Prognostic Implications of Creatine Kinase-MB Elevation After Percutaneous Coronary Intervention

Results From the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) Registry

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Background—Creatine kinase-MB (CK-MB) elevation after percutaneous coronary intervention (PCI) has been associated with increased risk for mortality. Although most studies have defined periprocedural myocardial infarction (pMI) as an elevation in CK-MB \(>3\times\) upper limit of normal (ULN), use of different CK-MB assays and variation in site-specific definitions of the ULN may limit the value of such relative thresholds.

Methods and Results—We used data from the multicenter Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry to examine the impact of variations in site-specific thresholds for CK-MB elevation on the incidence of pMI as well as the relationship between absolute peak levels of CK-MB after PCI and 1-year mortality. The study cohort consisted of 6347 patients who underwent nonemergent PCI and had normal CK-MB at baseline. Across the 59 study centers, the ULN for CK-MB ranged from 2.6 to 10.4 ng/mL (median, 5.0 ng/mL), and there was an inverse relationship between the site-specific ULN and the incidence of pMI (defined as CK-MB elevation \(>3\times\) ULN). Although any postprocedure elevation of CK-MB was associated with an adverse prognosis, in categorical analyses, only CK-MB \(\geq50\) ng/mL was independently associated with increased 1-year mortality (hazard ratio, 4.71; 95% confidence interval, 2.42 to 9.13; \(P<0.001\)). Spline analysis using peak CK-MB as a continuous variable suggested a graded, nonlinear relationship with 1-year mortality, with an inflection point at \(30\) ng/mL.

Conclusions—Among unselected patients undergoing PCI, there is a graded relationship between CK-MB elevation after PCI and 1-year mortality that is particularly strong for large CK-MB elevations (\(>30\) to \(50\) ng/mL). Future studies that include pMI as a clinical end point should consider using a core laboratory to assess CK-MB (to ensure consistency) and raising the threshold for defining pMI above current levels (to enhance clinical relevance). (Circ Cardiovasc Interv. 2011;4:474-480.)

Key Words: percutaneous coronary intervention ■ creatine kinase ■ myonecrosis ■ mortality prognosis

Creatine kinase-MB (CK-MB) elevation after percutaneous coronary intervention (PCI) remains common\(^1\) and has been shown to be associated with increased late mortality.\(^2\)-\(^10\) Although a definition of CK-MB \(>3\times\) the upper limit of normal (ULN) has been used frequently for defining periprocedural myocardial infarction (pMI) and is now the generally accepted “universal” definition of a post-PCI MI,\(^11\) only a few studies have evaluated whether this threshold is clinically relevant or whether a more lenient or stringent definition might be preferred.\(^2\)-\(^4\),\(^12\)-\(^14\) In addition, use of such relative CK-MB thresholds poses several challenges to the conduct and interpretation of multicenter studies, in which common practice is to assess levels of CK-MB using each site’s local laboratory. Although this approach is practical and inexpensive, variability in both the specific CK-MB assay used and the specific ULN across clinical site laboratories may limit the ability of such studies to provide interpretable and generalizable results. Consequently, some investigators have suggested that a core laboratory should be used for studies in which pMI is an important end point, so as to limit variability introduced by site-specific CK-MB measurements.\(^15\)

In this study, we used data from the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) registry to examine the relationship between the absolute level of CK-MB elevation after PCI and 1-year mortality among unselected...
PCI patients in routine clinical practice. We also sought to examine the variability in the ULN of CK-MB among enrolling centers and its impact on the incidence of pMI using standard definitions.

**WHAT IS KNOWN**

- Elevated creatine kinase-MB (CK-MB) levels after percutaneous coronary intervention are associated with increased risk of mortality.
- Although periprocedural myocardial infarction (pMI) is commonly defined as a CK-MB level >3 times the upper limit of normal, use of different laboratory specific assays may translate into variability in relative thresholds, therefore affecting the identification of pMI.

**WHAT THE STUDY ADDS**

- The present study identified substantial variability in the upper limit of normal for CK-MB across centers (range, 2.6 to 10.4 ng/mL).
- A CK-MB level of 30 to 50 ng/mL appears to identify patients with at least a 2-fold increase in 1-year mortality.
- Use of a threshold CK-MB level to define pMI may decrease variability in pMI detection caused by assay variability and provide additional prognostic information.

**Methods**

The methods and population of the EVENT registry have been described previously. Briefly, EVENT was a collaborative effort to assess the contemporary practice of coronary stenting by performing a prospective evaluation of unselected patients undergoing attempted implantation of an approved intracoronary stent at more than 50 PCI centers in the United States. Enrollment in the registry was limited to prespecified recruitment time intervals (“waves”), and specific efforts were made to enroll patients consecutively during each enrollment period (for example, on predetermined days of the week) to minimize selection bias.

**Study Population**

The patient population for the present study was based on all patients who underwent PCI in EVENT (n=10 144) between July 2004 and December 2007. Patients were excluded if the primary indication for PCI was treatment of ST-elevation–MI (STEMI) or if baseline CK-MB levels were missing or elevated (because of difficulty in differentiating ongoing MI from pMI in such individuals) (Figure 1).

