Minor Myocardial Damage and Prognosis
Are Spontaneous and Percutaneous Coronary Intervention–Related Events Different?

K. Martijn Akkerhuis, MD; John H. Alexander, MD; Barbara E. Tardiff, MD; Eric Boersma, PhD; Robert A. Harrington, MD; A. Michael Lincoff, MD; Maarten L. Simoons, MD

Background—The relevance of the adverse prognostic implications of CK-MB elevation after percutaneous coronary intervention (PCI) remains controversial. Therefore, we compared the relationship between the level of postprocedural CK-MB elevation and 6-month mortality in patients undergoing PCI with the relationship between the level of spontaneous, non–PCI-related CK-MB elevation and 6-month mortality in patients with acute coronary syndromes (ACS) treated medically.

Methods and Results—In the PURSUIT trial, 5583 of 9461 patients who presented with a non–ST-elevation ACS did not undergo PCI or CABG and had at least 1 CK-MB sample collected during index-hospitalization. There was a gradual increase in 6-month mortality with higher CK-MB levels: 4.1%, 8.6%, 9.0%, 14.3%, 15.5% for CK-MB ratios 0 to 1, >1 to 3, >3 to 5, >5 to 10, and >10 times the upper limit of normal. A combined analysis in 8838 patients undergoing PCI in 5 large, clinical trials revealed a proportional relationship between postprocedural CK-MB levels (≤48 hours after PCI) and 6-month mortality. In patients with CK-MB ratios 0 to 1, >1 to 3, >3 to 5, >5 to 10, and >10, the risk of death was 1.3%, 2.0%, 2.3%, 4.3%, and 7.4%, respectively. The absolute mortality rates were lower after procedure-related infarcts compared with spontaneous infarcts. Yet, the relative increase in 6-month mortality with each increase in peak CK-MB level was similar for PCI-related myocardial necrosis and spontaneous myocardial necrosis, as all tests for heterogeneity of the odds ratios were nonsignificant.

Conclusions—The present analysis indicates that the adverse prognostic implications of periprocedural myocardial necrosis should be considered similar to the adverse consequences of spontaneous myocardial necrosis. (Circulation. 2002;105:554-556.)

Key Words: angioplasty • creatine kinase • myocardial infarction • prognosis

Creatine kinase (CK) or CK-MB isoenzyme elevations occur in 5% to 30% of patients undergoing percutaneous coronary intervention (PCI).1–4 Multiple studies have shown a proportional relationship between the level of postprocedural CK-MB elevation and the risk of adverse outcome during follow-up, even in patients with an otherwise apparently uncomplicated and successful intervention and after adjustment for other prognostic factors2–5; however, the clinical significance of asymptomatic PCI-related cardiac enzyme elevation remains controversial. In contrast, the prognostic significance of (small) myocardial infarctions (MI) occurring spontaneously in the setting of unstable angina or after acute MI has been well established.6,7

We evaluated whether the adverse prognostic implications of PCI-related myocardial necrosis are similar to those of spontaneous, non–procedure-related myocardial necrosis. Therefore, we compared the relationship between the level of postprocedural CK-MB elevation and 6-month mortality in 8838 patients undergoing PCI with the relationship between the level of spontaneous, non–PCI-related CK-MB elevation and 6-month mortality in 5583 patients with acute coronary syndromes treated medically.

Methods and Results
Prognostic Significance of CK-MB Elevation in Acute Coronary Syndromes
The relationship between peak CK-MB level and 6-month mortality in patients with acute coronary syndromes treated medically was evaluated in a retrospective analysis of data from the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial.8 PURSUIT compared the glycoprotein IIb/IIIa inhibitor eptifibatide with placebo in addition to standard therapy in 9461 patients with unstable angina or evolving MI without persistent ST-elevation.6

The study group for this analysis consisted of the 5583 PURSUIT patients who did not undergo PCI or coronary artery bypass grafting

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Prognostic Significance of CK-MB Elevation After PCI

