Differential Impact on Survival of Electrocardiographic Q-Wave Versus Enzymatic Myocardial Infarction After Percutaneous Intervention
A Device-Specific Analysis of 7147 Patients

Gregg W. Stone, MD; Roxana Mehran, MD; George Dangas, MD; Alexandra J. Lansky, MD; Ran Kornowski, MD; Martin B. Leon, MD

Background—The relative prognostic importance of ECG myocardial infarction (MI) after intervention compared with varying degrees of enzymatic elevation has not been characterized, and the device-specific implications of periprocedural MI are also unknown.

Methods and Results—Serial creatine phosphokinase (CPK)-MB levels were determined after elective percutaneous intervention of 12,098 lesions in 7147 consecutive patients at a tertiary referral center. Procedural, in-hospital, and follow-up data were collected by independent research nurses, and clinical and ECG events were adjudicated by a separate committee. Stents were implanted in 50.6% of lesions, atheroablation was performed in 54.8%, and PTCA alone was performed in 9.8%. The peak periprocedural CPK-MB level was ≥3× the upper limit of normal (ULN) in 17.9% of patients, and Q-wave MI developed in 0.6%. By multivariate analysis, the periprocedural development of new Q waves was the most powerful independent determinant of death (2-year mortality rate, 38.3%; hazard ratio, 9.9; P<0.0001). Non–Q-wave MI with CPK-MB >8×ULN was also a strong predictor of death (2-year mortality rate, 16.3%; hazard ratio, 2.2; P<0.0001); survival was unaffected by lesser degrees of CPK-MB elevation. Though CPK-MB elevation was more common after atheroablation and stenting than PTCA, the rates of Q-wave MI and survival were device-independent.

Conclusions—Myonecrosis after percutaneous intervention is common in a high-risk referral population dominated by atheroablation and stent use. Large periprocedural infarctions (signified by new Q waves and CPK-MB >8×ULN) are powerful determinants of death, whereas lesser degrees of CPK-MB release and specific device use do not adversely affect survival. (Circulation. 2001;104:642-647.)

Key Words: angioplasty ■ stents ■ complications

Creatine phosphokinase (CPK)-MB elevation after interventional procedures has been associated with increased rates for early and late death in most1–7 but not all8–10 prior studies. Although it is generally agreed that periprocedural CPK-MB release does indeed represent myocardial necrosis,11 earlier reports have not systematically addressed 2 important issues: (1) What is the prognostic significance of major ECG evidence of periprocedural myocardial infarction (MI) compared with enzymatic myonecrosis? (2) Does the relative importance of periprocedural MI vary with device selection? This latter query is especially relevant because the frequency of CPK-MB elevation may vary with device choice.1,8–10

To evaluate the device-specific relation between periprocedural enzymatic and ECG infarction on subsequent outcome, we prospectively initiated routine collection of serial CPK-MB determinations in all patients undergoing percutaneous intervention since 1994 at a tertiary referral practice and established independent research data collection pathways and ECG and clinical event adjudication committees. The present study reports the principal analysis from this database.

Methods

Study Population
The study population was drawn from 10,315 consecutive patients undergoing none emergent percutaneous intervention at the Washington Hospital Center in whom CPK-MB levels were routinely assessed after the procedure. Since 1994, CPK-MB levels were systemically evaluated at baseline, 8 to 12 hours, and 16 to 24 hours after all interventional procedures. If either postprocedure value was
Categorical variables were compared by \( \chi^2 \) analysis or Fisher’s exact test. Continuous variables are presented as mean±SD and were compared by Student’s \( t \) test or Mann-Whitney U test. All probability values are 2-tailed. The independent predictors of periprocedural MI (defined as CPK-MB >3 normal or the development of Q-wave infarction) and correlates of in-hospital death were examined by stepwise logistic regression. Late death stratified by the presence or absence of Q waves and peak CPK-MB after the index procedure was analyzed with actuarial methods and displayed as Kaplan-Meier curves. Before analysis, it was prespecified that non-Q-wave MI would be stratified into the following categories by peak CPK-MB level: normal, 1 to 3× normal, 3 to 5× normal, 5 to 8× normal, and >8× normal.

