

Creatine Kinase-MB Elevation After Coronary Intervention Correlates With Diffuse Atherosclerosis, and Low-to-Medium Level Elevation Has a Benign Clinical Course

Implications for Early Discharge After Coronary Intervention

Annapoorna Kini, MD, Jonathan D. Marmur, MD, FACC, Subhash Kini, MD, George Dangas, MD, Thomas P. Cocks, MD, FACC, Sylvan Wallenstein, PhD, Eppie Brown, RN, John A. Ambrose, MD, FACC, Samin K. Sharma, MD, FACC

New York, New York

- OBJECTIVES** The study evaluated the incidence and predictors of creatine kinase-MB isoenzyme (CK-MB) elevation after successful coronary intervention using current devices, and assessed the influence on in-hospital course and midterm survival.
- BACKGROUND** The CK-MB elevation after coronary intervention predominantly using balloon angioplasty correlates with late cardiac events of myocardial infarction (MI) and death. Whether CK-MB elevation after nonballoon devices is associated with an adverse short and midterm prognosis is unknown.
- METHODS** The incidence and predictors of CK-MB elevation after coronary intervention were prospectively studied in 1,675 consecutive patients and were followed for in-hospital events and survival.
- RESULTS** CK-MB elevation was detected in 313 patients (18.7%), with 1–3× in 12.8%, 3–5× in 3.5% and >5× normal in 2.4% of patients. Procedural complications or electrocardiogram changes occurred in only 49% of the CK-MB-elevation cases; CK-MB elevation was more common after nonballoon devices (19.5% vs. 11.5% after percutaneous transluminal coronary angioplasty; $p < 0.01$). Predictors of CK-MB elevation on multivariate analysis were diffuse coronary disease ($p = 0.02$), systemic atherosclerosis ($p = 0.002$), stent use ($p = 0.04$) and absence of beta-blocker therapy ($p = 0.001$). Adverse in-hospital cardiac events were more frequent in patients with >5× CK-MB elevation, with no significant difference between 1–5× CK-MB elevation versus normal CK-MB group. During a mean follow-up of 13 ± 3 months, the incidence of death in the CK-MB-elevation group was 1.6% versus 1.3% in the normal CK-MB group ($p = \text{NS}$).
- CONCLUSIONS** The CK-MB elevation after coronary intervention was observed even in the absence of discernible procedural complications and was more common in patients with diffuse atherosclerosis. In-hospital clinical events requiring prolonged monitoring were higher in >5× CK-MB-elevation patients only. Midterm survival of CK-MB-elevation patients was similar to those with normal CK-MB. Our prospective analysis shows a lack of adverse in-hospital cardiac events and suggests that early discharge of stable 1–5× normal CK-MB-elevation patients after successful coronary intervention is safe. (J Am Coll Cardiol 1999;34:663–71) © 1999 by the American College of Cardiology

Elevation of creatine kinase-MB isoenzyme (CK-MB) has been shown to occur after 6% to 30% of otherwise successful percutaneous coronary interventions (1–5). Recently, much

controversy has arisen regarding the postprocedure minor CK-MB elevation, commonly called “infarctlets,” and its clinical relevance on short- and long-term prognosis after

From the Cardiac Catheterization Laboratory of the Zena and Michael A. Weiner Cardiovascular Institute, Mount Sinai Hospital, New York, New York. This study was presented in part at the 9th Annual Symposium of Transcatheter Cardiovascular Therapeutics, Washington, DC, October 1997, and the 47th Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, March 1998.

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interventions. Numerous earlier reports, mostly involving percutaneous transluminal coronary angioplasty (PTCA), have demonstrated that elevation of CK-MB is associated

Abbreviations and Acronyms

ACC/AHA	= American College of Cardiology/American Heart Association
CABG	= coronary artery bypass grafting
CCS	= Canadian Cardiovascular Society
CHF	= congestive heart failure
CK-MB	= creatine kinase-MB isoenzyme
ECG	= electrocardiogram
IAMP	= intra-aortic balloon pump
LAD	= left anterior descending artery
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
PRCA	= percutaneous rotational coronary atherectomy
PTCA	= percutaneous transluminal coronary angioplasty
RCA	= right coronary artery
SVG	= saphenous vein graft
TIMI	= thrombolysis in myocardial infarction
TLR	= target lesion revascularization

not only with a higher mortality but also with a higher risk of subsequent cardiac events and higher cost (5–10). In these studies, the risk of adverse outcome increased proportional to the magnitude of CK-MB elevation. Recent trials involving newer devices have revealed higher incidence of CK-MB elevation postprocedure but a lack of correlation with midterm adverse cardiac events and survival (11–13). It is possible that a stable and larger postprocedure lumen, attained after successful new device intervention with a lower target lesion revascularization (TLR), primarily determines subsequent cardiac events, and the influence of CK-MB elevation is overshadowed in the overall outcome.

