b</sup>Includes ventricular tachycardia or fibrillation, atrial fibrillation or flutter, and atrioventricular block. PCI=percutaneous coronary intervention; ULN=upper limit of normal.

3–5×ULN (Table 5). Cumulative mortality rates through 30 days and 6 months were also increased with higher peak CK-MB ratio categories and the highest 6-month mortality rate seen in the group with peak CK-MB ratios >10×ULN. While there was a marginally significant difference in 6-month mortality rates among the groups with peak CK-MB ratios of 3–5, 5–10, and >10×ULN (three-way *P*-value=0.0498), Kaplan–Meier mortality curves showed early separation between these peak CK-MB categories and the lower peak CK-MB categories (Table 5 and Fig. 1). The continuous relationship of peak CK-MB ratio with 6-month mortality demonstrated that higher peak CK-MB

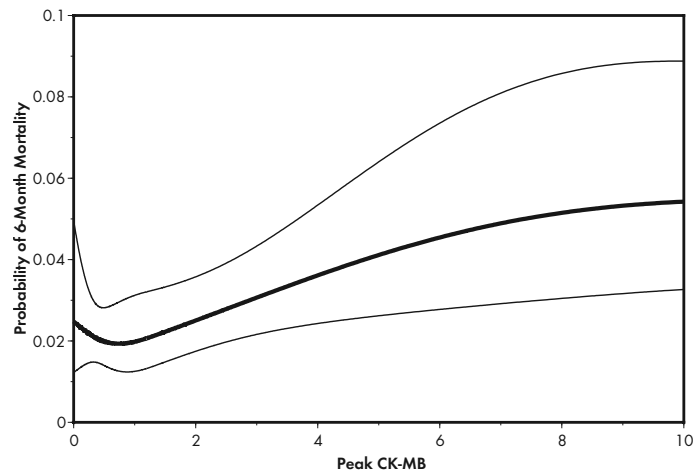
ratios were associated with a greater risk of 6-month mortality compared with lower levels of CK-MB elevation (Fig. 2).

### Multivariable predictors of mortality

After adjustment for clinical, angiographic, and treatment characteristics, age, three-vessel coronary disease, unsuccessful PCI, peak CK-MB ratio as a continuous variable, and previous angina were significant predictors of 6-month mortality (Table 6). The interaction term between experimental treatment versus placebo and peak



**Fig. 1** Kaplan–Meier curves for unadjusted mortality after percutaneous coronary intervention through 6 months, for increments of periprocedural peak creatine kinase (CK)-MB elevation as a multiple of the upper limit of normal ( $\times$ ULN).



**Fig. 2** Continuous, unadjusted relationship between peak creatine kinase (CK)-MB, as a multiple of the upper limit of normal, and 6-month mortality. Thin lines represent 95% confidence intervals.

CK-MB ratio was not significant (risk ratio [RR], 1.02; 95% confidence interval [CI], 0.94–1.12;  $P=0.58$ ) and was therefore dropped from the model.

When peak CK-MB ratios were analysed by distinct categories in the regression model, linear hypothesis testing revealed a non-significant trend for an association for an increased risk of 6-month mortality with higher peak CK-MB categories (Wald chi square, 8.63;  $df=4$ ,  $P=0.07$ ). The adjusted risk of 6-month mortality was not increased significantly with peak CK-MB ratios of 1–3 $\times$ ULN (RR, 1.15; 95% CI, 0.53–2.48;  $P=0.72$ ) compared with the reference group of peak CK-MB ratios of 0–1 $\times$ ULN, but was increased to similar extents with peak CK-MB ratios of 3–5 $\times$ ULN (RR, 2.82; 95% CI, 1.11–7.16;  $P=0.03$ ), 5–10 $\times$ ULN (RR, 2.64; 95% CI, 1.04–6.72;  $P=0.04$ ), and >10 $\times$ ULN (RR, 2.13; 95% CI, 0.91–4.96;  $P=0.08$ ).