The influence of baseline variables on late survival was evaluated with the log rank test. Cox proportional hazards regression was then used to determine the independent predictors of late death. The baseline and procedural variables entered in the multivariate models included age, sex, hypertension, diabetes, hypercholesterolemia, current cigarette smoking, renal insufficiency (serum creatinine ≥2.0 mg/dL), angina class, history of angioplasty, prior bypass surgery or prior MI, left ventricular ejection fraction (LVEF), the number of lesions and vessels intervened on, vessel type (native coronary artery versus bypass graft conduit), vessel territory (left main, left anterior descending, left circumflex, or right coronary artery), de novo versus restenotic lesion, intervention type (stent, atheroablation, stent plus atheroablation, or balloon angioplasty only), IIb/IIIa inhibitor use, and periprocedural Q-wave and non-Q-wave MI (in total and separately by peak CPK-MB strata). Because LVEF was available in only 4048 patients (57%), the multivariate models were run with and without this variable, and any discrepant results were noted.

### Results

#### Demographic Characteristics and Baseline Procedures

Baseline features of the 7147 patients appear in Table 1. The population was characterized by a relatively high incidence of women, patients with diabetes, prior MI, and prior heart surgery. The mean LVEF was 48±12%. Intervention was performed in 12,098 lesions (mean, 1.7±1.0 lesions per procedure) in 8763 vessels (1.2±0.5 vessels per patient). Stents were implanted in 50.6% of procedures, and atheroablation (directional, rotational or extraction atherectomy, or excimer laser) as sole or adjunctive therapy was performed in 54.8% of procedures; balloon angioplasty alone was performed in only 9.6% of procedures. Glycoprotein IIb/IIIa
inhibitors were used in only 287 patients (4.0%) during the period of this study.

Device-Specific Myocardial Infarction After Percutaneous Intervention

The peak CPK-MB was normal (≤4 ng/mL) in 62.7% of patients, 1 to 3× normal in 19.4%, 3 to 5× normal in 6.1%, 5 to 8× normal in 4.1%, and >8× normal in 7.7% of patients. Thus, enzymatic criteria for non–Q-wave periprocedural MI (peak CPK-MB level >3× normal) was met in 17.9% of patients. By independent adjudication, new pathologic Q-waves in ≥2 leads developed as a complication of the index procedure in 40 patients (0.6%). The peak CPK-MB was 114±99 ng/mL (median, 104 ng/mL) in patients with Q-wave MI versus 48±62 ng/mL (median, 27 ng/mL) in patients with non–Q-wave MI (P=0.0001). The frequency of periprocedural CPK-MB release significantly varied by the type of intervention, being most common with combined atheroablation plus stenting, intermediate with stenting alone, and least common with balloon angioplasty alone (Figure 1). Periprocedural infarction, defined as peak CPK-MB >3× normal or Q-wave development, occurred in 26.5% of patients undergoing stent plus atheroablation, 17.0% after stenting, 16.2% after atheroablation, and 12.5% after PTCA only (P=0.0001 for trend). The occurrence of periprocedural Q-wave MI was device-independent, however (Figure 1).

In-Hospital Death

In-hospital death occurred in 68 patients (1.0%). By univariate analysis, hospital death was strongly associated with the maximal CPK-MB level after intervention; peak CPK-MB was 79±114 ng/mL in patients who died (median, 28 ng/mL) versus 10±29 ng/mL (median, 3 ng/mL) in hospital survivors (P<0.0001). Mortality rate was 0.3% in patients without periprocedural CPK-MB elevation, 0.4% in patients with peak CPK-MB 1 to 3× normal, 1.1% for 3 to 5× normal, 1.1% for 5 to 8× normal, and 4.8% for >8× normal (P<0.0001). In-hospital mortality rate was 25.6% if Q-wave MI developed (P<0.0001). By logistic regression analysis, the most powerful independent determinants of in-hospital death were the periprocedural development of Q-wave MI and non–Q-wave infarction with an elevated CPK-MB >8× the upper limit of normal (ULN) (Table 2). Lesser elevations of CPK-MB were not significantly related to hospital death.