Several experimental studies have identified the pathologic substrate for CK-MB release from the myocardium, which is either myocardial necrosis or profound ischemic injury but retention of cell viability (14,15). The causes of CK-MB elevation postprocedure are multifactorial and include transient vessel closure, slow flow, distal thromboembolism, side branch closure, hypotension and prolonged ischemia caused by longer balloon inflations (16–20). Moreover, it is unclear whether CK-MB elevation after a successful procedure is a reflection of the procedure itself or a marker of diffuse atherosclerosis involving the vessel (5,9,10). The present prospective study was conducted with the following objectives: 1) to evaluate the incidence of CK-MB elevation after various coronary interventional devices, 2) to identify the clinical, angiographic and procedural predictors of CK-MB elevation, 3) to assess in-hospital course for any adverse cardiac events, 4) to evaluate the safety of early postprocedure discharge of clinically stable patients despite elevated CK-MB levels and 5) to evaluate if CK-MB elevation has an effect on midterm ($\approx$ 12 months) survival.

METHODS

Patients. All patients undergoing percutaneous coronary interventions at Mount Sinai Hospital, New York, between January 1997 and February 1998 were included in the study. Patients who had coronary intervention within 24 h of acute myocardial infarction (MI) ($n = 82$), urokinase infusion ($n = 8$), elevated preprocedure CK-MB ($n = 16$) and incomplete CK-MB values ($n = 32$) were excluded from the analysis. Patients with major complications occurring in the catheterization laboratory including emergency coronary artery bypass grafting (CABG) or death were also excluded ($n = 8$). The study population consisted of 1,675 consecutive patients with preprocedure, 6 to 8 h and 16 to 24 h postprocedure CK-MB values available for analysis. After coronary intervention, patients were admitted either to the coronary care unit or postprocedure telemetry care unit. If the second postprocedure CK-MB was elevated, values were further monitored (every 4 to 6 h) until levels declined.

Protocol. All patients had blood drawn for CK-MB measurement and lipid profile at the time of femoral sheath insertion and had a baseline 12-lead electrocardiogram (ECG) within 24 h before the procedure. During the interventional procedure, two noncontiguous ECG leads were continuously monitored for heart rate and ST-T wave changes. Continuous hemodynamic monitoring was done by displaying the arterial line pressure. Interventional procedures were carried out in a standard fashion, and procedural complications such as coronary spasm, arterial dissection, thromboembolism, transient vessel closure, abrupt closure, slow flow, side branch closure, prolonged hypotension (systolic blood pressure <80 mm Hg lasting for >5 min), prolonged balloon inflation (>5 min) and persistent chest pain (>30 min postprocedure) were recorded.

Subsequently, blood samples were drawn at 6 to 8 h and 16 to 24 h after the procedure for cardiac enzymes, routine chemistry and complete blood cell counts. A 12-lead ECG was routinely recorded after the procedure and on the following morning (for in-patients). In cases of an adverse clinical outcome, recurrent postprocedure chest pain and prolonged hospitalization, further blood tests were performed and ECGs were recorded, as deemed clinically necessary. All ECGs were independently analyzed for ST segment and T-wave changes, and for the appearance of new Q-waves. During the initial four months of the study period, patients with elevated CK-MB values were monitored in-hospital for cardiac events, and CK-MB was serially measured every 6 to 8 h until CK-MB declined to <16 units and only then were patients discharged. Subsequently, by observing a total lack of any adverse clinical events while waiting for CK-MB to return to baseline in the $1\text{--}5\times$ normal CK-MB-elevation group, the policy was changed to discharge clinically stable patients with declining yet elevated CK-MB values.

The Mass technique was used to measure CK-MB. Total

creatinine kinase (CK) was measured by an Hitachi 747 analyzer, and CK-MB was measured by immunoinhibition using a Johnson and Johnson Vitros 950 analyzer (Rochester, New York). If the CK-MB was abnormal (absolute total ≥ 16 units or $\geq 10\%$ of total CK) then it was further confirmed using enzyme mass immunoassay by Baxter Stratus-2 analyzer. Final CK-MB values of mass immunoassay were used for the analysis.

Intervention. Most (98%) of the coronary interventional procedures were performed via the femoral route, with 2% done by radial and brachial approaches. All patients received aspirin 325 mg orally and a 70–100-USP units/kg intravenous bolus of heparin. The activated clotting time was maintained between 250 to 350 s throughout the procedure using periodic IV boluses of heparin with a trend toward lower values if abciximab was used. A 6–10F guiding catheter was used. The distribution of various devices for coronary interventions were: PTCA 10.4%; PRCA (percutaneous rotational coronary atherectomy) 25.1%; stent 28.5%; PRCA + stent 31.9%; and other devices (directional coronary atherectomy, transluminal extraction catheter or Angiojet [Possis Medical Inc., Minneapolis, Minnesota] alone or in combination of stent or PRCA) 4.1%. All interventions were performed using conventional techniques, and the selection of a device was left to the operator's discretion. Abciximab was used in 38.8% of the cases, particularly in high-risk coronary interventions such as multivessel intervention, staged procedure, presence of thrombus, saphenous vein graft (SVG) lesion, American College of Cardiology/American Heart Association (ACC/AHA) type C lesion, ostial lesions, heavily calcified and bifurcation lesions. In some cases, abciximab was used only after procedural complications were noted. Postprocedure sheath was removed 4 to 6 h after intervention except in cases of recurrent chest pain or a planned staged procedure the next day.

