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# Differential Mortality Risk of Postprocedural Creatine Kinase-MB Elevation Following Successful Versus Unsuccessful Stent Procedures

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**OBJECTIVES** This study was designed to evaluate the effect of periprocedural myocardial infarction (MI) on mortality according to success of the stent procedure.

**BACKGROUND** The mortality effect of periprocedural MI relative to successful versus unsuccessful procedures has not been examined.

**METHODS** All-cause mortality during the first year was evaluated prospectively among 5,850 patients from coronary stent clinical trials. Myocardial infarction was classified according to creatine kinase-MB level as type 1 (>1 but <3 times normal), type 2 (≥3 but ≤8 times normal), or type 3 (>8 times normal or Q-wave MI). Procedures were classified as successful unless there was a final diameter stenosis >50%; final Thrombolysis In Myocardial Infarction flow grade <3; final National Heart, Lung, and Blood Institute dissection grade ≥D; repeat revascularization within 24 h; or stent thrombosis within 24 h.

**RESULTS** Myocardial infarction was more frequent after unsuccessful procedures (69.6% vs. 20.4%, $p < 0.001$). Mortality during the first year was higher in patients with MI (2.8% vs. 1.7%, $p = 0.01$), but the effect was significant only for type 3 MI (4.7% vs. 1.7%, $p = 0.008$). Moreover, the mortality difference for any MI was confined to patients with unsuccessful procedures (13.1% vs. 0%, $p = 0.03$), with no significant effect among patients with otherwise successful procedures (2.1% vs. 1.7%, $p > 0.20$). The independent predictors of mortality were unsuccessful procedure ($p < 0.001$), diabetes mellitus ($p = 0.001$), history of prior MI ($p = 0.003$), multivessel disease ($p = 0.006$), and advancing age ($p < 0.001$), but not periprocedural MI.

**CONCLUSIONS** The association of periprocedural MI with increased mortality during the first year following stent placement was confined to patients with unsuccessful procedures. (J Am Coll Cardiol 2004;44:1210–4) © 2004 by the American College of Cardiology Foundation

The incidence of creatine kinase-MB (CK-MB) isoenzyme elevation after percutaneous coronary intervention (PCI) ranges from 11% to 35% (1,2), including low-level elevations (<3 times normal) with no associated signs or symptoms as well as large non–Q-wave (CK-MB >8 times normal) and Q-wave myocardial infarction (MI). Whereas the deleterious effect on survival of large periprocedural MIs has been well documented (3), the clinical impact of isolated CK-MB elevation following otherwise successful procedures remains controversial. Some studies have reported that mild to moderate CK-MB elevation after interventional procedures has no adverse clinical consequences (1–3), whereas others have found that even minimal elevations are associated with increased mortality (4–6). Many of these studies, however, had methodologic limitations, including retrospective analysis, incomplete ascertainment of CK-MB data, or failure to control for potentially confounding covariates. One potential confounder is the success of the procedure itself, and the fundamental question remains whether isolated enzyme elevation after "otherwise successful" procedures has an independent impact on subsequent survival (7).

Unsuccessful procedures may result from angiographic complications occurring during the procedure, such as severe dissections associated with impaired flow and/or acute vessel closure, or from early clinical events such as stent thrombosis. Any of these failure modes may be associated with periprocedural MI and thus severely confound analyses of effect on subsequent mortality.

We hypothesized that periprocedural MI would have significantly different effects on early survival after coronary stenting, depending on success of the index procedure.

## METHODS

**Patient population.** Patients enrolled in six major clinical trials of native coronary artery stenting with relatively homogenous inclusion criteria and study protocols were eligible. The details of the study protocols and justification for pooling have been previously reported (8). Briefly, the population included 6,186 patients who underwent stenting of 6,219 native target vessels. All of the studies utilized the same angiographic core laboratory, and all CK-MB elevations were reviewed by an independent clinical events committee, classifying MIs according to a previously re-

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**Abbreviations and Acronyms**

CK-MB = creatine kinase-MB
MI = myocardial infarction
PCI = percutaneous coronary intervention

ported MI classification scheme (9). Patients with baseline CK or CK-MB elevation or with clinical evidence of acute MI (n = 117) were classified as having a preprocedure MI and were excluded from this analysis. Patients in whom CK data were incomplete (missing CK and/or CK-MB before PCI, after PCI, or both; n = 219 [3.6%]) were also excluded, leaving 5,850 patients (5,880 treated lesions) for analysis.

