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Creatine kinase-MB elevation after coronary artery bypass grafting surgery in patients with non-ST-segment elevation acute coronary syndromes predict worse outcomes: results from four large clinical trials

Kenneth W. Mahaffey[1]*, Matthew T. Roe[1], Rakhi Kilaru[1], John H. Alexander[1], Frans Van de Werf[2], Robert M. Califf[2], Maarten L. Simoons[3], Eric J. Topol[4], and Robert A. Harrington[1]

[1]*Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715, USA;* [2]*Catholic University Hospital, Leuven, Belgium;* [3]*Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands; and* [4]*Cleveland Clinic Foundation, Cleveland, OH, USA*

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Myocardial infarction;
Clinical endpoints

Aims To assess the significance of creatine kinase (CK)-MB elevations in outcomes of patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS) who have undergone coronary artery bypass grafting (CABG) surgery.

Methods and results This analysis includes data from 26 465 patients with NSTE ACS enrolled in four major trials. In total, 4626 (17.5%) of patients had CABG within 30 days. Patients were excluded if CK-MB was elevated within 24 h before surgery and there was no CK-MB measured after surgery. Overall, 4401 patients were included in these analyses. The incidence of mortality increased with peak CK-MB ratios of 0–1, >1–3, >3–5, >5–10, and >10 × the upper limit of normal measured at the local lab ($P < 0.001$ across categories): 1.1, 2.8, 2.4, 3.1, and 10.8% in hospital; 1.1, 3.0, 2.9, 3.5, and 10.2% at 30 days; and 1.6, 4.4, 4.7, 6.0, and 10.9% at 180 days. Multivariable predictors of 6-month mortality included age, heart rate and randomization, peak CK-MB ratio, time to CABG, prior angina, signs of congestive heart failure and randomization, three- and two-vessel coronary disease, enrolment infarction, ST-segment depression at enrolment, female sex, experimental treatment, and systolic blood pressure.

Conclusion CK-MB elevations after CABG are independently associated with increased risk of mortality in patients with NSTE ACS.

Introduction

The clinical significance of myocardial infarction (MI) in patients following major cardiac surgery, including valvular replacement and coronary artery bypass grafting (CABG) surgery, has been investigated previously. Some investigators have documented that perioperative MI, defined primarily by electrocardiographic (ECG) criteria, was associated with a worse long-term prognosis,[1–3] while others found no correlation of MI with outcomes.[4] Fewer patients with perioperative Q-wave MI had 5-year event-free survival when compared with patients without perioperative events (76 vs. 90%).[5] Post-operative MI, age, left ventricular (LV) function, and number of comorbidities have been shown to be potent independent predictors of long-term survival.[6] In contrast, a subgroup analysis from the Coronary Artery Surgery Study showed that in-hospital mortality was higher in patients with new Q-waves compared with those patients without (10 vs. 1%), though 3-year mortality was similar (5%).[7]

Nearly all patients have some elevation in serum levels of cardiac biomarkers after CABG surgery. Marked elevations have been reported in 20–40% of patients.[8,9] In most studies, post-operative complications were more common in patients with significant biomarker elevations, but little information on long-term clinical outcomes has been reported. Several studies in elective CABG patients have more clearly defined the prognostic significance of creatine kinase (CK)-MB elevations, but controversy still exists.[8–12]

Patients with acute coronary syndromes (ACS) are likely to undergo coronary revascularization procedures. Although ~15–20% may undergo a surgical procedure,[13–15] the incidence and prognostic implications of CK-MB elevations in the ACS population undergoing CABG have not been well studied. About 50% of patients with ACS have evidence of

* Corresponding author. Tel: +1 919 668 8845; fax: +1 919 668 7059.
E-mail address: mahaf002@mc.duke.edu

myocardial necrosis shown by elevated biomarkers. Therefore, marked CK-MB elevations after CABG may have important clinical implications. In addition, many clinical trials include post-CABG MI events as endpoints, but no consensus has been reached on the level of CK-MB elevation that should be used to define perioperative MI. Thus, trials use different values.[9,10,15]

We have reported previously on the role of CK-MB elevation after percutaneous coronary intervention (PCI) using a pooled data set from four large ACS trials[16]—Global Use of Strategies To Open occluded coronary arteries in ACS (GUSTO-IIb), Platelet glycoprotein IIb/IIIa 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.[13,17–19] Each of these four trials evaluated new antithrombin or antiplatelet therapies for patients with non-ST-segment elevation (NSTE) ACS. In this study, we assess the significance of CK-MB elevations after CABG surgery on clinical outcomes in patients with ACS.