Coronary interventions were classified as single vessel if the intervention was done in one coronary vessel distribution (including branches) or multivessel if the intervention was done in two or more coronary vessel distributions. Single-vessel intervention was done in 89% and multivessel interventions in 11% of the cases. Of these interventions, 9% were performed in SVGs. In cases of multiple lesions, patients were grouped in the most adverse lesion characteristics. Lesion length was measured visually or by on-line quantitative coronary analysis using a digital caliper. Detailed quantitative coronary analysis of reference vessel size and pre- and postprocedure minimal lumen diameter using the CMS-MEDIS system was performed in 44% of the cases (21).

In-hospital course. All patients were monitored in-hospital for recurrent chest pain, heart failure, arrhythmia (atrial or ventricular), ECG changes, acute or subacute closure and the need for repeat catheterization, repeat intervention and in-hospital CABG. Clinically stable pa-

tients with normal CK-MB were discharged on the next day, on aspirin only following nonstent device use and on aspirin plus ticlopidine 250 mg twice daily for four weeks if a stent was implanted. In the beginning, patients with elevated CK-MB were discharged only when values declined to <16 units. After the initial four months of the study period, patients with 1–5 $\times$ normal CK-MB elevation were discharged once levels started declining and were stable clinically despite elevated CK-MB values.

Follow-up. All patients discharged from the hospital were followed at 1, 6, 12 and 18 months by telephone contact to the patient or private physician for adverse cardiac events and survival. Repeat hospital admissions within a week of discharge were monitored in both groups. The survival data were cross-checked with the New York State interventional database. The clinical follow-up was available in 99.0% of the CK-MB elevation group and 98.9% of the normal CK-MB group.

Definitions. CK-MB elevations: CK-MB <16 units = no elevation; CK-MB >16 units = any elevation; 16–48 units = 1–3 $\times$ normal; 49–80 units = 3–5 $\times$ normal; >80 units = 5 $\times$ normal. Low-to-medium-level CK-MB elevation: 1–3 $\times$ normal and 3–5 $\times$ normal CK-MB values. High CK-MB elevation: $>5\times$ normal CK-MB value. Angiographic success: $<50\%$ diameter obstruction postprocedure with $\geq$ TIMI (Thrombolysis in Myocardial Infarction) II flow at end of procedure. Major complications: Q-wave MI, emergent CABG or in-hospital death. Clinical success: angiographic success of at least one lesion and no major complications. Focal coronary disease: single lesion <20 mm in length in one or more vessels. Diffuse coronary disease: lesion ≥ 20 mm in length or multiple single lesions in one or more vessels. Acute closure: postprocedure out of the cath lab occlusion of the treated vessel within 24 h. Stent thrombosis: acute or subacute closure in the stented vessel within four weeks after stent deployment. Slow flow: delayed distal clearance of the dye in the absence of proximal dissection or spasm. Coronary dissection: coronary dissections were graded from A–F according to the NHLBI classification, and dissection grades A–C were considered minor and grades D–F were considered major. Coronary spasm: focal or diffuse narrowing of vessel without any evident coronary dissection. Side branch closure: $<$ TIMI III flow in a side branch of >1.5 mm diameter with normal flow preprocedure. ACC/AHA classification: modified ACC/AHA classification grading lesions into A, B₁, B₂ or C category. Calcification: readily apparent fluoroscopic densities in the lesion or vessel. Systemic atherosclerosis: defined as history of peripheral vascular, aortic or cerebrovascular disease.

Statistics. The data were entered in a Microsoft Excel database and transferred to the statistical program StatView 4.1 for analysis. Results are expressed as mean value $\pm$ SD or n (%). Comparison between two groups was done using

