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Clinical Outcomes After Detection of Elevated Cardiac Enzymes in Patients Undergoing Percutaneous Intervention

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Objectives. **We examined the relations of elevated creatine kinase (CK) and its myocardial band isoenzyme (CK-MB) to clinical outcomes after percutaneous coronary intervention (PCI) in patients enrolled in Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II (trial) (IMPACT-II), a trial of the platelet glycoprotein IIb/IIIa inhibitor eptifibatide.**

Background. **Elevation of cardiac enzymes often occurs after PCI, but its clinical implications are uncertain.**

Methods. **Patients undergoing elective, scheduled PCI for any indication were analyzed. Parallel analyses investigated CK (n = 3,535) and CK-MB (n = 2,341) levels after PCI (within 4 to 20 h). Clinical outcomes at 30 days and 6 months were stratified by postprocedure CK and CK-MB (multiple of the site's upper normal limit).**

Results. **Overall, 1,779 patients (76%) had no CK-MB elevation; CK-MB levels were elevated to 1 to 3 times the upper normal limit in 323 patients (13.8%), to 3 to 5 times normal in 84 (3.6%), to 5 to 10 times normal in 86 (3.7%), and to >10 times normal in 69 patients (2.9%). Elevated CK-MB was associated with an increased risk of death, reinfarction, or emergency revascularization at 30 days, and of death, reinfarction, or surgical revascularization at 6 months. Elevated total CK to above three times normal was less frequent, but its prognostic significance paralleled that seen for CK-MB. The degree of risk correlated with the rise in CK or CK-MB, even for patients with successful procedures not complicated by abrupt closure.**

Conclusions. **Elevations in cardiac enzymes, including small increases (between one and three times normal) often not considered an infarction, are associated with an increased risk for short-term adverse clinical outcomes after successful or unsuccessful PCI.**

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Although an association between non–Q-wave myocardial infarction (MI) and an increased risk of cardiac events has been established for spontaneously occurring enzyme elevations (1–5), the clinical significance of abnormal elevation of cardiac enzymes after percutaneous coronary intervention (PCI) has been controversial. Comprehensive understanding of the significance of periprocedural MIs is critical, because they may occur in as many as 20% of patients (1,6,7) and are often noted in asymptomatic patients and after uncomplicated procedures (1). Early data from small numbers of low-risk patients with limited long-term follow-up suggested that elevations of cardiac enzymes after an intervention were inconsequential (1). More recent findings, however, indicate that enzymatically defined postprocedure MIs carry an increased risk of adverse clinical outcomes during extended follow-up (2,3,8,9).

We hypothesized that postprocedural elevations of creatine kinase (myocardial band isoenzyme) (CK-MB) also are associated with adverse clinical outcomes at 30 days and at 6 months. To address this hypothesis and to delineate further the prognostic importance of these postprocedural enzyme elevations, we evaluated this relationship in patients enrolled in the Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) study, a trial of a new antiplatelet agent for reduction of ischemic complications of PCI (10). The 4,010 patients who enrolled in this trial represented the largest available multicenter database to include a cross section of patients undergoing elective, urgent, or emergency PCI.

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Abbreviations and Acronyms

CK-MB = creatine kinase (myocardial band isoenzyme)
IMPACT-II = Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II (trial)
MI = myocardial infarction
PCI = percutaneous coronary intervention

Methods

IMPACT-II protocol. From November 30, 1993, to November 9, 1994, the IMPACT-II trial enrolled 4,010 patients at 82 centers in the United States. Details of the study have been published (10). Patients were eligible if they were scheduled for elective, urgent, or emergency PCI with a Food and Drug Administration-approved device (balloon angioplasty, directional atherectomy, high-speed rotational atherectomy, or excimer laser ablation). Stent implantation was discouraged except to manage abrupt closure. The protocol excluded patients with coexisting conditions that could increase the risk of bleeding with the glycoprotein IIb/IIa inhibitor eptifibatide (Integrilin, COR Therapeutics, South San Francisco, California). The protocol was approved by the Institutional Review Board at each center, and patients gave informed consent before randomization.

Patients were randomly assigned to one of three treatments: 1) eptifibatide 135/0.5, 135 mg/kg bolus followed by 0.5 mg/kg/min infusion for 20 to 24 h; 2) eptifibatide 135/0.75, 135 mg/kg bolus followed by 0.75 mg/kg/min infusion for 20 to 24 h; or 3) placebo bolus plus placebo infusion. Aspirin 325 mg was given before the intervention and was to be continued indefinitely. Heparin was given according to an algorithm to maintain an activated clotting time (ACT) between 300 and 350 s throughout the procedure. The PCI was to be performed immediately after the study drug bolus was given and the target ACT had been obtained.

Blood samples for CK and CK-MB were obtained at enrollment and at 6, 12 and 24 h after the initial bolus of study drug. Additional samples were obtained if the patient developed signs or symptoms of ischemia. Enzymes were measured according to local hospital standards.

Study design and definitions. Patients were excluded from our analyses if they were scheduled to undergo direct or rescue PCI for an acute MI (n = 130), did not have a procedure (n = 151), lacked an enzyme measure in the 4 to 20 h after PCI (patients missing total CK, n = 187; patients with total CK who lacked an MB fraction, n = 1,359), or were missing procedure or event times or laboratory normals (CK, n = 7; CK-MB, n = 29) pertinent to these analyses. Clinical characteristics of the patients with incomplete data did not differ substantively from those of the remaining population (Table 1).