The prognostic significance of CK-MB elevation after PCI was assessed in retrospective analyses of data from the IMPACT-II (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II) and PURSUIT trials, as well as from a combined analysis of the CAPTURE (c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina), EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications), and EPILOG (Evaluation in Unstable Refractory Angina), EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications), and EPILOG (Evaluation in Unstable Refractory Angina) trials.3,4,6 The protocols and results of the studies have been published.3,4,6 In brief, CAPTURE, EPIC, and EPILOG were large, randomized trials evaluating the glycoprotein IIb/IIIa inhibitor abciximab in patients undergoing PCI for a variety of indications.4,6 The IMPACT-II trial evaluated eptifibatide in patients scheduled for elective, urgent, or emergency PCI.1 A similar analysis was done in the subgroup of PURSUIT patients who underwent PCI in the first 30 days after randomization and had at least one CK-MB sample collected during the index-hospitalization. Mortality at 6 months was assessed in 5 groups of patients who were stratified by peak CK-MB level at the index hospitalization (0 to 1, >1 to 3, >3 to 5, >5 to 10, or >10 times the upper limit of normal).

There was a gradual increase in 6-month mortality with higher peak CK-MB levels: 4.1%, 8.6%, 9.0%, 14.3%, and 15.5% for CK-MB ratios 0 to 1, >1 to 3, >3 to 5, >5 to 10, and >10 times the upper limit of normal, respectively.

The relative increase in 6-month mortality with each increase in peak CK-MB level was however similar for myocardial necrosis occurring spontaneously in the setting of acute coronary syndromes (Figure), as all tests for heterogeneity of the odds ratios were nonsignificant (Table). Similarly, there was no heterogeneity in the adverse prognostic implications of myocardial necrosis within each peak CK-MB category between glycoprotein IIb/IIIa inhibitor–treated patients and those receiving placebo (as represented by the odds ratios).

Discussion

This analysis in 8838 patients undergoing PCI for a variety of indications demonstrates that the risk of death at 6-month follow-up is directly proportional to the level of periprocedural CK-MB elevation. The most important message, however, is that, although the absolute mortality rates differed between the two study groups, the relative increase in 6-month mortality with each increase in peak CK-MB level was similar for myocardial necrosis occurring spontaneously in the setting of acute coronary syndromes and PCI-related (CABG) after randomization and had at least one CK-MB sample collected during the index-hospitalization. Mortality at 6 months was assessed in 5 groups of patients who were stratified by peak CK-MB level at the index hospitalization (0 to 1, >1 to 3, >3 to 5, >5 to 10, or >10 times the upper limit of normal).

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**Mortality at 6-Month Follow-Up Stratified by Peak CK-MB Level**

<table>
<thead>
<tr>
<th>Peak CK-MB Category</th>
<th>Spontaneous CK-MB Elevation (n=5583)</th>
<th>PCI-related CK-MB Elevation (n=8838)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>CK-MB 0–1×ULN</td>
<td>2658</td>
<td>108 (4.1)</td>
</tr>
<tr>
<td>CK-MB &gt;1–3×ULN</td>
<td>1567</td>
<td>134 (8.6)</td>
</tr>
<tr>
<td>CK-MB &gt;3–5×ULN</td>
<td>498</td>
<td>45 (9.0)</td>
</tr>
<tr>
<td>CK-MB &gt;5–10×ULN</td>
<td>461</td>
<td>66 (14.3)</td>
</tr>
<tr>
<td>CK-MB &gt;10×ULN</td>
<td>399</td>
<td>62 (15.5)</td>
</tr>
</tbody>
</table>

Odds ratios (OR) with 95% confidence intervals (CI) for risk of death at 6 months in each peak creatine kinase (CK)-MB category relative to risk in category without CK-MB elevation (CK-MB 0–1×upper limit of normal (ULN)). Breslow-Day indicates Breslow-Day test for heterogeneity of the odds ratio of PCI-related CK-MB elevation vs the odds ratio of spontaneous CK-MB elevation within each peak CK-MB enzyme category (P).