Table 1. Clinical Variables for CK-MB Elevation in 1,675 Patients

Clinical Characteristics	Incidence of CK-MB ↑ (%)	Any CK-MB Elevation (n = 313)	Normal CK-MB (n = 1,362)	p Value
Age (yrs)	18.7	65 ± 12	64 ± 12	NS
Female (%)	21.8	116 (37)	414 (30)	0.02
Hypertension (%)	18.5	218 (70)	957 (70)	NS
Hypercholesterolemia (%)	19.1	152 (48)	641 (47)	NS
Smoking (%)	20.3	59 (19)	231 (17)	0.08
Diabetes mellitus (%)	17.0	71 (23)	346 (25)	NS
CCS class III-IV (%)	26.6	163 (52)	449 (33)	0.001
Prior MI (%)	19.8	115 (37)	467 (34)	NS
Prior intervention (%)	17.1	66 (21)	321 (24)	NS
Prior CABG (%)	17.9	46 (15)	211 (15)	NS
Renal failure (%)	33.3	23 (7)	46 (3)	< 0.001
Systemic atherosclerosis (%)	26.8	51 (16)	139 (10)	< 0.001
LVEF (%)	18.7	48 ± 9.8	50 ± 14.2	NS
CHF (%)	20.8	38 (12)	145 (11)	0.1
Multivessel disease (%)	22.0	119 (38)	432 (32)	0.03
Abciximab use (%)	24.5	159 (51)	491 (36)	< 0.001
Beta-blocker therapy (%)	13.2	85 (27)	558 (41)	< 0.001
IABP use (%)	25	13 (4)	39 (3)	0.1

CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

chi-square analysis and continuous variables using the two-tailed Student *t* test. Statistical significance was defined at the level of $p < 0.05$. Variables with a significance level of p value of 0.1 or less in the univariate analysis were considered for the inclusion in the multivariate regression model. In the multiple logistic regression analysis, selection of the variables was achieved in a stepwise fashion, and results were reported as odds ratio (OR) and 95% confidence interval (CI).

RESULTS

Of the 1,675 patients and 4,068 lesions, angiographic success was attained in 94.5% of lesions and clinical success in 96.3% cases, with a 0.72% incidence of major complications. Any CK-MB elevation was noted in 313 of 1,675 patients (18.7%), with 1–3× normal in 12.6%, 3–5× normal in 3.7% and >5× normal in 2.4% of patients. The time to peak CK-MB release was 6 to 8 h in 69%, 16 to 24 h in 23% and >24 h in 8% of cases.

Patient characteristics. Baseline clinical characteristics for the normal and elevated CK-MB groups are presented in Table 1. Mean age for the entire group was 65 ± 13 years, with 31.6% being women. Variables correlated with CK-MB release on univariate analysis were as follows: female gender ($p = 0.02$); CCS (Canadian Cardiovascular Society) angina class III-IV ($p < 0.001$); smoking history ($p = 0.08$); renal failure ($p < 0.001$); systemic atherosclerosis ($p < 0.001$); multivessel disease ($p = 0.03$); abciximab use ($p < 0.001$); and absence of beta-blocker therapy ($p < 0.001$). Other factors such as hypertension, hypercholester-

olemia, level of LDL cholesterol, diabetes mellitus, prior MI, prior intervention, prior CABG, mean left ventricular ejection fraction (LVEF), severe LV dysfunction (LVEF <30%), congestive heart failure (CHF) and IABP (intra-aortic balloon pump) use were not different between the two groups.

Vessel location. The incidence of CK-MB elevation was 19.6% after left anterior descending artery (LAD) intervention, 17.2% after circumflex intervention, 16.9% after right

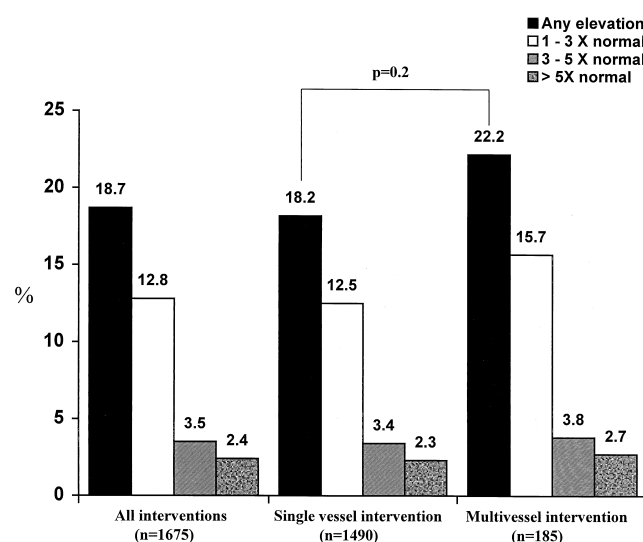


Figure 1. CK-MB elevation in relation to single- or multivessel intervention.

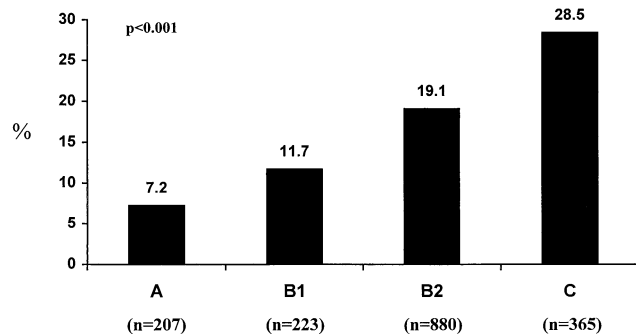


Figure 2. CK-MB elevation in relation to ACC/AHA lesion type.

coronary artery (RCA) intervention ($p = \text{NS}$; multiple comparisons) and 25.8% after SVG intervention ($p < 0.01$ vs. native vessel intervention). The CK-MB release was not different between single-vessel intervention versus multivessel intervention (18.2% vs. 22.2%; $p = 0.2$). The magnitude of CK-MB elevations after single- and multivessel intervention is shown in Figure 1.