Measurement of cardiac enzymes was specified by the trial protocol, which should have minimized the chance that enzymes (including MB fraction) may have been documented preferentially in patients at higher risk for cardiac events. In some cases, death or emergency bypass surgery shortly after

Table 1. Baseline Characteristics of Patients Included in and Excluded From Analysis

	Included in Analysis		Excluded From Analysis		
Variable	CK (n = 3,535)	CK-MB (n = 2,341)	CK (n = 345)	CK-MB (n = 1,539)	Both (n = 157)
Age (yr)	61 (52, 69)	60 (52, 78)	62 (54, 69)	61 (53, 69)	62 (54, 71)
Weight (kg)	84 (74, 95)	84 (75, 95)	83 (73, 93)	83 (73, 95)	84 (76, 93)
Male sex	2,637 (75)	1,755 (75)	250 (73)	1,132 (74)	113 (72)
Hypertension	1,934 (55)	1,289 (55)	183 (53)	828 (54)	83 (53)
Diabetes	805 (23)	542 (23)	77 (22)	340 (22)	32 (20)
History of smoking	2,295 (65)	1,551 (67)	222 (65)	966 (63)	101 (65)
Hyperlipidemia	1,934 (55)	1,306 (56)	179 (52)	807 (54)	81 (52)
Cerebrovascular disease	63 (2)	47 (2)	12 (4)	28 (2)	9 (6)
Previous infarction	1,437 (41)	984 (42)	150 (44)	603 (39)	65 (41)
Previous bypass surgery	577 (16)	415 (18)	57 (17)	219 (14)	25 (16)
Peripheral vascular disease	214 (6)	147 (6)	34 (10)	101 (7)	18 (12)
Status at enrollment*					
Unstable angina	1,262 (36)	845 (36)	141 (41)	558 (36)	71 (45)
Other (elective)	2,273 (64)	1,496 (64)	204 (59)	981 (64)	86 (55)
Reason for revascularization					
Asymptomatic/positive functional study	284 (8)	173 (7)	37 (11)	148 (10)	16 (10)
Pain only with MI	317 (9)	224 (10)	24 (7)	117 (8)	7 (5)
Stable angina	550 (16)	352 (15)	54 (16)	252 (16)	25 (16)
Unstable angina	2,383 (67)	1,591 (68)	230 (67)	1,022 (66)	109 (69)
Systolic blood pressure (mm Hg)	130 (116, 145)	130 (116, 146)	130 (116, 146)	130 (117, 145)	130 (115, 146)
Diastolic blood pressure (mm Hg)	72 (65, 80)	72 (65, 80)	72 (65, 80)	72 (64, 80)	70 (62, 80)
Heart rate (beats/min)	68 (60, 78)	68 (60, 79)	68 (61, 79)	68 (60, 77)	68 (61, 80)

*Patients enrolled with acute MI are excluded from these analyses. Data presented are median (25th, 75th percentiles) or number (%) of patients.

Table 2. Clinical Outcomes

Outcome*	Included in Analysis		Excluded From Analysis		
	CK (n = 3,535)	CK-MB (n = 2,341)	CK (n = 345)	CK-MB (n = 1,539)	Both (n = 157)
30-Day composite	179 (5.1)	139 (6.0)	43 (12.5)	83 (5.4)	25 (15.9)
Death	23 (0.7)	16 (0.7)	8 (2.3)	15 (1.0)	1 (0.6)
Myocardial infarction	87 (2.5)	74 (3.2)	7 (2.0)	20 (1.3)	3 (1.9)
Urgent bypass surgery	47 (1.3)	42 (1.8)	36 (10.4)	41 (2.7)	22 (14.0)
Urgent intervention	95 (2.7)	64 (2.7)	6 (1.7)	37 (2.4)	5 (3.2)
6-Month composite	928 (26.3)	647 (27.7)	139 (40.3)	420 (27.3)	45 (28.7)
Death	63 (1.8)	44 (1.9)	8 (2.3)	27 (1.8)	1 (0.6)
Myocardial infarction	187 (5.3)	137 (5.9)	15 (4.4)	65 (4.2)	6 (3.8)
Any bypass surgery	277 (7.8)	200 (8.5)	104 (30.1)	192 (11.8)	31 (19.7)
Any percutaneous intervention	657 (18.6)	441 (18.8)	38 (11.0)	254 (16.5)	18 (11.5)

*Patients enrolled with acute MI are excluded from these analyses. Data presented are number (%) of patients.

enrollment precluded completion of enzyme data. This is reflected in the high rates of death and emergency bypass in patients excluded from all analyses, including CK (Table 2). Measurement of CK-MB, particularly in patients with normal total CK, was determined by local laboratory protocol. Thus, 30-day and 6-month event rates in patients with complete CK-MB data (those analyzed) were similar to those of the overall population.

The 30-day composite endpoint for this analysis included death from any cause, or a new MI, or urgent or emergency repeat percutaneous or surgical intervention that occurred ≥24 h after the index intervention. Urgent or emergency bypass or repeat PCI was defined as an unanticipated procedure performed to manage abrupt closure or suspected or manifest ischemia. The MIs were classified by either enzyme or electrocardiographic (ECG) criteria. The 6-month composite end point for this analysis included death from any cause, MI, and all percutaneous or surgical interventions (regardless of urgency) occurring ≥24 h after the index PCI. As with the 30-day analyses, events associated with the index intervention were excluded.