Methods

Study population

The study design and enrolment criteria for the four trials were similar and have been previously reported.[13,17–19] Patients with NSTE ACS were enrolled if they had ischaemic chest pain within 12–24 h of presentation, along with ECG signs of ischaemia or elevated cardiac biomarkers (troponin I, T, or CK-MB). The ST-segment elevation cohort of GUSTO-IIb was not included in our analyses. An institutional review board or Ethics Committee approved the study protocols at each institution. All subjects gave informed consent.

Randomization and treatment

In GUSTO-IIb, patients randomly received intravenous unfractionated heparin or recombinant hirudin for 3–5 days.[17] In PURSUIT, patients were randomized to receive placebo or one of two doses of eptifibatide for 3–4 days.[13] In PARAGON-A, patients were randomized in a 2×2 factorial design to receive low-dose lamifiban, high-dose lamifiban with intravenous heparin, or placebo with intravenous heparin for 3–5 days.[18] In PARAGON-B, patients were randomized to receive lamifiban or placebo for 3–5 days, and study drug was adjusted for renal function.[19]

Concomitant treatment

Aspirin (80–325 mg daily) was recommended for all patients in each trial. Heparin was recommended but not required for all patients in PURSUIT and PARAGON-B.[13,19] Use of heparin was assigned by the randomization scheme in GUSTO-IIb and PARAGON-A.[17,18] All decisions regarding the use of other medications and the timing and use of coronary angiography and revascularization procedures were left to the discretion of the treating physicians. Each protocol mandated serial assessment of CK-MB levels at the time of patient recruitment, after recurrent ischaemic events, and after revascularization procedures, specifically every 8 h for three measurements after CABG. All samples were analysed at the local hospitals, but a central core laboratory was used to analyse samples from some patients at specific sites in PARAGON-B.

Patient identification

Patients included in our study were those from each of the four trials who underwent CABG during the initial hospitalization. Patients who did not have CK-MB levels measured during the 24 h after CABG and those who had a total CK or CK-MB level measuring >1 times the upper limit of normal (×ULN) in 24 h before CABG were excluded from the analysis. This step was taken to eliminate the complication of post-CABG CK-MB interpretation in patients with elevations owing to events occurring before CABG.

Endpoints

The primary endpoint of this analysis was all-cause mortality through 6 months. In-hospital outcomes assessed after CABG 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), atrial or ventricular flutter or fibrillation, and advanced atrioventricular block. The incidence of recurrent MI after CABG was not evaluated because the trials did not consistently collect data on repeat infarctions when patients had multiple recurrent ischaemic events. Therefore, MI events prior to CABG precluded subsequent reporting of MI events after CABG in many cases.

Comparison groups

Patients with at least one CK-MB level measured in 24 h after CABG were categorized by peak CK-MB ratios of 0–1, >1–3, >3–5, >5–10, and >10 × ULN for statistical comparisons. (The median and mean number of post-CABG CK-MB measurements across all four trials was 2.) Peak CK-MB ratios were calculated by dividing the peak CK-MB value by the ULN for CK-MB at the local institution. Baseline characteristics of patients undergoing CABG were compared across the four trials to assess differences among the populations and were also compared with patients not undergoing CABG.

Statistical analyses

These analyses were designed to resemble those of previous examinations of the PCI population[16] in order to maintain consistency and to enable better comparisons between the PCI and CABG populations.

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 χ^2 tests and Wilcoxon rank-sum tests were used to compare baseline categorical and continuous variables.