Lesion morphology. As shown in Figure 2 there was an increase in CK-MB elevation in relation to lesion complexity using the ACC/AHA classification (A lesion 7.2%; B₁ lesion 11.7%; B₂ lesion 19.1%; and C lesions 28.5%; $p < 0.001$ by ANOVA analysis). The mean lesion length was 18.2 mm in the CK-MB elevation group versus 13.4 mm in the normal CK-MB group ($p < 0.001$). Thrombotic lesions had a higher CK-MB release compared with nonthrombotic lesion (22.4% vs. 18.2%; $p = 0.02$). Other lesion characteristics such as eccentricity, calcification, ostial, total or subtotal occlusion and angulated lesions did not correlate with CK-MB release. Mean reference vessel size was not different between the two groups: 2.74 ± 0.63 mm in the CK-MB elevation group vs. 2.69 ± 0.74 mm in the normal

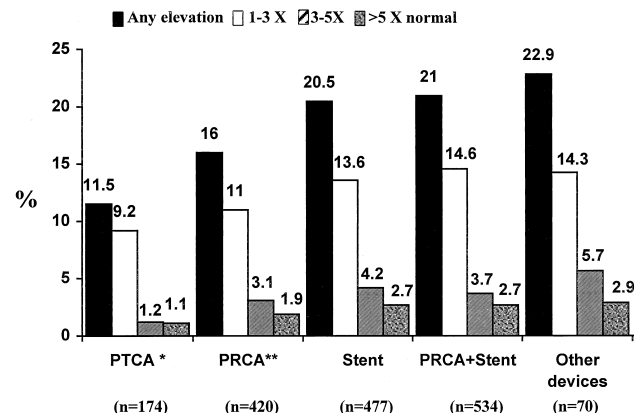


Figure 4. CK-MB elevation in relation to interventional device type. * $p = 0.01$ for PTCA vs. non-balloon devices; ** $p = 0.07$ for PRCA only vs. stent only.

CK-MB group. As shown in Figure 3, CK-MB release strongly correlated with diffuse coronary disease; diffuse disease had a CK-MB release of 24.5% versus 16.2% in focal disease ($p < 0.001$). This relationship was true in subgroups of single-vessel intervention (diffuse disease 24.1% vs. focal disease 16.4%; $p < 0.001$) and multivessel intervention (diffuse disease 29.8% vs. focal disease 15.8%; $p = 0.02$).

Device type. The incidence of CK-MB elevation after various interventional devices is shown in Figure 4. The PTCA has a significantly lower incidence of CK-MB release compared with nonballoon devices (11.5% vs. 19.5%; $p < 0.01$). The PRCA alone has a slightly lower incidence of CK-MB elevation compared to stent alone (16% vs. 20.5%; $p = 0.07$). There was no statistically significant difference in CK-MB elevation after PTCA versus PRCA (11.5% vs. 16%; $p = 0.16$).

Procedural complications. The occurrence of various major and minor procedural complications in the CK-MB elevated group is shown in Table 2. The most common procedural complication associated with CK-MB elevation was side branch closure (22.7%). The incidence of side branch closure was higher in the stent-only group (16.3%) as compared with the PRCA-only group (4.5%) or PRCA and stent group (6.7%); $p < 0.001$ by ANOVA analysis. Other minor complications were slow flow, abrupt closure, distal thromboembolism, intimal dissection, prolonged hypotension and prolonged balloon inflation. Persistent chest pain postprocedure was noted in 12.1% of cases. Minor or major ECG changes postprocedure were noted in 47.9% of patients with CK-MB elevation. In 32% of cases, more than one procedural complication was identified. Despite analysis of procedural complications, persistent chest pain and ECG changes, CK-MB elevation could only be predicted in 49% of cases. In the remaining 51% of cases, no apparent cause for elevated CK-MB elevation could be identified. The sensitivity for the prediction of CK-MB elevation by per-

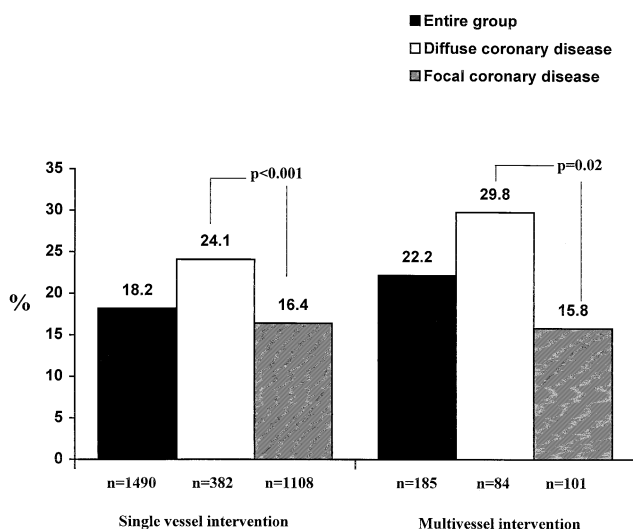


Figure 3. CK-MB elevation in relation to diffuse or focal coronary disease.