During the index hospitalization, MI was defined as elevation of CK-MB (or CK if CK-MB was unavailable) to at least three times the upper limit of normal for the site, or new Q waves ≥0.04 s in two or more anatomically contiguous leads. A postdischarge MI was classified by elevation of CK-MB (or CK if CK-MB was not available) to at least twice the site's upper limit of normal or new Q waves as described above. Procedure-related MI was timed as occurring at the point of first device activation.

All MIs occurring after enrollment were timed according to the following hierarchy: 1) time of onset of symptoms or new ECG changes if documented; 2) if no documentation of ischemia, time of PCI if within 24 h before an abnormal enzyme level or new Q waves; 3) if no documentation of ischemia and no procedures within 24 h, time of first abnormal enzyme or ECG with new Q waves. Importantly, cases in which the onset of signs and symptoms of infarction occurred before the end of the index procedure, and MIs within 24 h of the index PCI that were ascribed to this procedure, were excluded from composite and component end points.

An independent Clinical Events Committee blinded to treatment assignment adjudicated all 30-day and 6-month events. Length of hospital stay was defined as the difference (in days) between the date of discharge and the date of the index procedure.

Data management and statistical analysis. Demographic and clinical data were collected on standard case report forms and were verified against the medical record before being sent to the Coordinating Center (Duke Clinical Research Institute) for data entry. A follow-up visit ≥27 days after enrollment was performed to assess the primary end point, and a telephone interview was conducted at 6 months to evaluate long-term outcomes. Medical records were reviewed for deaths, readmissions, and angiograms reported by the patient at the 6-month interview. Missing or inconsistent data were investigated.

We stratified patients by peak CK and CK-MB within 4 to 20 h after the index PCI (normal, peak CK or CK-MB 1 to 3 times normal, peak 3 to 5 times normal, peak 5 to 10 times normal, and peak >10 times normal). For specific analyses, patients were also stratified according to procedural complications, ultimate success, and device used. Procedural success was defined as residual stenosis <50% without a major clinical event (thrombus, side-branch occlusion, or distal embolization) as reported by the investigator.

Binary outcome variables are reported as frequencies and percentages. Events during the 30-day and 6-month follow-up periods are also depicted with Kaplan-Meier techniques (11). We used multiple logistic regression analysis to construct a model for the relationship between periprocedural elevations of CK-MB, known baseline predictors of the 30-day end point (weight, unstable angina, baseline platelet count, baseline heart rate, previous bypass) (12), and treatment regimen with the outcome of death, later MI, or later urgent or emergency revascularization within 30 days of randomization, and death or later MI within 6 months. The variables were analyzed to assess the assumption that the log-odds of death or MI

Table 3. Postprocedure Peak CK and CK-MB by Diagnostic Category

	All Patients		Unstable Angina		Elective	
Postprocedure Peak	CK (n = 3,535)	CK-MB (n = 2,341)	CK (n = 1,262)	CK-MB (n = 845)	CK (n = 2,273)	CK-MB (n = 1,496)
Normal	3,111 (88.0)	1,779 (76.0)	1,084 (85.9)	609 (72.1)	2,027 (89.2)	1,170 (78.2)
1–3 times normal	327 (9.3)	323 (13.8)	135 (10.7)	139 (16.5)	192 (8.5)	184 (12.3)
3–5 times normal	58 (1.6)	84 (3.6)	29 (2.3)	32 (3.8)	29 (1.3)	52 (3.5)
5–10 times normal	24 (0.7)	86 (3.7)	8 (0.6)	30 (3.6)	16 (0.7)	56 (3.7)
>10 times normal	15 (0.4)	69 (2.9)	6 (0.5)	35 (4.1)	9 (0.4)	34 (2.3)

Data presented are number (%) of patients.

independently related to the magnitude of postintervention CK-MB elevation.

Results

Postprocedural CK and CK-MB. Table 3 shows the stratification of patients according to peak CK and CK-MB fraction after the index PCI. The incidence and magnitude of observed elevations were higher for patients with unstable rather than stable angina ($p = 0.001$ for CK-MB; $p = 0.004$ for total CK).

Patients scheduled for an elective PCI were included in these analyses regardless of the indication or baseline CK or CK-MB values. In most cases, a baseline CK value was available (93%; 3,285/3,535) and was normal (89.0%; 2,925 patients). Of patients with available data, elevated CK before the index PCI was reported in 13.6% of patients with unstable angina (165/1,214) and in 9.4% of other patients (195/2,071). Baseline elevations of CK-MB were noted in 13.5% of patients with available data, in 19.5% of patients with unstable angina (118/604), and in 10.2% of other patients (11/1,091). Patients with baseline CK or CK-MB elevations were more likely to have postprocedural elevations and to have larger elevations.