## Discussion

We have shown an association between higher levels of peak CK-MB elevation after PCI and an increased risk of adverse outcomes in patients with NSTEMI/ACS. This study provides unique insight into the relationship between periprocedural myocardial necrosis and adverse clinical outcomes, given that peak CK-MB levels after PCI were analysed both continuously and categorically in a high-risk population that was previously not well-studied. Furthermore, the prognostic implications of periprocedural CK-MB elevations were confirmed with an expanded version of a validated multivariable regression model that also adjusted for angiographic and procedural factors known to be significant predictors of mortality. Therefore, these results further highlight the adverse

**Table 6** Multivariable predictors of 6-month mortality

Variable	Wald chi square	Risk ratio (95% confidence interval)	P value
Age <sup>a</sup>	10.99	1.06 (1.02–1.09)	<0.001
Three-vessel coronary disease	10.43	3.36 (1.61–7.02)	0.001
Unsuccessful procedure <sup>b</sup>	6.47	2.46 (1.23–4.93)	0.011
Peak creatine kinase (CK)-MB ratio <sup>a</sup>	5.66	1.06 (1.01–1.11)	0.017
Previous angina	3.98	7.98 (1.04–61.35)	0.05
Male sex	2.23	1.47 (0.89–2.44)	0.14
ST-segment depression	1.58	0.64 (0.32–1.28)	0.21
Heart rate <sup>a</sup>	1.27	1.01 (0.99–1.03)	0.26
Systolic blood pressure <sup>a</sup>	1.26	0.99 (0.98–1.00)	0.26
Signs of congestive heart failure	0.83	1.51 (0.62–3.67)	0.36
Experimental treatment <sup>c</sup>	0.57	1.28 (0.68–2.40)	0.45
Enrolment infarction	0.48	0.79 (0.40–1.56)	0.49
Time to percutaneous coronary intervention	0.12	1.00 (0.99–1.01)	0.73
Two-vessel coronary disease	0.05	0.90 (0.37–2.20)	0.82

<sup>a</sup>Continuous variables.

<sup>b</sup>Stenosis >50% or TIMI grade <3 flow after the procedure.

<sup>c</sup>Hirudin, eptifibatide, or lamifiban. Overall model chi square, 64.12 with 14 degrees of freedom.

prognostic implications of periprocedural myocardial necrosis and underscore the importance of routine surveillance of CK-MB levels after PCI.

Despite the demonstrated association between periprocedural myocardial necrosis and mortality, the pathophysiological mechanisms underlying cardiac enzyme elevation and subsequent adverse clinical outcomes remain controversial. Periprocedural necrosis is often caused by procedural complications such as side-branch occlusion, abrupt closure, or coronary dissection.<sup>6,18</sup> Our results show a correlation between lower rates of procedural success and higher peak CK-MB levels after PCI, but embolization of atherosclerotic and thrombotic material to the distal coronary circulation is thought to occur commonly during PCI, even without obvious procedural complications.<sup>7</sup> Contrast-enhanced magnetic resonance imaging has shown that patients with minor CK-MB elevations after uncomplicated PCI have regions of hyper-enhancement within the perfusion territory of the target vessel, corresponding to small infarctions that may be caused by embolization of small amounts of thrombus not seen on angiography.<sup>19</sup> However, greater atherosclerotic plaque burden has been shown to be associated with an increased likelihood of periprocedural CK-MB release in this analysis and other studies, so cardiac enzyme elevations after PCI may also be a marker of high-risk features in patients without an obvious MI.<sup>20,21</sup> Thus, although a definite cause-and-effect relation between periprocedural myocardial necrosis and later adverse outcomes has not been shown, CK-MB elevations after PCI have clear adverse prognostic implications for risk stratification of patients with NSTEMI ACS undergoing PCI.

Although the degree of periprocedural myocardial necrosis appears to be related quantitatively to the risk of adverse outcomes, the classification and definition of periprocedural MI has been extensively debated.<sup>1,2,4,5,15</sup> We evaluated periprocedural CK-MB levels in a continuous fashion and showed an association between the risk

of mortality and higher levels of CK-MB elevation (above a threshold with low peak CK-MB ratios). Furthermore, the association between peak CK-MB levels and mortality was not as strong when peak CK-MB ratios were analysed as distinct categories in the regression model, perhaps due to the relatively small numbers of patients in each category. Recent retrospective studies have suggested that only major categories of CK-MB elevations (>5–10×ULN) delineate an independent contribution to mortality risk after elective PCI, but patients with lower levels of CK-MB elevations did have a slightly higher risk of mortality in these studies and the risk associated with CK-MB levels was not evaluated in a continuous fashion.<sup>22–24</sup> However, consensus statements suggest that any degree of CK-MB elevation after PCI is associated with adverse prognostic implications.<sup>1,15</sup> Therefore, CK-MB elevation after PCI appears to be associated with a continuum of risk, but further analyses are needed to clearly define a clinically useful threshold of CK-MB elevation for risk stratification of patients undergoing PCI.