Kaplan–Meier event rates through 6 months were determined for each category of peak CK-MB ratio. Unadjusted clinical event rates among patients with different peak CK-MB ratio categories were compared using log-rank statistics.

Continuous covariates eligible to enter the multivariable model were tested for linearity for the 6-month mortality model. Given that there was no suitable cut-off value for categorization of the MB ratio and that the linearity assumption for CK-MB truncated at 30 was satisfied, a continuous form of MB ratio was incorporated into the multivariable model. This has many advantages, an important one being that continuous MB ratio has a smaller standard error when compared with CK-MB categories, which results in an increase of the inferential potential.

A multivariable regression model of 6-month mortality developed from the PURSUIT database[20] was used to construct a model in the CABG populations. Variables added to the established model for these analyses included age, systolic blood pressure (BP), heart rate, previous angina, male sex, ST-segment depression, enrolment infarction, and signs of CHF. The following clinically important variables were added to the established model stated above: time to CABG, two-vessel disease, three-vessel disease, peak CK-MB, and experimental treatment. Adjustment for the baseline characteristics from the PURSUIT model and additional relevant clinical characteristics accounts for potential risk profile differences across different categories of CK-MB.

CK-MB was added to the Cox proportional hazards 6-month mortality model as a continuous variable defined by the peak CK-MB

ratio after CABG. The results further justified CK-MB to be incorporated in a continuous form. Proportional hazards assumption was checked by assessing interactions between covariates in the model and time-to-event variable to be certain of a constant hazard over time.

Trial enrolment was not included in the final regression model because it depended linearly on experimental treatment, but a separate version of the model which included experimental treatment showed no interaction between trial enrolment and peak CK-MB ratio with linear hypothesis testing (Wald χ^2, 0.82; $P = 0.66$). Linear hypothesis testing also was used to evaluate the relation of stratified peak CK-MB ratio categories with 6-month mortality in another version of the regression model.

For all analyses, a two-tailed P-value < 0.05 was considered statistically significant. All analyses were performed using SAS statistical software (SAS Institute, Cary, NC, USA).

Results

Overall, the pooled trials included 26 465 patients with NSTE ACS. A total of 4626 (17.5%) patients underwent CABG during the index hospitalization. CK or CK-MB levels were elevated in 225 patients (5%) in 24 h prior to CABG, and 2995 (65%) did not have CK-MB measured after CABG. Therefore, 4401 (16.6%) patients from the total pooled population or 1406 (30%) of all patients undergoing CABG were included in the analyses. The number and proportion of patients with CABG and with CK-MB data from each of the four trials are shown in *Table 1*.

Table 1 Proportion of patients from each trial with CABG and appropriate CK-MB data

	Total (n)	CABG n(%)	Included in analyses (n)[a]
GUSTO-IIb			
Non-ST	8010	1088/8002 (13.6%)	1088 (0 omitted)
All	12 142[b]		
PARAGON-A	2282	250/2276 (10.98%)	248 (2 omitted)
PARAGON-B	5225	1023/5075 (20.16%)	939 (84 omitted)
PURSUIT	10 948	2265/10 887 (20.8%)	2126 (139 omitted)
Total	26 465[c]	4626	4401

[a]Patients included in the final analyses were those who did not have elevated CK-MB <24 h prior to surgery.
[b]This number includes ST-segment elevation patients who were excluded from the present analyses.
[c]Total only considers the NSTE ACS population from GUSTO-IIb.

Table 2 shows the baseline characteristics by trial for all patients who underwent CABG. *Table 3* shows the baseline and angiographic demographics of patients undergoing CABG who had CK-MB data collected and were included in our analyses and of patients undergoing CABG who were not included because of missing CK-MB data. Medication use at time of hospital discharge is shown in *Table 4* by peak CK-MB ratio category.