Prognostic significance of postintervention elevated CK and CK-MB. Figures 1 and 2 show the point estimates and 95% confidence intervals for the 30-day composite and component event rates by total CK and CK-MB stratum. Of patients with minimally elevated CK-MB (one to three times normal), 9.0% experienced reinfarction (after the index PCI), death, or urgent or emergency revascularization by 30 days, about three times the composite event rate of patients with normal postprocedural CK-MB (2.9%; $p < 0.0001$) (complete data may be obtained from Dr. Tardiff). A proportionate relation between magnitude of the CK-MB and the composite 30-day event rate was noted for elevations up to five times the upper limit of normal. The incidence of later adverse outcomes was high, but not consistently proportional to the magnitude of the peak CK-MB, in patients with elevations >5 times normal. A similar relation between elevated postprocedure level and later adverse outcomes was seen for total CK.

Patients with postprocedural enzyme elevations were also more likely to have late cardiac events within 6 months (Figs. 3 and 4). Of patients who had modest (one to three times normal) postprocedural elevations, 8.7% had a new MI within 6 months, over twice the rate of MI in patients with normal postprocedural CK-MB. Again, findings were similar for total CK. Although a strong proportionate relation between elevation of CK-MB after the index PCI and 6-month event rates was seen for death and MI, a less consistent trend was

Figure 1. Point estimates and 95% confidence intervals for frequency of later clinical events at 30 days, by postintervention CK stratum (from **left to right**): 0–1 times normal, 1–3 times normal, 3–5 times normal, 5–10 times normal, or >10 times normal. MI = myocardial infarction; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty.

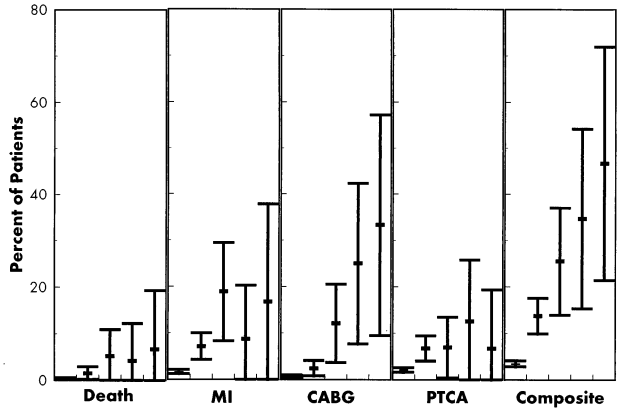
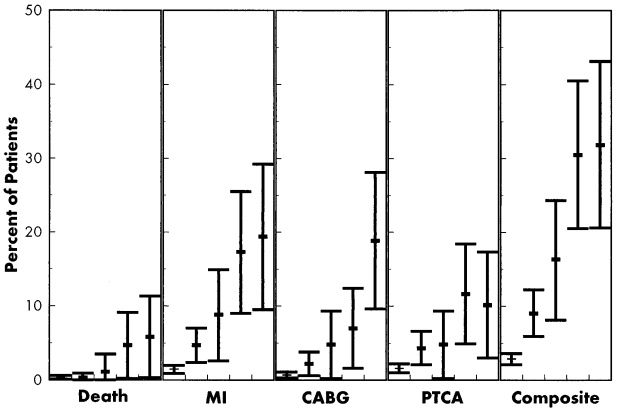


Figure 2. Point estimates and 95% confidence intervals for frequency of later clinical events at 30 days, by postintervention CK-MB stratum (from **left to right**): 0–1 times normal, 1–3 times normal, 3–5 times normal, 5–10 times normal, or >10 times normal. Abbreviations as in Figure 1.



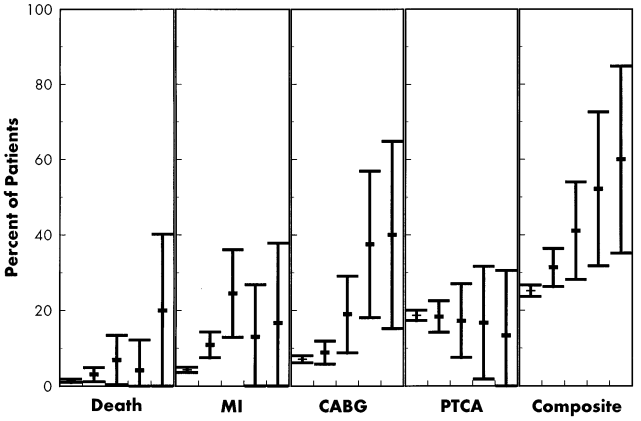


Figure 3. Point estimates and 95% confidence intervals for frequency of later clinical events at 6 months, by postintervention CK stratum (from **left to right**): 0–1 times normal, 1–3 times normal, 3–5 times normal, 5–10 times normal, or >10 times normal. Abbreviations as in Figure 1.

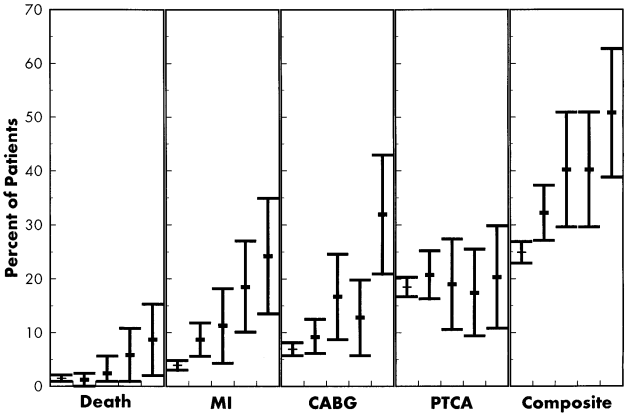


Figure 4. Point estimates and 95% confidence intervals for frequency of later clinical events at 6 months, by postintervention CK-MB stratum (from **left to right**): 0–1 times normal, 1–3 times normal, 3–5 times normal, 5–10 times normal, or >10 times normal. Abbreviations as in Figure 1.

observed for bypass, and no apparent relationship was noted for repeat interventions. All revascularizations, regardless of urgency, were included in the 6-month composite end point.