The relative increase in 6-month mortality with each increase in peak CK-MB level was however similar for myocardial necrosis occurring spontaneously in the setting of acute coronary syndromes (Figure), as all tests for heterogeneity of the odds ratios were nonsignificant (Table). Similarly, there was no heterogeneity in the adverse prognostic implications of myocardial necrosis within each peak CK-MB category between glycoprotein IIb/IIIa inhibitor–treated patients and those receiving placebo (as represented by the odds ratios).

**Discussion**

This analysis in 8838 patients undergoing PCI for a variety of indications demonstrates that the risk of death at 6-month follow-up is directly proportional to the level of periprocedural CK-MB elevation. The most important message, however, is that, although the absolute mortality rates differed between the two study groups, the relative increase in 6-month mortality with each increase in peak CK-MB level was similar for myocardial necrosis occurring spontaneously in the setting of acute coronary syndromes and PCI-related (CABG) after randomization and had at least one CK-MB sample collected during the index-hospitalization. Mortality at 6 months was assessed in 5 groups of patients who were stratified by peak CK-MB level at the index hospitalization (0 to 1, >1 to 3, >3 to 5, >5 to 10, or >10 times the upper limit of normal).
myocardial necrosis. The higher absolute mortality rate within each peak CK-MB category among the acute coronary syndrome patient population with spontaneous myocardial necrosis, as well as the distribution of patients across the 5 peak CK-MB categories, might be explained by the fact that patients presenting with an acute coronary syndrome represent a population at high risk of thrombotic complications due to acute (and ongoing) intracoronary thrombosis, whereas more elective and low-risk patients were included in the PCI cohort. This was also apparent in the differences in baseline variables known to be important predictors of mortality.

As MI is defined as myocardial cell death that results in the release of specific biomarkers into the circulation, the present findings imply that any abnormal elevation of specific cardiac biomarkers, whether associated with PCI and regardless of magnitude, should be interpreted as myocardial necrosis. Most PCI-related infarcts are small and result from microemboli from the atherosclerotic plaque that has been disrupted during angioplasty or from thrombus particles. As these small infarcts do not impair myocardial function, pathophysiological mechanisms other than heart failure may explain the impaired prognosis associated with periprocedural myocardial necrosis. It is conceivable that microinfarcts provide a nidus for ventricular arrhythmias via a microreentry or a focal mechanism. Indeed, previous studies have demonstrated the association between small PCI-related infarcts and subsequent sudden death. Furthermore, myocardial necrosis occurring during the procedure may be an expression of vascular instability. It is likely that patients who develop coronary emboli and small infarcts during PCI have atherosclerotic lesions that are apparently unstable and continue to represent a substrate for plaque rupture with subsequent thrombosis resulting in adverse events such as MI or sudden death. Although this study underscores the adverse prognostic implications of periprocedural myocardial necrosis, it has certain limitations. A small proportion of patients with myocardial infarction before PCI may have been misidentified as having periprocedural myocardial necrosis, although patients in the PCI cohort were excluded from analysis if they had elevated CK-MB values before PCI. Furthermore, techniques of percutaneous revascularization have evolved since completion of the PCI trials in which the majority of the patients underwent balloon angioplasty. The use of intracoronary stents portends a higher risk of periprocedural myocardial necrosis although mortality is lower. Therefore, the incidence and prognostic implications of periprocedural myocardial necrosis need to be studied further in the current era of percutaneous coronary revascularization. Finally, the longest common period of follow-up was 6 months. Accordingly, further studies are needed to evaluate the longer-term consequences of periprocedural myocardial necrosis.

The present analysis indicates that the adverse prognostic implications of periprocedural myocardial necrosis should be considered similar to the adverse consequences of spontaneous myocardial necrosis. The results further support the need for systematic assessment of cardiac markers after PCI and validate the inclusion of periprocedural myocardial necrosis in clinical trial endpoints. Finally, treatment strategies that limit periprocedural myocardial necrosis are warranted in patients undergoing PCI.

References