Unadjusted clinical outcomes by CK-MB ratio category are shown in *Table 5*. For comparison with some PCI reports, outcomes were also evaluated with dichotomous CK-MB levels of $<3 \times$ ULN; ≥ 3 and $<5 \times$ ULN; ≥ 5 and $<8 \times$ ULN; and $\geq 8 \times$ ULN. Rates of in-hospital mortality, 30-day mortality, and 180-day mortality were 2.4, 2.4, 2.5, and 9.1%; 2.5, 2.9, 3.1, and 8.6%; 3.7, 4.7, 6.1, and 9.6%, respectively. *Figures 1* and *2* show the Kaplan–Meier curves for 6-month mortality with CK-MB ratio as a continuous variable and as a dichotomous variable. To further explore relationships between excess mortality and CK-MB elevations, the CK-MB increase associated with 10, 20, and 25% increase in relative risk (RR) of mortality was calculated: adjusted RR of 1.10 [95% confidence interval (CI) 1.02–1.18] associated with 1.7 unit increase in CK-MB ratio; adjusted RR of 1.21 (95% CI 1.04–1.42) associated with 3.5 unit increase in CK-MB ratio; and adjusted RR of 1.25 (95% CI 1.04–1.49) associated with 4.0 unit increase in CK-MB ratio.

Multivariable predictors of 6-month mortality included age, heart rate, peak CK-MB ratio, time to CABG, prior angina, signs of congestive heart failure, three- and two-vessel coronary disease, enrolment infarction, ST-segment depression, female sex, experimental treatment, and systolic BP (*Table 6*). Discharge aspirin was added to the 6-month mortality model and was an independent predictor of outcomes (hazard ratio 0.05, 95% CI 0.024–0.104, $P < 0.0001$), however no propensity adjustment was performed.

A total of 308 (7.08%) patients had redo-CABG in this data=set. Rates of in-hospital, 30-day, and 180-day mortality

Table 2 Baseline characteristics by trial for all patients undergoing CABG

	GUSTO-IIb ($n = 1088$)	PURSUIT ($n = 2126$)	PARAGON-A ($n = 248$)	PARAGON-B ($n = 939$)	P-value[a]
Age (years)	66 (59, 73)	65 (57, 71)	67 (60, 73)	65 (56, 71)	<0.001
Male sex (%)	71.7	72.4	74.2	72.9	0.846
Heart rate (b.p.m.)	74 (64, 84)	71 (62, 80)	76 (64, 90)	77 (66, 90)	<0.001
Systolic BP (mm Hg)	140 (120, 152)	130 (117, 144)	150 (130, 166)	142 (130, 160)	<0.001
Diabetes (%)	18.7	26.3	20.2	25.7	<0.001
Enrolment infarction (%)	42.0	44.8	35.8	47.4	0.005
Prior infarction (%)	34.0	35.7	38.3	32.9	0.279
Prior CABG (%)	7.4	8.2	5.2	5.9	0.068
Prior CHF (%)	5.9	9.3	6.9	9.2	0.006
ECG findings					
ST-depression (%)	55.8	43.4	66.9	51.8	<0.001
Transient ST-elevation (%)	9.8	8.0	12.1	15.0	<0.001
T-wave inversion (%)	43.3	50.6	49.6	46.9	0.001

[a]Across trials.