Timing of postprocedural events. Figures 5 and 6 show the Kaplan-Meier curves for the incidence of death and later MI to 30 days and 6 months as a function of postprocedural CK-MB. Although a large proportion of events occurred within the first several days after the index intervention, the curves separated even more after this initial period, most notably for patients with small elevations (one to three times normal).

Relationship between procedural events and prognostic significance. Of 562 patients with elevated postprocedural CK-MB, 441 of 557 patients (79.2%) with complete procedural data met criteria for PCI success and had no abrupt closure. Acute symptomatic events consistent with abrupt closure were evident in 53 (9.5%) of the patients whose CK-MB became elevated, and another 63 patients (11.3%) did not achieve procedural success (Table 4). Procedures complicated by abrupt closure were associated with highest risk for later events. Not surprisingly, procedural success was associated with lower event rates, whether abrupt closure occurred or not.

Table 5 shows the relationship between CK-MB elevations and later clinical outcomes at 30 days and 6 months in patients with uncomplicated, successful procedures. Again, a proportionate relation between the postprocedural enzyme level and clinical outcomes was shown for the composite and component endpoints at 30 days and 6 months. Patients with the smallest postprocedure elevations (one to three times normal), which did not meet the definition of a periprocedural MI, were more than twice as likely as patients with normal postprocedural enzymes to have had a later MI at 30 days (3.6% vs. 1.5%). The

Figure 5. Kaplan-Meier curves illustrating the incidence of occurrence of death and later infarction at 30 days in patients with postprocedural CK-MB elevation 0–1 times normal (**heavy solid line**), 1–3 times normal (**light solid line**), 3–5 times normal (**heavy short dashes**), 5–10 times normal (**light short dashes**), or >10 times normal (**long dashes**).

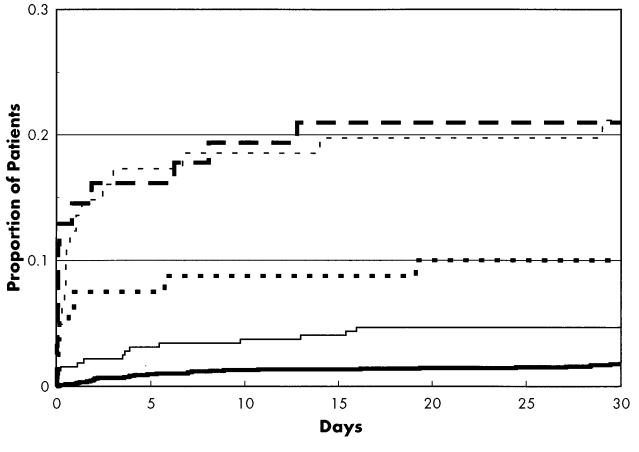


Figure 6. Kaplan-Meier curves illustrating the incidence of occurrence of death and later infarction at 6 months in patients with postprocedural CK-MB elevation 0–1 times normal (**heavy solid line**), 1–3 times normal (**light solid line**), 3–5 times normal (**heavy short dashes**), 5–10 times normal (**light short dashes**), or >10 times normal (**long dashes**).

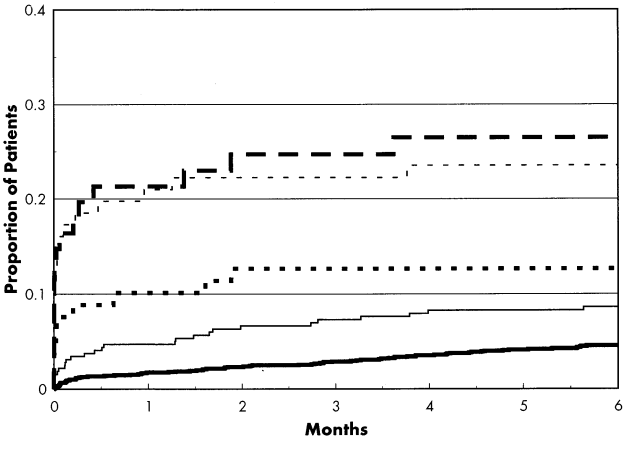


Table 4. Procedural Success and Abrupt Closure and Clinical Outcome

	Composite	Death	Infarction	Bypass*	Angioplasty*
CK-MB normal (n = 1,779)					
30 days	51 (2.9)	6 (0.3)	26 (1.5)	12 (0.7)	29 (1.6)
6 months	443 (24.9)	27 (1.5)	70 (3.9)	123 (6.9)	329 (18.5)
CK-MB abnormal, successful,† no abrupt closure (n = 441)					
30 days	49 (11.3)	5 (1.1)	27 (6.2)	11 (2.5)	26 (5.9)
6 months	151 (34.6)	10 (2.3)	45 (10.4)	48 (10.9)	93 (21.1)
CK-MB abnormal, successful, abrupt closure (n = 27)					
30 days	8 (32.0)	0 (0)	7 (28.0)	1 (3.7)	4 (14.8)
6 months	12 (46.2)	0 (0)	7 (28.0)	5 (18.5)	7 (25.9)
CK-MB abnormal, unsuccessful, no abrupt closure (n = 63)					
30 days	13 (21.7)	1 (1.6)	6 (10.2)	7 (11.1)	2 (3.2)
6 months	22 (36.7)	2 (3.2)	7 (11.9)	12 (19.1)	7 (11.1)
CK-MB abnormal, unsuccessful, abrupt closure (n = 26)					
30-days	15 (60.0)	4 (15.4)	7 (29.2)	8 (30.8)	3 (11.5)
6 months	16 (61.5)	4 (15.4)	7 (29.2)	9 (34.6)	5 (19.2)