**Cardiac enzyme determination and myocardial infarction classification.** Creatine kinase and CK-MB measurements were made preprocedure, 6 to 12 h postprocedure, and at the earlier of 24 h postprocedure or hospital discharge. The Q-wave MI was defined as the development of new pathologic Q waves (at least one mV in depth and 40 ms in duration) in two or more contiguous leads. Myocardial infarction was then classified as follows:

Type 1: CK-MB >1 and <3 times normal (total CK >1 and ≤2 times normal if CK-MB data missing) in the absence of new Q waves.

Type 2: CK-MB ≥3 and ≤8 times normal (total CK >2 and ≤3 times normal if CK-MB data missing) in the absence of new Q waves.

Type 3: New Q-wave MI assessed with CK-MB >1 times normal or CK-MB >8 times normal (total CK >3 times normal if CK-MB not available).

**Study definitions.** The primary outcome was cumulative all-cause mortality. Procedures were considered unsuccessful if final diameter stenosis was >50%; final Thrombolysis In Myocardial Infarction flow grade was <3; final National Heart, Lung, and Blood Institute dissection was grade ≥D; or if the patient developed stent thrombosis or required urgent repeat revascularization within 24 h.

**Statistical methods.** Analyses were performed using SAS for Windows version 6.12 (SAS Institute, Cary, North Carolina). Continuous variables were expressed as mean ± SD and were compared using analysis of variance. Discrete variables were expressed as proportions and were compared using chi-square statistics. The effects of baseline clinical and angiographic variables as well as of procedural MI and procedural success on mortality were assessed using Cox proportional hazards regression. One-year mortality was evaluated using Kaplan-Meier survival analysis and compared using the log-rank statistic. Results were considered statistically significant at $p < 0.05$.

## RESULTS

**Baseline patient and lesion characteristics.** Tables 1 and 2 show baseline patient and lesion characteristics. Patients who sustained a periprocedural MI were slightly older and were more likely to have had a prior MI, unstable angina presentation, multivessel disease, and de novo lesions treated. Pretreatment lesion length was also significantly longer for MI patients and was progressively longer for each higher MI classification.

**Incidence of myocardial infarction and relationship to procedure success.** Of the 5,850 patients, 1,248 (21.3%) sustained a periprocedural MI, including 738 (12.6%) type 1, 356 (6.1%) type 2, and 154 (2.6%) type 3 MI. Using the study definition, the procedure was unsuccessful in 115 (2.0%) patients. Figure 1 demonstrates the significant difference in MI frequency according to procedure success. Of note, although the MI rate was 20.4% after successful procedures, it was significantly higher after unsuccessful procedures (69.6%, $p < 0.0001$), with a greater difference for the larger type 3 MIs (32.2% vs. 2.0%, $p < 0.0001$). Type 3 MIs thus accounted for only 10% of all MIs after a successful procedure, compared with 46% of the MIs seen after an unsuccessful procedure.

**Mortality.** The follow-up duration was 300 ± 90 days. Overall unadjusted mortality was 1.9% and was significantly

**Table 1.** Baseline Patient Characteristics

| | No MI (n = 4,602) n (%) | Type 1 (n = 738) n (%) | Type 2 (n = 356) n (%) | Type 3 (n = 154) n (%) | p Value |
|---|---|---|---|---|---|
| Age, yrs (mean ± SD) | 62 ± 11 | 64 ± 11 | 64 ± 11 | 63 ± 12 | <0.001 |
| Female | 1,394 (30.3) | 233 (31.6) | 119 (33.4) | 51 (33.1) | >0.20 |
| Previous MI | 1,494 (33.1) | 268 (36.8) | 122 (34.7) | 66 (43.1) | 0.02 |
| Current smoking | 1,001 (21.8) | 162 (22.0) | 62 (17.4) | 32 (20.8) | >0.20 |
| Dyslipidemia* | 1,936 (42.8) | 293 (40.2) | 133 (37.6) | 60 (39.7) | 0.15 |
| Diabetes mellitus | 988 (21.5) | 135 (18.3) | 75 (21.1) | 28 (18.2) | 0.19 |
| Hypertension | 2,614 (57.2) | 436 (59.6) | 227 (63.8) | 90 (58.4) | 0.08 |
| Previous CABG | 394 (8.6) | 70 (9.5) | 30 (8.4) | 16 (10.4) | >0.20 |
| Restenosis | 555 (12.1) | 61 (8.3) | 29 (8.2) | 15 (9.7) | 0.004 |
| Multivessel disease | 1,496 (32.5) | 267 (36.2) | 139 (39.0) | 66 (42.9) | 0.002 |
| Unstable angina | 1,943 (42.2) | 295 (40.0) | 167 (46.9) | 77 (50.0) | 0.04 |
| Ejection fraction, % (mean ± SD) | 56 ± 11 | 55 ± 11 | 56 ± 12 | 57 ± 11 | >0.20 |

*Defined as total cholesterol >200 mg/dl or on lipid-lowering therapy. The p values reflect a comparison across the four groups of no MI and the three MI classes.
CABG = coronary artery bypass grafting; MI = myocardial infarction.