When baseline LVEF was entered into the model, reduced LVEF was also a strong independent predictor of hospital death (Wald χ²=10.1, P=0.001), though Q-wave MI and CPK-MB >8× ULN remained the strongest correlates.

Late Death

Follow-up was available in 7106 hospital survivors (99.4%) at a mean time of 1.4±1.2 years. Cumulative late mortality rate was markedly elevated in patients with Q-wave MI, moderately elevated in patients with non–Q-wave MI and peak CPK-MB >8× ULN, and not significantly increased with lesser degrees of CPK-MB elevation (Figure 2). By Cox proportional hazards regression (Table 3), periprocedural Q-wave MI was the strongest independent determinant of late death (hazard ratio, 9.9, 95% CI, 5.8 to 17.0; P<0.0001); peak CPK-MB >8× ULN in the absence of Q waves also significantly correlated with cumulative death (hazard ratio, 2.2; 95% CI, 1.4 to 3.5; P<0.0001). Lesser degrees of periprocedural CPK-MB elevation were not significantly related to survival. When baseline LVEF was forced into the model, reduced LVEF was also an independent predictor of cumulative mortality (Wald χ²=36.2, 95% CI, 17.0 to 71.2; P<0.0001); periprocedural Q-wave MI and CPK-MB >8× ULN remained strongly correlated with death.

Determinants of Large Periprocedural MI

Given the relation identified between large periprocedural MI and death, logistic regression analysis was used to determine

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**Figure 1.** Device-specific distribution of peak CPK-MB levels and Q-wave MI after intervention.

**Figure 2.** Cumulative survival (including in-hospital events) after percutaneous intervention, stratified by periprocedural infarct size. Compared with group with no enzyme rise after intervention, cumulative survival was decreased in patients with Q-wave MI (log rank, P<0.0001) and non–Q-wave MI with CPK-MB >8× ULN (P<0.0005). Survival of patients with lesser degrees of CPK-MB elevation were not statistically different than group with no elevation (P>0.3 for all comparisons).

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**Table 2. Multivariate Correlates of In-Hospital Death**

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Wald χ² test</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-wave MI</td>
<td>98.4</td>
<td>67.1 (30.2, 166.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CPK-MB &gt;8× ULN*</td>
<td>41.7</td>
<td>8.0 (4.4, 14.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Advanced age</td>
<td>16.3</td>
<td>1.08 (1.03, 1.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>5.4</td>
<td>2.8 (1.2, 6.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior MI</td>
<td>4.1</td>
<td>1.9 (1.1, 3.4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*In the absence of new Q waves.
the independent determinants of Q-wave MI and CPK-MB >8× ULN (Table 4). The occurrence of large non–Q-wave MI strongly correlated with combined stent plus atheroablation use, advanced age, diabetes, unstable angina, and treatment of saphenous vein graft and multiple lesions. In contrast, unstable angina was the only independent predictor of Q-wave MI.

**Device-Specific Death**

There was no difference in hospital mortality rates stratified by device selection (0.8% after stenting plus atheroablation, 0.9% after stenting alone, 1.1% after atheroablation alone, and 0.7% after balloon angioplasty alone; P = 0.64). Similarly, there was no difference in cumulative mortality rate at late follow-up stratified by device selection, either by univariate or multivariate analysis (Figure 3 and Table 3). The relative effect of periprocedural MI on survival after intervention was similar among the 4 device strata, with mortality rates increased the greatest after Q-wave MI, modestly after non–Q-wave MI with CPK-MB >8× ULN, and inconsistently with lesser degrees of enzymatic elevation (Figure 4).

**TABLE 3. Multivariate Correlates of Cumulative Late Mortality (Including Hospital Deaths)**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Wald x² test</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-wave MI</td>
<td>81.9</td>
<td>9.9 (6.0, 16.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Advanced age</td>
<td>72.8</td>
<td>1.04 (1.03, 1.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>47.0</td>
<td>2.7 (2.1, 3.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42.5</td>
<td>2.5 (1.8, 3.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CPK-MB &gt;8× ULN*</td>
<td>38.4</td>
<td>2.2 (1.6, 3.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Saphenous vein graft intervention</td>
<td>21.6</td>
<td>1.5 (1.2, 2.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>18.1</td>
<td>1.5 (1.3, 1.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>6.8</td>
<td>1.4 (1.1, 1.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Left main intervention</td>
<td>6.6</td>
<td>1.4 (1.2, 1.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>5.4</td>
<td>1.3 (1.1, 1.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>5.0</td>
<td>1.2 (1.1, 1.4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*In the absence of new Q waves.