Table 3 Baseline and angiographic characteristics by peak CK-MB ratio category

	Peak CK-MB elevation after CABG, ×ULN							
	Not measured ($n = 2995$)	>1 × ULN, 24 h pre-CABG ($n = 225$)	0–1 ($n = 192$)	>1–3 ($n = 543$)	>3–5 ($n = 256$)	>5–10 ($n = 232$)	>10 ($n = 183$)	*P*-value[a]
Age (years)	65 (58, 71)	66 (55, 71)	64 (57, 70)	66 (57, 72)	65 (56, 71)	66 (59, 73)	66 (58, 72)	0.068
Male sex (%)	72.5	76.4	70.3	74.4	75.4	67.2	69.9	0.180
Heart rate (b.p.m.)	73 (64, 84)	75 (68, 85)	75 (65, 88)	75 (64, 86)	72 (64, 80)	72 (63, 84)	72 (64, 82)	0.111
Systolic BP (mm Hg)	135 (120, 150)	130 (116, 145)	134 (120, 150)	135 (120, 152)	132 (120, 150)	132 (120, 150)	135 (120, 155)	0.978
Hypertension (%)	54.9	58.7	54.7	56.0	52.0	56.0	59.6	0.617
Diabetes (%)	23.5	22.7	25.5	23.8	24.2	29.3	22.4	0.477
Current smoking (%)	27.2	27.4	30.6	29.1	31.1	28.2	27.3	0.913
Enrolment infarction (%)	43.9	70.6	37.9	42.3	47.4	51.3	45.6	0.048
Prior infarction (%)	35.1	35.0	38.5	32.8	32.9	35.3	34.6	0.667
Prior CABG (%)	6.8	9.8	8.3	5.2	6.6	9.9	18.6	<0.001
Prior CHF (%)	8.1	7.1	7.8	8.3	11.3	7.8	7.1	0.495
Prior angina (%)	83.6	78.1	81.8	84.9	85.2	85.8	86.9	0.702
ECG findings								
ST-depression (%)	51.0	50.7	43.8	46.8	46.9	46.6	48.1	0.938
Transient ST-elevation (%)	10.8	7.1	8.3	8.3	10.2	10.3	8.2	0.823
T-wave inversion (%)	47.4	41.8	50.0	49.2	47.7	51.3	47.0	0.902
No. of diseased vessels								
1 (%)	8.5	6.2	9.9	8.7	2.7	4.3	6.6	0.005
2 (%)	24.2	25.3	26.6	27.6	28.1	22.4	25.1	0.581
3 (%)	45.3	60.9	49.0	53.6	56.3	61.6	60.7	0.046
LV systolic function								
Normal, EF >55% (%)	43.5	30.7	45.9	49.8	44.9	44.7	38.2	0.270
Mild, EF 40–55% (%)	35.0	40.7	31.2	32.1	32.1	39.8	40.7	0.216
Moderate, EF 30–40% (%)	13.9	19.3	11.9	11.1	18.6	9.9	15.4	0.112
Severe, EF <30% (%)	7.6	9.3	11.0	6.9	4.5	5.6	5.7	0.281

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

Table 4 Medication use by peak CK-MB ratio category

	Peak CK-MB elevation after CABG, ×ULN					
	0–1 ($n = 192$)	>1–3 ($n = 543$)	>3–5 ($n = 256$)	>5–10 ($n = 232$)	>10 ($n = 183$)	*P*-value[a]
In-hospital						
Aspirin (%)	94.3	96.9	96.1	98.3	95.1	0.189
Beta-blockers (%)	67.7	65.6	68.8	64.7	63.9	0.792
ACE-inhibitors (%)	32.3	27.3	27.7	31.0	30.1	0.631
Anti-arrhythmics (%)	13.0	20.6	19.9	24.6	30.6	0.001
Lipid-lowering agents (%)	16.7	21.4	19.5	17.7	14.8	0.276
Discharge						
Aspirin (%)	83.0	83.3	83.7	82.2	71.9	0.028
Beta-blockers (%)	37.0	37.9	44.1	33.6	30.1	0.030
ACE-inhibitors (%)	21.4	16.2	16.8	14.2	13.7	0.259
Anti-arrhythmics (%)	4.2	8.1	7.8	9.6	10.4	0.200
Lipid-lowering agents (%)	8.9	15.3	12.5	13.8	10.4	0.152