**Table 2.** Baseline Angiographic and Procedural Characteristics

| | No MI (n = 4,621) | Type 1 (n = 744) | Type 2 (n = 359) | Type 3 (n = 156) | p Value |
|---|---|---|---|---|---|
| Target vessel | | | | | |
| Left main, n (%) | 17 (0.4) | 2 (0.3) | 0 | 0 | 0.001 |
| LAD, n (%) | 1,912 (41.4) | 305 (41.0) | 151 (42.1) | 59 (37.8) | |
| LCX, n (%) | 919 (19.9) | 192 (25.8) | 102 (28.4) | 43 (27.6) | |
| RCA, n (%) | 1,773 (38.4) | 245 (32.9) | 106 (29.5) | 54 (34.6) | |
| Vessel diameter, mm, mean ± SD | 2.98 ± 0.51 | 2.95 ± 0.51 | 2.98 ± 0.53 | 2.99 ± 0.54 | >0.20 |
| Preprocedure MLD, mm, mean ± SD | 1.04 ± 0.44 | 1.03 ± 0.38 | 1.01 ± 0.43 | 0.96 ± 0.41 | >0.20 |
| Postprocedure MLD, mm, mean ± SD | 2.82 ± 0.43 | 2.78 ± 0.44 | 2.80 ± 0.46 | 2.70 ± 0.55 | 0.004 |
| Lesion length, mm, mean ± SD | 12.6 ± 6.8 | 13.4 ± 7.3 | 14.5 ± 8.0 | 15.0 ± 8.5 | <0.001 |
| Implanted stent length, mm, mean ± SD | 20.9 ± 10.8 | 23.8 ± 13.4 | 25.6 ± 15.8 | 31.9 ± 24.6 | <0.001 |
| Glycoprotein IIb/IIIa inhibitor, n (%) | 355 (7.7) | 54 (7.3%) | 35 (9.8%) | 22 (14.3) | 0.01 |

p value reflects a chi-square statistic comparing no MI and the three MI classes. The p values reflect a comparison across the four groups of no MI and 3 MI classes.
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MI = myocardial infarction; MLD = minimum lumen diameter; RCA = right coronary artery.

higher among patients with periprocedural MI compared with those without (Fig. 2). There was a suggestion of higher mortality with increasing MI type, but only type 3 MI demonstrated significantly higher mortality compared with patients with no MI (4.7% vs. 1.7%, p = 0.008). Moreover, the adverse effect of any MI on mortality was confined to patients who had unsuccessful procedures. When analysis was restricted to patients with successful procedures, mortality was similar for those with or without MI (2.1% vs. 1.7%, p > 0.20) and by MI type. Survival curves for MI types and those with no MI over the first year are shown in Figure 3A for the overall group and in Figure 3B for patients with otherwise successful procedures.

The independent predictors of mortality are shown in Table 3. Neither MI versus no MI or any MI type was significantly associated with mortality after adjustment for an unsuccessful procedure or in an analysis restricted to successful patients.

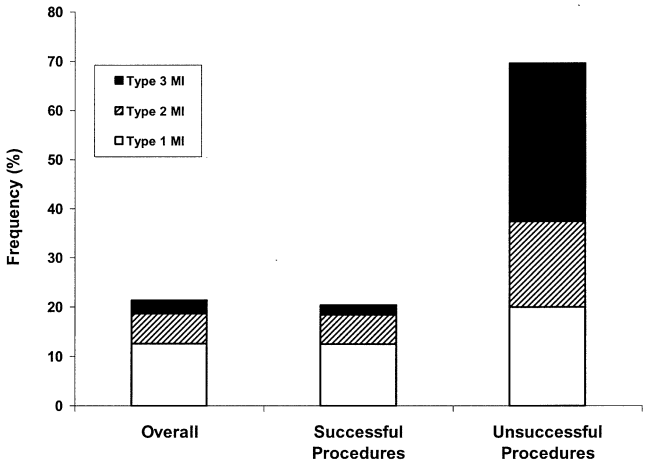


**Figure 1.** Incidence of periprocedural myocardial infarction by type (type 1 = creatine kinase-MB [CK-MB] isoenzyme >1 but <3 times normal; type 2 = CK-MB elevation ≥3 but ≤8 times normal; type 3 = >8 times normal or Q-wave myocardial infarction) after coronary intervention in patients with successful and unsuccessful procedures.