*30-Day bypass and angioplasty include urgent/emergency procedures only; 6-month bypass and angioplasty include all procedures. †Success = residual stenosis <50% and no thrombus, side-branch occlusion, or distal embolization. For no elevation vs. elevation with success, $p < 0.0001$ (infarction, the composite end point), $p = 0.006$ (bypass surgery). For no elevation vs. elevation without success, $p = 0.0001$ (infarction, bypass, and the composite end point); $p = 0.002$ (death). Data presented are number (%) of patients.

relation between outcome and postprocedural CK-MB at 6 months was prominent for death and MI, less consistent for bypass surgery, and not apparent for angioplasty, as was observed in the larger population.

Relation between device type and prognostic significance. Angioplasty was the predominant technique used in the IMPACT-II study. Use of a directional or high-speed rotational atherectomy device in conjunction with angioplasty was associated with a greater incidence of postprocedural increases in CK-MB than was angioplasty ($p < 0.0001$; Table 6). Because intracoronary stent use was discouraged during the index PCI except as a bailout device, the number of stented patients was small. For all devices, including stents, a relation between enzyme elevations and the 30-day and 6-month composite event rates was observed (Table 7).

Relationship between elevated cardiac enzymes and length of hospital stay. Elevated cardiac enzymes above three times normal after PCI were associated with a longer initial hospital stay. A proportionate relation between postprocedure CK or CK-MB and time from procedure to discharge was seen. The

Table 5. Clinical Outcomes in Patients With Successful Procedures Without Abrupt Closure

CK-MB	Composite	Death	Infarction	Bypass*	Angioplasty*
Normal (n = 1,634)					
30 days	43 (2.6)	5 (0.3)	25 (1.5)	8 (0.5)	24 (1.5)
6 months	400 (24.5)	25 (1.5)	66 (4.0)	105 (6.4)	298 (18.2)
1–3 times normal (n = 281)					
30 days	22 (7.9)	1 (0.4)	10 (3.6)	5 (1.8)	12 (4.3)
6 months	91 (32.4)	4 (1.4)	23 (8.2)	24 (8.5)	60 (21.4)
3–5 times normal (n = 68)					
30 days	9 (13.9)	1 (1.5)	5 (7.7)	2 (2.9)	3 (4.4)
6 months	25 (37.9)	2 (2.9)	7 (10.8)	8 (11.8)	14 (20.6)
5–10 times normal (n = 51)					
30 days	11 (21.6)	1 (2.0)	6 (12.0)	2 (3.9)	7 (13.7)
6 months	18 (35.3)	1 (2.0)	7 (14.0)	5 (9.8)	11 (21.6)
>10 times normal (n = 41)					
30 days	7 (18.0)	2 (4.9)	6 (15.4)	2 (4.9)	4 (9.8)
6 months	17 (43.6)	3 (7.3)	8 (20.5)	11 (26.8)	8 (19.5)

Success denotes residual stenosis <50% and no thrombus, side-branch occlusion, or distal embolization; abrupt closure, abrupt closure during index procedure. *30-Day bypass and angioplasty include urgent and emergency procedures only; 6-month bypass and angioplasty include all revascularizations. Data presented are number (%) of patients.

Table 6. Postprocedure CK-MB by Device Type

CK-MB	Angioplasty (n = 1616)	Atherectomy* (n = 369)	Rotablator* (n = 292)	Stent (n = 102)
Normal	1,331 (82)	214 (58)	193 (66)	55 (54)
1–3 times normal	176 (11)	85 (23)	55 (19)	19 (19)
3–5 times normal	36 (2.2)	30 (8)	17 (6)	6 (6)
5–10 times normal	37 (2.3)	26 (7)	13 (4)	16 (16)
>10 times normal	36 (2.2)	14 (4)	14 (5)	6 (6)

*Includes use in combination with other devices. Data presented are number (%) of patients.

CK elevations were associated with prolongation of the time from procedure to discharge from a median of 2 days (range, 0 to 31 days; interquartile range, 1 to 2 days) for patients with normal postprocedure CK to 5 days (1 to 26 days, 3 to 6 days) for patients with a postprocedure peak CK from three to five times normal. Patients with markedly elevated CK (>10 times normal) had the longest hospital stays with a median time from procedure to discharge of 7 days (1 to 46 days, 4 to 11 days). A subtler but similar relationship was evident for CK-MB. There was a gradual rise in the upper quartile limit for CK-MB elevations up to five times normal. The median stay increased from 2 days (0 to 37 days, 1 to 2 days) for patients with no elevation to 3 days (1 to 14 days, 2 to 6 days) for patients with increases from 5 to 10 times normal, and to 4 days (1 to 46 days, 3 to 7 days) for patients with postprocedure CK-MB >10 times normal.