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

Table 5 Unadjusted clinical outcomes by peak CK-MB ratio category

	Not measured ($n = 2995$)	(1 × ULN 24 h pre-CABG ($n = 225$)	Peak CK-MB elevation after CABG, ×ULN					Log-rank statistics/ χ^2 statistic (*P*-value)[a]
			0–1 ($n = 192$)	> 1–3 ($n = 543$)	> 3–5 ($n = 256$)	> 5–10 ($n = 232$)	> 10 ($n = 183$)	
In-hospital								
Mortality (%)	3.56	6.34	1.14	2.81	2.43	3.07	10.76	28.44 (<0.001)
CHF (%)	1.60	2.6	1.56	2.76	2.34	5.17	1.56	13.21 (0.01)
Cardiogenic shock (%)	1.003	1.33	0.5	1.47	0.78	0.86	2.73	4.95 (0.29)
Arrhythmias (%)[b]	10.37	18.3	12.5	16.6	16.6	19.05	19.78	4.52 (0.34)
Stroke (%)	1.10	2.22	1.56	1.47	2.34	2.15	2.73	1.68 (0.80)
Major bleed (%)[c]	23.6	35	42.2	40.41	43.9	43.3	49.2	4.48 (0.343)[c]
Moderate–severe bleed or intermediate bleed (%)[c]	34.4	64	52.6	57.9	61.6	65.8	62.8	9.41 (0.051)[c]
30-day mortality (%)	3.77	7.3	1.14	3.0	2.85	3.51	10.16	22.61 (<0.001)
180-day mortality (%)	3.97	8.89	1.56	4.42	4.68	6.03	10.92	19.12 (<0.001)

[a]Across peak CK-MB ratio categories of 0–1, >1–3, >3–5, >5–10, and >10× ULN (excluding missing).
[b]Includes ventricular tachycardia or fibrillation, AF or flutter, and atrioventricular block.
[c]Bleeding rates are not KM rates, they are proportions of patients in that category times 100; χ^2 statistic testing for homogeneity across peak CK-MB ratio categories of 0–1, >1–3, >3–5, >5–10, and >10×.

for the peak CK-MB ratios of 0–1, >1–3, >3–5, >5–10, and >10 × ULN were 1.1, 2.8, 2.4, 3.1, and 10.8%; 1.1, 3.0, 2.9, 3.5, and 10.2%; 1.6, 4.4, 4.7, 6.0, and 10.9%, respectively (Table 5).

Discussion

These data show a clear association between increased levels of CK-MB after CABG and an increased risk of mortality through 6 months in patients with NSTE ACS. These results are from the largest dataset used so far to evaluate this relationship and also in a higher-risk patient population not yet thoroughly studied. The modelling performed—which incorporates clinical demographics, medication therapies, and angiographic information and includes peak CK-MB ratios as categorical and continuous variables—was comprehensive and justifies the confidence in the associations revealed. These data confirm and extend observations in previous work by other researchers.

A substantial proportion of patients with perioperative CK-MB elevations are at increased risk for long-term adverse outcomes. These data suggest that increased efforts are needed to provide myocardial protection during ischaemia and reperfusion in the setting of cardiopulmonary bypass. Recent successes with off-pump surgery[21] and complement inhibition[9] show some promise. In addition, use of long-term treatment with evidence-based therapies may improve clinical outcomes for this patient population, despite revascularization. Recent information from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE) Quality Improvement