## DISCUSSION

This prospective study of 5,850 patients undergoing bare metal coronary stenting is the first analysis of the differential impact of periprocedural MI on mortality during the first year relative to procedure success. The results demonstrate that the association of MI with mortality during this interval is limited to those patients with clearly defined and evident unsuccessful procedures. Indeed, the association of an unsuccessful procedure with MI carries an ominous prognosis. In contrast, successful procedures with or without procedural MI and unsuccessful procedures without associated CK-MB elevation have excellent early survival.

**Comparison with other studies.** Previous studies on the clinical significance of elevated cardiac markers after PCI have produced a spectrum of results (2,3,6,9). Few question the importance of large periprocedural MI, but the inconsistency of data for an association of mortality with lower level CK-MB elevation has nurtured an ongoing debate whether enzyme elevation after otherwise successful PCI actually affects survival.

At least part of the confusion arises from inadequate

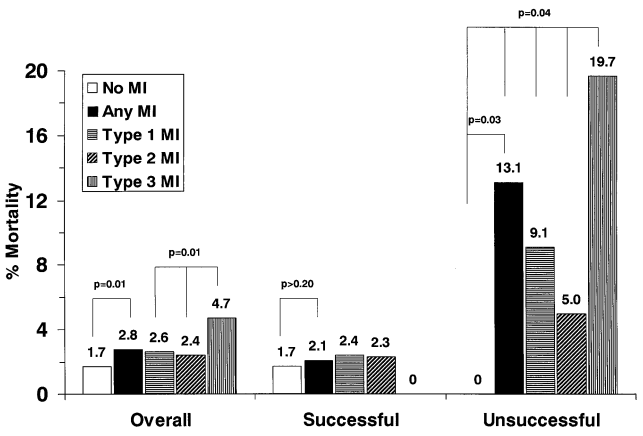


**Figure 2.** Mortality among patients with and without periprocedural myocardial infarction (MI) by type (definitions as in Figure 1) and for successful and unsuccessful procedures.

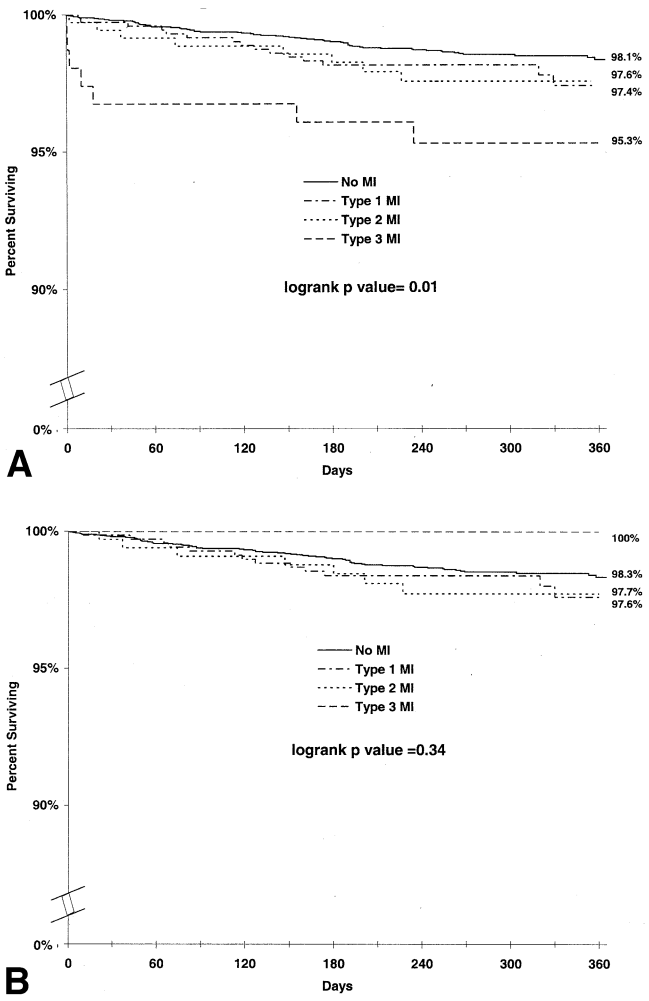


**Figure 3.** Kaplan-Meier estimates of survival among all patients with and without periprocedural myocardial infarction by type (**A**, definitions as in Figure 1) and for those with successful procedures only **(B)**. MI = myocardial infarction.