Predictive modeling. The magnitude of the peak CK-MB after the index PCI had a highly significant, nonlinear relationship to the composite 30-day (death or MI) and 6-month (death, MI, or revascularization) end points. The effect was nearly linear for CK-MB elevations of up to six times normal, then reached a plateau at higher levels (for 30-day composite with spline, $\chi^2 = 147.66$, $p < 0.0001$; for 6-month composite with spline, $\chi^2 = 42.41$, $p < 0.0001$; for 6-month death or infarction with spline, $\chi^2 = 72.66$, $p < 0.0001$; Fig. 7).

After adjustment for known baseline predictors of the 30-day end point (weight, unstable angina, baseline platelet count, baseline heart rate, previous bypass surgery) (12), postprocedure CK-MB remained significantly associated with 30-day ($\chi^2 = 135.09$, $p < 0.0001$) and 6-month outcomes ($\chi^2 = 32.56$, $p < 0.0001$). This persisted for the 30-day composite outcome after further adjustment for age and the presence of diabetes ($\chi^2 = 139.74$, $p < 0.0001$).

Eptifibatide treatment had no significant relationship with the clinical effects of postintervention enzyme elevations. We found only a trend toward an interaction ($\chi^2 = 2.75$; $p = 0.097$) between eptifibatide 135/0.75 treatment and degree of enzyme elevation for the 30-day composite outcome, such that the risk of adverse outcomes by 30 days in patients with elevations was somewhat lower for patients in the eptifibatide 135/0.75 arm than for those in the other treatment arms. This trend remained after adjustment for age and diabetes ($\chi^2 = 3.027$, $p = 0.082$).

Discussion

In this study, patients who had an elevated CK-MB level after coronary procedures were at increased risk for death, MI, and urgent revascularization at 30 days, and for death, MI, and surgical revascularization at 6 months. The degree of risk was proportional to the magnitude of the rise in CK-MB. We observed no threshold for a substantial increase in postprocedural events in any category of serum CK and CK-MB elevation, although there was little added risk associated with levels of CK-MB greater than six times normal. Importantly, even patients with minimal (one to three times normal) increases in CK-MB—elevations usually not recognized as cardiac events in the context of clinical trials—were at increased risk for later adverse outcomes. After controlling for clinical factors such as weight, acuteness of presentation, baseline heart rate, and previous

Table 7. Clinical Outcomes by CK-MB Level and Device Type

CK-MB	30-Day Composite	6-Month Composite
Normal		
Angioplasty only	41 (3.1)	337 (25.3)
Atherectomy	3 (1.4)	54 (25.2)
Rotablator	4 (2.1)	39 (20.2)
Stent	4 (7.3)	15 (27.3)
1–3 times normal		
Angioplasty only	19 (10.9)	52 (29.6)
Atherectomy	5 (5.9)	29 (34.1)
Rotablator	4 (7.3)	22 (40.0)
Stent	3 (15.8)	7 (36.8)
3–5 times normal		
Angioplasty only	7 (20.6)	16 (44.4)
Atherectomy	3 (10.3)	7 (24.1)
Rotablator	3 (18.8)	9 (56.3)
Stent	1 (16.7)	2 (33.3)
5–10 times normal		
Angioplasty only	10 (28.6)	15 (41.7)
Atherectomy	6 (26.1)	8 (34.8)
Rotablator	3 (25.0)	5 (41.7)
Stent	2 (28.6)	6 (42.9)
>10 times normal		
Angioplasty only	8 (22.9)	18 (50.0)
Atherectomy	1 (8.3)	4 (28.6)
Rotablator	4 (40.0)	7 (58.3)
Stent	4 (66.7)	5 (83.3)

Data presented are number (%) of patients.

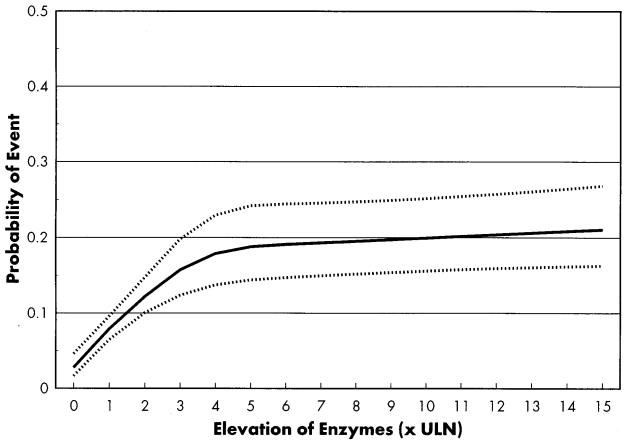


Figure 7. Probability of the 6-month composite of death and infarction as a function of CK-MB elevation. ULN = upper limit of normal.

bypass surgery, we found that an increased CK-MB remained an important predictor of adverse outcomes.

Not surprisingly, the gradient of risk was defined by the success of the procedure, whether abrupt closure occurred, and by the magnitude of the postprocedural elevation. However, even among patients with successful PCI (no residual stenosis >50%, and no thrombus, side-branch occlusion, distal embolization, or abrupt closure), those with postprocedural elevations were at higher risk for new cardiac events within 6 months than were those without an abnormal increase in postprocedural CK-MB.