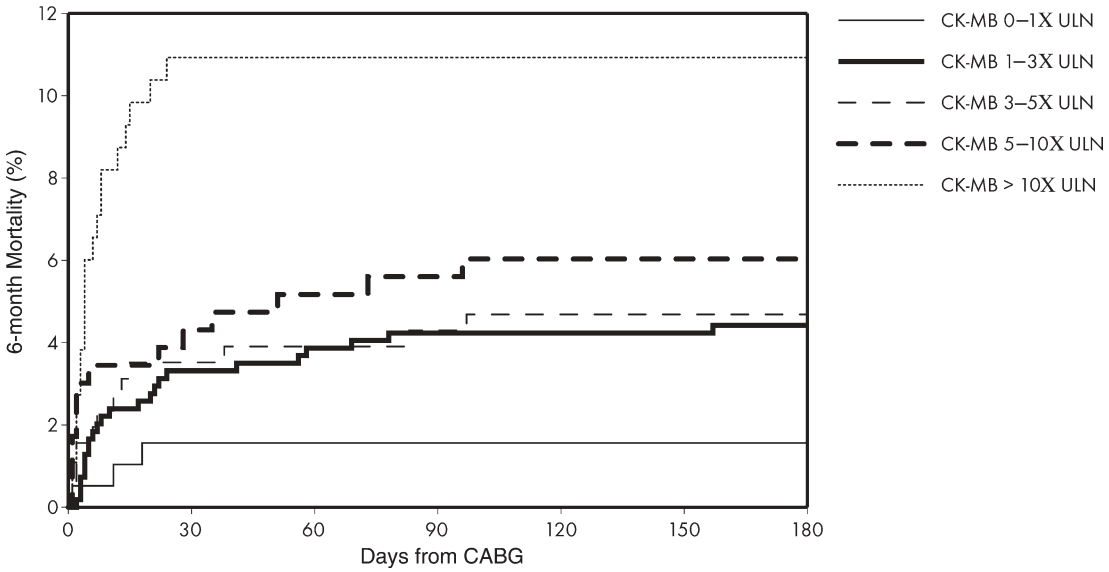

Figure 1 Kaplan–Meier curves for unadjusted mortality after CABG surgery up to 6 months.

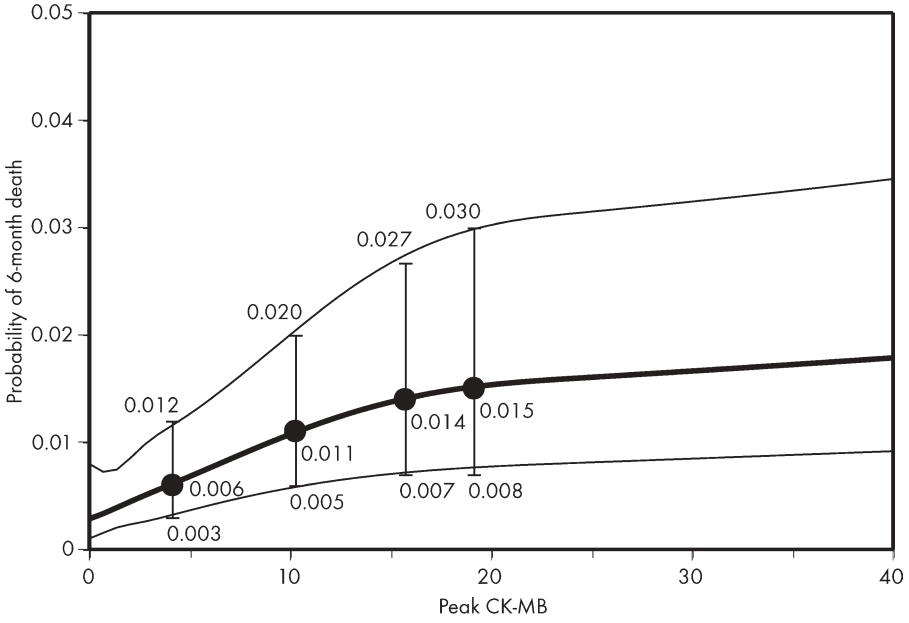

Figure 2 Continuous unadjusted relationship between peak CK-MB as a multiple of the upper limit of normal and 6-month mortality.

Initiative suggests that patients with NSTE ACS who undergo bypass surgery are under-treated, particularly in discharge care, with angiotensin-converting enzyme-inhibitor, statins, and β-blockers as directed by cardiac surgeons compared with cardiologists.[22]

Although these data and data from other investigations have clearly shown an association between perioperative infarctions defined by CK-MB elevations and worse outcomes, the lack of a clear pathophysiologic mechanism has given rise to controversy and debate. However, several small studies have evaluated patients with magnetic resonance imaging (MRI) after bypass surgery, and the data from these studies demonstrate that nearly 50% of post-CABG patients show evidence of MI as detected by hyper-enhancement on MRI scans made 6 days after surgery.[23,24] Also, the magnitude of CK-MB elevation correlated positively and significantly with the infarct size, and more than half of the patients showed evidence of transmural or focal endocardial injury rather than patchy necrosis.[25] These data support the hypothesis that the observed CK-MB elevations after CABG are likely not due only to cardiac manipulation or incomplete cardioplegia, but isolated myocardial necrosis is contributory.