**Discussion**

**Incidence and Impact of MI After Percutaneous Intervention**

In the present study, periprocedural myonecrosis was remarkably frequent, with abnormal CPK-MB levels detected in 37% of patients. Indeed, periprocedural subendocardial MI, defined by the most commonly accepted criteria (CPK-MB >3× ULN without new Q waves), occurred in 18% of patients. The high incidence of periprocedural MI may be explained by the tertiary referral nature of the patient population (in whom vein graft intervention was frequent, diffuse atherosclerosis was evident, and multiple lesion intervention was common) as well as the routine systematic collection and analysis of serial CPK-MB samples by a sensitive radioimmunoassay. Given the high incidence of myonecrosis after percutaneous intervention, it is essential to identify in which patients the prognosis is adversely affected.

When the impact of the level of periprocedural CPK-MB on early and late mortality rates was considered in context with the development of ECG Q-wave MI (the occurrence of which is a well-known negative prognostic event after angioplasty), a consistent pattern emerged; large periprocedural infarctions, as evidenced by Q-wave MI or non–Q-wave MI with CPK-MB >8× ULN, were found to be strongly and independently predictive of reduced survival. In contrast, lesser degrees of enzymatic necrosis did not affect survival; the extended prognosis of patients with CPK-MB ≤8× ULN was similar to those in whom no periprocedural myonecrosis was detected. Notably, the development of new Q waves after percutaneous intervention, which typically occurs in concert with a clinically evident major procedural adverse event, though infrequent, was the most powerful independent predictor of early and late death, significantly more so than any degree of enzymatic elevation without ECG Q-wave progression. These data are thus concordant with accepted dogma from the prereperfusion era in which numerous studies conclusively demonstrated that reduced survival resulted from naturally occurring large transmural or subendocardial infarctions, whereas the prognosis was favorable in patients with smaller infarcts and lesser degrees of myonecrosis. These results also confirm the classic teachings in which the risk period for death after MI occurs predominantly early after the event, with gradual attrition thereafter.

**Comparison With Prior Studies**

Previous contemporary investigations may be cited to support the alternative positions that CPK-MB elevations after percutaneous intervention are either benign, result in reduced survival only if associated with clinical or angiographic abnormalities, or are dangerous only if markedly elevated, or are a harbinger of early and late death regardless of the level. However, most of these reports were limited either because of small sample size, retrospective analysis, evaluation of a low-risk population, minimal or absent follow-up, lack of multivariate analysis, restriction to balloon angioplasty or directional atherectomy, inconsistent or infrequent measurements of CPK or CPK-MB, variable methodology of CPK-MB measurement, and/or absence of independent data.
collection or event adjudication pathways. Furthermore, these studies either did not examine for and adjudicate Q-wave MI and/or did not consider the prognostic import of new Q-wave formation relative to varying levels of enzymatic myonecrosis.

The present multivariate analysis, derived from intervention in a large tertiary referral population in which “new device” angioplasty use was common and performed with the use of independent free-standing ECG and clinical event committees to adjudicate both Q-wave and enzymatic infarctions, has thus overcome many of the limitations of earlier studies. Furthermore, many prior investigations have defined “large” subendocardial MI as CPK-MB > 8× ULN, without stratification into the 5 to 8× and > 8× categories as prespecified in the present and other studies. Our data suggest that survival is adversely affected only by truly large periprocedural infarctions, evidenced by the development of new Q waves or peak CPK-MB elevation > 8× ULN. As the largest study to date examining the relation between periprocedural enzyme elevations and survival, an effect of lesser degrees of CPK-MB release on death would probably have been detected if truly present. It is possible, however, that varying sensitivity and accuracy of the radioimmunoassay (or electrophoretic) methodologies used between studies also may account for the different enzymatic thresholds observed in different analyses.