The definition of MI has evolved with the introduction of new cardiac markers, such as the troponins I and T, but distinctions between spontaneous and periprocedural myocardial damage in patients with ACS remain poorly characterized.<sup>25</sup> The degree of spontaneous CK-MB elevation in patients with ACS who do not undergo revascularization correlates with an increased risk of adverse outcomes, and infarctions that occur after hospital admission are associated with an even greater risk of mortality than are infarctions present at admission.<sup>26,27</sup> In this analysis, patients with elevated CK-MB levels after PCI had a higher risk of mortality compared with patients with elevated CK or CK-MB levels <24 h before PCI, indicating that periprocedural myocardial necrosis may confer a worse prognosis than spontaneous necrosis from the presenting ischaemic event.<sup>27</sup> Furthermore, periprocedural CK-MB elevation may reflect greater cumulative myocardial damage in



ACS patients with spontaneous myocardial necrosis and may partly explain the adverse consequences of post-admission infarctions.<sup>27</sup> Although larger, prospective studies are needed to determine the ideal thresholds and markers for the classification of spontaneous and periprocedural infarctions in patients with ACS, the long-term risks of myocardial necrosis appear to be similar irrespective of the mechanism of ischaemic insult.<sup>2,3,7,15,27</sup>

Although this study represents the largest evaluation of periprocedural CK-MB elevations in patients with ACS, it has several limitations. First, because CK-MB sampling after PCI was not mandated by the study protocols, the sample size was limited and a selection bias was present, in that CK-MB levels may have been measured only in higher-risk patients. However, other contemporary ACS databases do not include routine cardiac enzyme data in all patients after PCI, so this analysis represents the largest accumulation of periprocedural CK-MB data in patients with ACS. We also presented results for patients who did not have CK-MB levels measured after PCI in an attempt to account for this selection bias. Second, patients with myocardial necrosis before PCI may have been misidentified as having periprocedural infarctions. Although we excluded patients with elevated CK or CK-MB levels <24 h before PCI to limit confounding from spontaneous infarctions, the median time to PCI was progressively shorter with higher peak CK-MB ratios. This suggests that patients with large CK-MB elevations after PCI may have had spontaneous infarctions at arrival that were not identified before PCI was performed. Third, we could not assess the impact of symptoms of ischaemia, ECG changes, or detailed angiographic complications on the unfavourable prognosis associated with periprocedural CK-MB elevations, because these data were not systematically collected. Fourth, distal protection devices have been shown to limit embolization of atherosclerotic and thrombotic debris to the coronary microcirculation and reduce the incidence of periprocedural infarctions.<sup>28</sup> However, distal protection devices were not clinically available during the time periods of these studies (1994–1999), so we could not assess the impact of these devices on our findings.<sup>10–12,14</sup> Fifth, we could not adjust for ejection fraction in the regression model because it was not recorded on the case report form in almost half of the patients. However, the regression model did include the variable ‘signs of congestive heart failure’, which represented the clinical manifestations of left ventricular dysfunction. Sixth, differences among the trial populations may have influenced the results, but the inclusion criteria of the trials were similar and there was no interaction between trial enrolment and peak CK-MB ratio in the regression model. Finally, glycoprotein IIb/IIIa inhibitors reduce periprocedural CK-MB elevations and could therefore have limited CK-MB release after PCI, but there was no interaction between experimental treatment and peak CK-MB ratio in the regression model to indicate that such treatment affected the findings.

## Conclusions

In summary, periprocedural CK-MB elevation was independently associated with an increased risk of mortality and other early adverse outcomes in patients with NSTEMI-ACS, but a definite cause and effect relationship was not established. However, these results suggest that risk stratification of ACS patients should include routine surveillance of CK-MB levels after PCI to assess an individual patient's risk of adverse outcomes and that independent adjudication of suspected periprocedural ischaemic events should be incorporated into end-point definitions for clinical trials that include ACS patients.<sup>13</sup>

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