definition of unsuccessful procedures and thus inability to appropriately adjust outcome data. For example, a recent meta-analysis of seven studies suggested a significant progressive dose-response relationship between CK-MB elevations and subsequent mortality (10). Unfortunately, three of the studies used for this analysis did not adjust for procedure success and two others excluded only patients who died or required emergency bypass surgery. Moreover, one of these studies included patients with abrupt closure or large spontaneous preprocedure MI among the cardiac deaths at one year, accounting for 4 of 13 deaths (11). In another case-control study, 17% of periprocedural MI patients had final Thrombolysis In Myocardial Infarction coronary flow grade <3 (5). It is unlikely that the prognostic value of periprocedural MI in such patients with unsuccessful procedures can be extended to patients who have an isolated CK-MB elevation after an otherwise successful intervention.

The current study highlights the interaction of procedure success with the relationship of periprocedural MI and mortality during the first year. Similar to a recent report by Stone et al. (3), the effect on unadjusted early mortality in our study was significant only after large MI. The difference in our study is the adjustment for unsuccessful procedures and the demonstration that these large MIs are almost always associated with clearly recognizable angiographic complications or early clinical events rather than otherwise successful procedures (7).

**MI after successful PCI and mortality association.** The 0.4% risk attributable to MI after successful procedures was not statistically significant in our study, but this does not exclude a potential clinical difference. It is also possible that more effect would be seen beyond one year, as noted in other studies (4). This has focused attention on periprocedural CK-MB elevation as a marker for other causes of mortality, with diffuse atherosclerosis the leading contender for such an explanation (12). Failed microvascular perfusion, which has been shown to have an imperfect correlation with CK-MB elevation and a significant association with early and late clinical outcomes, may provide another (13). Our study suggests that in the first year these contributions are small relative to those resulting from more easily identified unsuccessful procedures.

**Table 3.** Cox Proportional Hazards Results for One-Year Mortality

| Variable | Hazard Ratio | 95% Confidence Interval |
|---|---|---|
| All patients (n = 5,850) | | |
| Any procedural MI* | 1.33 | 0.85–2.07 |
| Unsuccessful procedure | 5.63 | 2.87–11.04 |
| Age (per yr) | 1.06 | 1.04–1.08 |
| Diabetes | 2.00 | 1.32–3.03 |
| Prior MI | 1.83 | 1.23–2.74 |
| Multivessel disease | 1.77 | 1.18–2.66 |
| Successful patients (n = 5,735) | | |
| Any procedural MI* | 0.95 | 0.70–1.30 |
| Age (per yr) | 1.06 | 1.04–1.08 |
| Diabetes | 2.07 | 1.34–3.22 |
| Prior MI | 1.86 | 1.21–2.84 |
| Multivessel disease | 1.71 | 1.11–2.62 |

Data presented with any myocardial infarction (MI) versus no MI forced into the model. *Neither "any MI" versus "no MI" or "MI type" as a dummy variable was significant.

**Clinical implications.** It is intuitive that no MI should be considered inconsequential, and available options to avoid all procedural MIs should be exercised. Our study directs attention to the special importance of these events in the setting of recognizable angiographic and early clinical complications. Given that these complications cannot always be predicted, therapies shown to reduce periprocedural MI and angiographic complications, such as glycoprotein IIb/IIIa inhibitors, should perhaps be considered routinely (14–16).

Finally, what should we tell patients who sustain CK-MB elevation despite these efforts and otherwise have a successful procedure? Our results show that these patients are not at significantly higher risk of death in the next year and additional monitoring or specific pharmacologic management is probably not indicated. Their mortality risk is determined more by other factors, such as previous spontaneous MI, baseline left ventricular dysfunction, presence of diabetes, and multivessel disease, and therapy should be directed at secondary prevention of recurrent events.

**Study limitations.** Although provocative, our study has several limitations. It represents a pooled analysis of multiple PCI trials involving coronary stenting of lower risk patients; the results thus may not be generalizable to other populations with higher baseline risk. The studies pooled for this analysis were conducted before widespread use of glycoprotein IIb/IIIa inhibitors, so the effect of these agents on outcomes cannot be evaluated. Clinical follow-up was limited to the first year after the procedure. Longer follow-up may show a more significant association of periprocedural MI and mortality regardless of procedure success, but it would still be uncertain whether the effect of periprocedural MI is causal or confounded by other clinical factors.

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