Clinical and research implications

The definition of MI in clinical practice has been revised during the past several years owing to a better understanding of the significance of cardiac biomarker elevations. The ACC/ESC consensus document[15] does not provide clear guidelines and thresholds for defining MI after CABG but does recognize the importance of these events. The data

Table 6 Multivariable predictors of 6-month mortality

Variable	Wald χ^2	RR (95% CI)[a]	*P*-value
Age	7.57	1.04 (1.01–1.08)	0.006
Heart rate	6.41	1.02 (1.01–1.04)	0.011
Peak CK-MB ratio	5.14	1.05 (1.01–1.10)	0.023
Time to CABG	3.27	1.001 (1.000–1.002)	0.071
Prior angina	3.10	3.58 (0.87–14.85)	0.078
Signs of CHF	2.99	1.99 (0.91–4.35)	0.084
Three-vessel coronary disease	2.69	2.26 (0.85–6.01)	0.101
Two-vessel disease	1.59	1.96 (0.69–5.60)	0.207
Enrolment infarction	0.82	0.78 (0.45–1.34)	0.364
ST-segment depression	0.69	1.26 (0.73–1.16)	0.406
Female sex	0.55	0.85 (0.54–1.32)	0.460
Experimental treatment	0.39	1.19 (0.70–2.01)	0.530
Systolic BP	0.20	0.10 (0.99–1.01)	0.657

[a]Per unit increase in peak CK-MB ratio.

from these analyses along with the mechanistic information from recent MRI studies provide convincing evidence that increased CK-MB elevations are associated with larger areas of myocardial necrosis and, consequently, worse long-term outcomes. Similar associations have been shown for elevations in CK-MB among patients presenting with NSTE ACS[26] and patients with NSTE ACS undergoing PCI.[16] However, an exact cause-and-effect relationship cannot be proven from these analyses.

These data underscore the necessity of measuring CK-MB levels following CABG surgery in NSTE ACS patients to identify perioperative MI events. In addition, our results support the continued use of post-CABG MI events (as defined by CK-MB elevations) as an important outcome measure. The precise threshold of CK-MB elevation for use in defining clinically important MI is not yet clear, and, while our data suggest that any increase in MB elevation is prognostically important, until there is better understanding of the mechanisms of MB increases and more rigorous assessment from larger datasets, it would be quite helpful to identify a cut-point at which there is significant increase in mortality. This, however, is a challenge with this data set. Modelling was performed with CK-MB as a continuous variable or as dichotomous categories of peak ratios. The model outputs (data not shown) further justified CK-MB to be incorporated in a continuous form. In addition, low event rates and patient numbers within higher dichotomous categories of CK-MB ratios make it difficult to draw inferential conclusions on the strength of relationship between peak categories and 6-month mortality. However, 20% and 25% RR increases in mortality were associated with 3.5–4.0 unit increases in the CK-MB ratio. The typical cut-point in clinical trials has been 5- to 10-fold increases in CK-MB. More work in large data sets is needed to further refine an accepted and validated cut-point.

Limitations

This database from four large clinical trials provides the means for the most extensive evaluation to date of CK-MB elevation after CABG in patients with NSTE ACS. Despite the size of the database, however, there are a number of limitations. CK-MB samples and ECGs for evaluation of Q-waves were not collected from all patients after CABG in the trials. Higher risk patients or those undergoing complicated procedures or post-operative course may have been more likely to have CK-MB samples collected. However, 6-month survival in patients with missing CK-MB values was similar to that in patients with the lowest CK-MB ratio category. Techniques and approaches for protecting the myocardium during cardiopulmonary bypass continue to evolve. However, we saw no heterogeneity in the results across these trials, which spanned nearly 10 years of investigative work.

Conclusions

CK-MB elevations after CABG are common and are independently associated with increased risk of mortality in patients with NSTE ACS. These data support the routine surveillance of CK-MB after CABG to identify patients with increased risk of long-term mortality, and they confirm the importance of this endpoint in clinical trials. Further study is needed to evaluate approaches for reducing the long-term consequences of intraoperative events.

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