Table 2. Procedural Complications in CK-MB Elevation and Normal CK-MB Group

Complications*	Any CK-MB Elevation (n = 313)	Normal CK-MB (n = 1,362)	p Value
Side branch closure (%)	71 (22.7)	94 (6.9)	< 0.001
Slow flow/no reflow (%)	21 (6.7)	6 (0.4)	< 0.001
Coronary spasm	5 (1.6)	11 (0.8)	NS
Transient abrupt vessel closure (%)	14 (4.5)	8 (0.6)	< 0.001
Distal thromboembolism (%)	7 (2.2)	6 (0.4)	< 0.001
NHLBI dissection grade C-F (%)	9 (2.9)	15 (1.1)	0.01
Prolonged balloon inflation (%)	13 (4.2)	8 (0.6)	< 0.001
Prolonged hypotension (%)	7 (2.2)	7 (0.5)	< 0.002
Acute closure (%)	8 (2.5)	2 (0.1)	< 0.001
Stent thrombosis (%)	2 (0.6)	3 (0.2)	NS
Persistent chest pain postprocedure (%)	38 (12.1)	31 (2.3)	< 0.001

*In 32% of patients, more than one complication occurred.
NHLBI = National Heart, Lung, and Blood Institute.

sistent/recurrent chest pain was 28.6% and by ECG changes was 63.6%.

Multivariate predictors of CK-MB elevation. On multiple logistic regression analysis as shown in Table 3, CCS angina class III-IV, multivessel disease, diffuse coronary disease, systemic atherosclerosis, stent use and SVG intervention remained significant independent predictors of CK-MB release. Use of beta-blockers had a negative correlation on CK-MB release. Other factors such as female gender, diabetes mellitus, smoking, abciximab use, LAD location and PRCA use did not correlate with CK-MB elevation in our multivariate model.

Hospital course. In-hospital course of CK-MB elevation group is shown in Table 4. The overall incidence of major complications was 0.72%. In-hospital cardiac events were clustered mostly in the $>5\times$ CK-MB elevation group (n = 40) requiring prolonged postprocedure hospital stay. In this group there was a significantly higher incidence of arrhythmia

(20.5%; $p < 0.001$), CHF (36%; $p < 0.001$), persistent recurrent chest pain (60%; $p < 0.001$), repeat catheterization (36%; $p < 0.001$) and repeat intervention (17.7%; $p < 0.001$) compared with $>1-5\times$ normal CK-MB elevation group. In 25 of these 40 patients, pre- and postprocedure analysis of LV function was available, and mean decrease in LVEF was $12 \pm 9\%$ ($p < 0.01$), with $<5\%$ decrease in 18 patients (64%). Patients with low-to-medium CK-MB elevation ($1-5\times$ normal) had incidences of arrhythmia (2%), CHF (7%), recurrent chest pain (9%), repeat catheterization (8%) and repeat intervention (2%) similar to the normal CK-MB group. There were no early clinical events noted in patients waiting in-hospital for CK-MB levels to return to normal in the low-to-medium CK-MB elevation group. Repeat hospital admissions within one week from discharge occurred in 5.1% of $>5\times$ CK-MB-elevation patients, but were similar among $3-5\times$ normal CK-MB (1.7%), $1-3\times$ normal CK-MB (1.9%) and normal CK-MB (1.2%) group; $p = \text{NS}$.

Follow-up. During a mean follow-up of 13 ± 3 months (range 9 to 18 months), 5 deaths (4 cardiac, 1 noncardiac) have occurred in the CK-MB elevation group (1.6%) at a mean period of 212 days after discharge, as compared with 18 deaths (15 cardiac, 3 noncardiac) in the normal CK-MB group (1.3%) at a mean period of 246 days from discharge. This difference was not statistically significant ($p = 0.43$). There were three cardiac deaths (7.5%) in $>5\times$ normal CK-MB group ($p = 0.01$), one cardiac death (1.7%) in $3-5\times$ normal CK-MB group and one noncardiac death (0.5%) in $1-3\times$ normal CK-MB group. The observed incidence of death in $>5\times$ normal CK-MB group was significantly higher as compared with other groups ($p = 0.016$). There was a lower incidence of death in patients on beta-blockers at the time of intervention versus those who were not on beta-blocker therapy (0.78% vs. 1.74%; $p = 0.045$).