Postprocedure MI has been reported to carry an increased risk for cardiac mortality during extended follow-up (8,13). These data extend previous findings in that only modest enzymatic elevations (not usually classified as MI in this setting) are associated with increased risk, and that periinterventional MI is associated with short-term as well as long-term adverse outcomes.

Study limitations. The interpretation of these data may be complicated by several possible limitations. Patients referred for enrollment in IMPACT-II could represent a high-risk subgroup. This is unlikely, as prospective risk stratification indicated that the largest proportion of patients (97%) were referred for elective coronary interventions (10). The incidence of periprocedural elevations of CK-MB is similar to that reported in other interventional studies (2,3).

Because CK-MB is more specific for myocardial damage than total CK, and because increases in total CK may not always correlate with increases in CK-MB (13), patients who did not have an MB fraction measured were excluded from some analyses. The IMPACT-II protocol called for enzyme sampling at designated times, but CK-MB may have been measured preferentially in patients with elevated CK or at high risk of cardiac events. To address this limitation, parallel analyses were performed of total CK instead of CK-MB. Results of these analyses compared well with those limited to patients with CK-MB, indicating that the sample used in this analysis appeared to represent the overall study population. Overall event rates at 30 days and 6 months for patients from whom no enzymes were obtained suggest that they were similar in terms of cardiac risk to those for whom complete enzyme data were available (Table 2). Exclusion of the high-risk patients who experienced early death or bypass surgery (which precluded capture of postprocedure enzyme data) strengthens rather than limits the results.

A drawback to multicenter trials is the variation among investigative sites. Different methods to determine enzyme levels, and varying standards of normal, can confound assessment of abnormal CK-MB levels. Reported CK-MB values were divided by meticulously verified institutional normals, to translate them into a measure that was reasonably consistent from site to site. The use of these myocardial enzyme ratios should permit generalizable comparisons.

Implications. Although several studies have shown the relation between postprocedural enzyme elevations and long-term outcomes (13), this is the first report suggesting that the survival curves of CK-MB-positive and -normal patient groups may separate within the first year.

The prognostic relationship observed for periprocedural elevations is similar to that seen with spontaneously occurring non–Q-wave MIs. This implies that abnormal elevation of cardiac enzymes, whether associated with PCI and regardless of magnitude, should be interpreted as an MI. Although it remains to be seen whether strategies that improve outcomes after spontaneous MI are also effective for periprocedural MI, it follows that close clinical management is indicated for these patients. Perhaps more important, therapeutic strategies that aim to reduce the incidence and severity of peri-intervention MI are clearly warranted. Antiplatelet agents, particularly the glycoprotein IIb/IIIa inhibitors, have been shown to reduce the incidence of recurrent acute coronary events and should be strongly considered for routine use (10,14).

It has been unclear whether procedures using newer interventional devices are equally predictive of periprocedural infarction. The use of directional or high-speed rotational atherectomy was associated with more frequent and greater increases in CK-MB after intervention in IMPACT-II, confirming previous reports (3). Measured increases in CK-MB were associated with increased 30-day and 6-month composite event rates, regardless of device. Although we did not adjust for differences in lesion characteristics, these findings suggest that increases in CK-MB observed with these newer devices carry prognostic significance. Prospective evaluation of devices should include long-term follow-up as well as an assessment of the incidence of periprocedural MI, to document their effects on morbidity and mortality.

The interpretation of periprocedural enzyme elevations is particularly complex for patients with evolving MIs and elevated enzymes at the time of PCI. These data suggest that such patients are more likely to have elevated enzymes after the procedure. Later risk could relate to a preintervention MI or a procedural event. However, adjustment for a diagnosis of

unstable angina at presentation did not abolish the prognostic significance of elevated CK-MB after intervention.

The relation between postintervention microinfarctions and later adverse outcomes has not been fully settled. It is not clear whether myocardial necrosis or the severity of the patient's underlying illness is responsible for the associated risk. Several investigators have failed to show that the prognostic import of elevated enzymes is explained by more severe underlying disease (4,9). Although baseline factors known to predict the 30-day end point were used in the predictive modeling, these analyses may not have included complete consideration of important coronary morphology or procedural characteristics. Further study of these variables and extended patient follow-up are needed to clarify this relationship and provide insight into the mechanism of enzyme elevations after coronary intervention.

In any case, the consistency of these data—the strong dose-response relationship between the magnitude of the postprocedural CK and CK-MB elevation and 30-day and 6-month outcomes, and the results of multivariable modeling—strongly argue against these observations being a result of chance. These data clearly justify the classification of a CK-MB elevation above three times normal as an MI within the context of a clinical trial and suggest consideration of lesser elevations. Although postprocedural enzyme elevations should be interpreted with consideration of lesion morphology and the clinical setting, these findings solidly support systematic assessment of CK-MB or other cardiac markers after all coronary interventions. Patients who have a CK-MB elevation greater than three times normal may benefit from close observation in an inpatient setting after the procedure and from medical therapies appropriate for an uncomplicated non–Q-wave MI. A more limited period of observation appears safe for patients with small (one to three times normal), transient CK-MB elevations. Even in these cases, however, there should be a heightened awareness of the increased risk for later events and careful outpatient monitoring.

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