**Device-Specific Periprocedural MI and Death**

As previously suggested, periprocedural enzyme release was found to vary markedly with different devices, being most common with combined stenting and atheroablation, intermediate in occurrence with either stenting or atheroablation, and least common with PTCA alone. Long-term survival, however, was device-independent, also consistent with recent randomized trials. This apparent paradox may be reconciled by the fact that the development of Q-wave MI, by far the most potent determinant of death, was rare and occurred with similar frequency with each device or device combination (being predicted only by unstable angina). Moreover, the occurrence of large non–Q-wave MI (CPK-MB > 8× ULN) was similar with PTCA, stenting and atheroablation alone; only combined stent plus atheroablation use resulted in increased rates of large subendocardial MI (Figure 1). The increased incidence of enzymatic release after stenting and atheroablation may also simply reflect the baseline presence of more diffuse atherosclerotic disease and calcification rather than meaningful clinical complications. Finally, stenting and atheroablation may have other salutary but poorly characterized effects that otherwise offset the negative impact of periprocedural myonecrosis.

**Limitations**

First, the results of the present study primarily apply to a high-risk referral population characterized by advanced age and a high incidence of diabetes, prior MI, and vein graft lesions. Second, despite the fact that this is the largest analysis to date relating periprocedural MI to survival, all the limitations of a single center study apply. Third, although the representation of atheroablative techniques in the present study is greater than in most current practices (including ours), stent use has risen to > 75% at most centers, and thus the results are more applicable than many prior reports in which stenting was less common or absent. Fourth, as in other previous large series, independent angiographic and IVUS core laboratory analyses were not performed, which, as mentioned above, if available may have provided further insight into the device- and lesion-specific occurrence of periprocedural enzymatic elevations and the impact of increasing plaque burden on death. This relation is currently being explored in a subset of patients from this study in whom baseline IVUS data are available. However, because IVUS

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**Figure 4.** Cumulative mortality rates after percutaneous intervention, stratified by device use and presence of periprocedural MI.
is used in only a small minority of interventions, the analysis from the present study is relevant to most patients. Fifth, given skepticism at the Washington Hospital Center during the course of this study whether glycoprotein IIb/IIIa inhibitors improve survival after percutaneous coronary intervention or are cost-effective, these agents were rarely used. Thus, no conclusions may be drawn from this study regarding the impact of the proven efficacy of these agents in reducing periprocedural myonecrosis on survival. Finally, periprocedural myonecrosis may develop either as a result of an apparent complication (e.g., acute vessel closure or no reflow) or occur without obvious cause; it is unclear whether the underlying cause of a given level of CPK-MB elevation independently affects prognosis. Unfortunately, no large study (including ours) has rigorously tracked all periprocedural clinical, angiographic, and ECG events, the knowledge of which would be required to fully understand the origin and consequence of unexpected or asymptomatic enzymatic elevations.

**Clinical Implications**

These data are reassuring in that they suggest the clinical course of patients with a periprocedural peak CPK-MB ≤8×ULN (without Q waves), representing 80% of all patients with elevated CPK-MB levels, will primarily be determined by the baseline presence of high-risk anatomic and clinical features and not by the limited amount of myonecrosis per se. Furthermore, the use of atheroablative and stents, though resulting in greater enzymatic release than PTCA alone, are not associated with increased mortality rates. Nonetheless, periprocedural large MI characterized by CPK-MB >8×ULN or the development of new pathologic Q waves still occurs in ~8% of high-risk patients and has a major negative impact on survival. The present analysis therefore supports the proactive use of measures such as glycoprotein IIb/IIIa inhibitors, which have been shown to reduce the periprocedural incidence of both Q-wave and large non-Q-wave MI, especially in patients at high risk for large periprocedural infarction (Table 4) or increased mortality rate (Tables 2 and 3), though to date the completed randomized trials of IIb/IIIa inhibitors have not been of sufficient size to definitively demonstrate reductions in large MI as herein defined or in mortality rates. Finally, randomized trials would be required to determine whether small degrees of periprocedural myonecrosis may be clinically ignored or if other measures such as prolonged hospitalization or β-blockade are warranted.

**References**


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