Table 3. Multivariate Predictors of CK-MB Elevation

Variables	Odds Ratio	95% CI	p Value
Female gender	1.02	0.92-1.11	0.8
CCS angina class III-IV	1.48	1.08-2.46	0.01
Beta-blocker therapy	0.71	0.58-0.92	0.001
Abciximab use	1.07	0.86-1.11	0.2
Multivessel disease	1.31	1.09-1.82	0.04
Systemic atherosclerosis	1.89	1.29-2.21	0.002
Diffuse coronary disease	1.41	1.09-1.98	0.02
ACC/AHA type C lesion	1.83	1.08-3.68	0.01
LAD vessel intervention	1.01	0.86-1.14	0.2
SVG intervention	2.21	1.12-4.11	0.0001
Stent use	1.26	0.98-1.84	0.04
PRCA use	1.04	0.92-1.26	0.1

ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; CI = confidence interval; LAD = left anterior descending artery; PRCA = percutaneous rotational coronary atherectomy; SVG = saphenous vein graft.

Table 4. In-Hospital Course and Adverse Cardiac Events in all Patients

Variables	CK-MB >5× (n = 40)	CK-MB 3-5× (n = 59)	CK-MB 1-3× (n = 214)	Normal CK-MB (n = 1,362)
Persistent/recurrent chest pain (%)	23 (57.5)†	7 (11.9)	19 (8.9)	122 (8.9)
ECG changes (%)	38 (95)†	43 (72.8)‡	69 (32.2)	86 (6.3)
Arrhythmia (%)	8 (20)†	1 (1.7)	5 (2.3)	28 (2)
Repeat cardiac catheterization (%)	14 (35)†	5 (8.5)	15 (7)	89 (6.5)
Repeat intervention (%)	7 (17.5)†	1 (1.7)	5 (2.3)	8 (0.6)
CHF (%)	14 (35)†	4 (6.8)	15 (7)	78 (5.7)
Hospital stay postprocedure, days*	5.8 ± 3.1†	2.8 ± 1.3	2.9 ± 1.1	2.6 ± 1.5

CHF = congestive heart failure; ECG = electrocardiogram.

*For patients after first four months of study. †p < 0.001 compared to other groups. ‡p < 0.01 compared to 1-3× elevation and normal CK-MB group.

DISCUSSION

Many studies have established that CK-MB elevation is more specific and sensitive for myocardial damage rather than total creatine phosphokinase elevation after MI and coronary intervention (22-25). The CK-MB isoenzyme could be released either from myocardial necrosis or profound ischemic injury with retention of cell viability (23). Several reports have shown that CK-MB elevation following coronary intervention is associated with higher late cardiac events of MI and death (7-10,26-28). Most of these data were in the era of PTCA. The CK-MB elevation during coronary interventional procedure is device dependent, and enzyme release is higher for nonballoon devices (11,29-31). Recent trials with newer devices have shown a higher incidence of CK-MB release with otherwise successful coronary interventions (12,32). The cause of CK-MB enzyme release is multifactorial and includes transient abrupt vessel closure, dissection, spasm, slow flow, distal thromboembolization, side branch closure, prolonged ischemia due to balloon inflation or prolonged hypotension (5,10,18,26,33,34). Side branch closure was the most frequent procedural complication noted in the CK-MB-elevation group and was significantly higher after stent use and in thrombotic lesions (5,35). Despite numerous minor procedural adverse events, CK-MB elevation has been shown to occur even in the absence of discernable complications. In the present study, procedural complications, prolonged/recurrent chest pain or ECG changes were observed in only 49% of cases with CK-MB elevation. In the remaining patients, CK-MB elevation was unsuspected and could not have been predicted after the procedure.

Correlation of CK-MB with new devices and survival.

In our study, CK-MB elevation was seen in 18.7% of procedures, which is similar to other published studies (5,7,10,27). Like other studies, CK-MB elevation was higher after nonballoon devices. In a report by Abdelmeguid et al. (10), minor CK-MB elevation in 4,484 patients at a mean follow-up of 36 ± 22 months had a worse long-term prognosis, but most of these patients underwent PTCA or directional coronary atherectomy. Ghazzal et al. (27) in a large study reported that CK-MB elevation post-PTCA

had a negative influence on survival, but only in patients with SVG interventions. Numerous recent studies of CK-MB elevation postprocedure involving new devices have reported a lack of correlation of CK-MB release on survival. Kugelmass et al. (11), using DCA and stents, reported CK-MB elevation in 64 of 558 patients (11.5%), and patients with low-to-medium CK-MB elevation had benign event-free survival on follow-up but in-hospital adverse events were not mentioned.

Similarly, Cutlip et al. (12) examined three randomized multicenter trials Balloon vs. Optional Atherectomy Trial (BOAT), STent Anti-thrombotic Regimen Study (STARS), Study to Determine Rotablator and Transluminal Angioplasty Strategy (STRATAS) of new devices involving 3,387 patients and reported the lack of association of CK-MB elevation and mortality at a mean follow-up of 15 ± 5 months. The lack of correlation of CK-MB elevation with mortality after new-device intervention despite its higher incidence as reported in the present study may be explained on the basis of achieving a stable large lumen, resulting in lower in-hospital events (≈1% major complications) and possible lower repeat revascularization. This is in accordance with studies reporting that a large postprocedure lumen independently correlates with better prognosis (11,30). Long-term data (three to five years) of present cohort and other studies will be required to establish convincingly the observed lack of correlation between mortality and low-to-medium CK-MB elevation after new devices. Also, it is possible that CK-MB elevation in this setting may represent ischemic injury with retention of cell viability rather than true myocardial necrosis (36). This is supported by the fact that in our study 18 of the 25 patients with >5 times CK-MB elevations and a pre- and postprocedure analysis of LV function revealed no significant decline (>5%) in LVEF. Moreover, patients with low-to-medium CK-MB elevation had no higher in-hospital adverse cardiac events compared with normal CK-MB patients.

CK-MB elevation after rotational atherectomy. Rotational atherectomy has traditionally been implicated in CK-MB elevation postprocedure. Our center performs

PRCA in a high percentage of interventions ($\approx 50\%$), and CK-MB elevation after PRCA (by univariate analysis only) was slightly higher than PTCA but lower than stent alone (35). This probably is attributed to technical advances in PRCA like slow burr advancement, short ablation runs, multiple burr approach and avoidance of hypotension during ablation (37).

CK-MB elevation and need for in-hospital monitoring.

In most of the previous studies, prolonged postprocedure hospital stay for observation and monitoring until CK-MB reached baseline was done and thereby increased the cost of intervention (7,11,28). Califf et al. (5) have suggested that patients with elevated CK-MB of $3\times$ normal after intervention should be managed like noninterventional, non-Q-wave MI patients. In our study, stable patients with low-to-medium CK-MB elevation were routinely discharged once CK-MB started declining and not necessarily returned to baseline without any apparent short-term adverse events. Therefore, prolonged hospital stay of low-to-medium CK-MB elevation patients may not be necessary and may result in significant cost savings.

Multivariate predictors of CK-MB elevation. Diffuse coronary disease, multivessel disease and systemic atherosclerosis correlated independently with CK-MB release. These data suggest that CK-MB elevation postprocedure may be a marker for diffuse atherosclerosis and thus might explain adverse prognosis as seen in some studies (9,10). Another important variable was stent use, perhaps due to a higher incidence of side branch occlusion in this group and distal microembolization of atheromatous debris by high-pressure balloon inflation (13,35). Our data are consistent with earlier studies reporting SVG intervention, unstable angina, ACC/AHA type C lesion and stent use correlating with CK-MB release (8-13). In the randomized trials, use of glycoprotein IIb/IIIa inhibitors have been shown to reduce CK-MB release, which was not observed in our study largely because of selective use of abciximab in high-risk coronary lesions (38,39).

One unique observation noted in our study was a protective effect of beta-blocker therapy at the time of intervention on CK-MB release as well a lower mortality at midterm follow-up. To our knowledge, this is the first report of the protective effects of beta-blocker therapy on CK-MB release after coronary intervention, and it may be explained largely on the basis of decreasing myocardial oxygen demand during intervention.

Study limitations. The present study needs to be interpreted with the following limitations. Only two sets of CK-MB values were routinely measured postprocedure, and it is possible that in some cases CK-MB might be elevated after 24 h of interventions. The number of patients discharged with declining but elevated CK-MB values are relatively small ($n = 162$) and a large cohort would be preferable. Some patients on beta-blocker therapy did not

take beta-blockers on the day of procedure but were nevertheless included for our analysis. Microembolization during intervention was not ruled out by any perfusion or physiologic flow studies. Although lesion length was measured visually with use of an on-line digital caliper in questionable cases, it is unlikely to bias our results as classification of focal versus diffuse coronary disease was done during the procedure before any postprocedure CK-MB values were obtained. Troponin, a more sensitive marker of myocardial necrosis, was not measured in the present study because of its unavailability at our center until July 1998 (40). Another important limitation of the present study is duration of follow-up (13 ± 3 months), and it is possible that mortality curves between CK-MB elevation and normal CK-MB groups may diverge after three years of follow-up. However, long-term follow-up of these patients is ongoing.

Conclusions and study implications. The present study shows a close association between markers of diffuse coronary atherosclerosis and CK-MB elevation after otherwise successful coronary intervention as well as lack of an apparent adverse effect of low-to-medium CK-MB elevation on in-hospital course and midterm survival. Our data suggest that early discharge of uncomplicated CK-MB-elevation ($1-5\times$ normal) patients despite elevated values is safe and may be cost-effective. The effect of CK-MB elevation after nonballoon devices on long-term follow-up requires further evaluation. Finally, a randomized trial of preintervention beta-blocker use to prevent CK-MB elevation after percutaneous coronary intervention may be warranted.

Reprint requests and correspondence: Dr. Samin K. Sharma, Mount Sinai Hospital, Box 1030, One Gustave L. Levy Place, New York, New York 10029-6574. E-mail: samin_sharma@smtplink.mssm.edu

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