**Data Collection and End Points**

Data regarding patient characteristics, presentation, treatment, and outcomes were collected prospectively on standardized case report forms and submitted to the data coordinating center. Absolute CK-MB levels were assessed at baseline (within 1 hour before the procedure) and every 8 hours for a minimum of 2 samples after the procedure using each site’s clinical laboratory and reference values. If an MI was suspected clinically at a later point, additional biomarkers were obtained as indicated.

Patients were contacted by telephone at 6 and 12 months after the index PCI to ascertain the occurrence of specific complications including death, MI, and repeat revascularization. One-year follow-up was available for 97% of patients. For all suspected events, efforts were made to confirm their occurrence by review of medical records, and all clinical outcomes were adjudicated by 2 cardiologists blinded to treatment factors and subsequent outcomes.

Per the EVENT protocol, pMI was defined as elevation of CK-MB ≥3× ULN as determined by the local laboratory; if the baseline CK-MB level was elevated, the peak value was required to be at least 2× the baseline level as well. The study protocol was approved by ethical review committees at all participating institutions, and all patients provided written informed consent before participation.

**Statistical Methods**

For the purposes of our analysis, patients were divided into 5 groups, based on the magnitude of postprocedural CK-MB elevation (<5 ng/mL, 5 to <15 ng/mL, 15 to <25 ng/mL, 25 to <50 ng/mL, and ≥50 ng/mL). The ranges for these groups were defined a priori to correspond to clinically meaningful thresholds of <1×, 1 to <3×, 3 to <5×, 5 to <10×, and ≥10× ULN under the assumption of a common ULN of 5 ng/mL (the most frequent reference value among the EVENT sites).

Continuous variables are described as mean±SD, and categorical variables are described as counts and percentages. Comparisons across categories of peak-CK-MB were performed using linear regression trend tests for continuous variables and the Cochran-Armitage trend test for categorical variables. One-year mortality was estimated by the Kaplan–Meier method, and univariate associations were assessed by the log-rank test for each of the 5 CK-MB groups (using CK-MB <5 ng/mL as the reference group). We used hierarchical logistic regression with enrolling center as a second level to determine the association between pMI (using the EVENT definition) and the specific ULN of CK-MB as determined by each clinical site.

To examine the independent association between the level of post-PCI CK-MB elevation and 1-year mortality, multivariable-adjusted hazard ratios (HR) and their 95% confidence intervals (CI) were calculated using the Cox proportional hazards model. First, we used stepwise proportional hazards regression to identify independent correlates of 1-year mortality. Candidate variables for the model included demographic variables (age, sex), clinical variables (body mass index, diabetes mellitus, hypertension, hypercholesterolemia, congestive heart failure, peripheral arterial disease, estimated glomerular filtration rate, previous MI, previous coronary artery bypass surgery, acute coronary syndrome at presentation), angiographic and procedural variables (multivessel PCI, PCI of a saphenous vein graft, PCI of the proximal left anterior descending coronary artery), and in-hospital complications (vascular complications, transfusion, Thrombolysis In Myocardial Infarction major or minor bleeding). We then added the peak CK-MB level (as a categorical variable) to

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**Figure 1.** Study flow diagram. STEMI indicates ST-elevation myocardial infarction; CK-MB, creatine kinase-MB fraction.
this parsimonious model to determine the independent association between CK-MB category and mortality. The association between CK-MB and 1-year mortality was also evaluated as a continuous variable by means of spline regression, using methods as described by Desquilbet and Mariotti. For this analysis, restricted cubic spline functions were used in the adjusted proportional hazards model relating 1-year mortality to natural log-transformed CK-MB to identify the shape of the relationship (with reference at CK-MB = 5) and to test the hypothesis of nonlinearity of this relationship.

Probability values of < 0.05 (2-tailed) were considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient Population and In-Hospital Outcomes

Baseline characteristics of the study population and index revascularization procedures are described in the Table. Overall, the mean age was 65 ± 11 years, 69% were male, 36% had diabetes, and 23% were current smokers. The indication for PCI was unstable angina without a preprocedural elevation in CK-MB in 34% and stable coronary artery disease in 59%. Drug-eluting stents were used frequently (92%) as was bivalirudin (35%). Among the 6347 patients, the peak postprocedural CK-MB level was < 5 ng/mL in 74.5% of patients, 5 to < 15 ng/mL in 17.6%, 15 to < 25 ng/mL in 3.9%, 25 to < 50 ng/mL in 2.5%, and ≥ 50 ng/mL in 1.5%. The overall 1-year mortality rate was 2.8% (n = 149).

Compared with patients with lower peak CK-MB levels, those with higher peak CK-MB levels were older and more likely to have had a previous MI, have undergone PCI of a saphenous vein graft, have complex lesions, have more stents implanted, and had longer total stent lengths (Table).

Impact of CK-MB Threshold on the Frequency of Periprocedural MI

Although standardized assays were used at all 59 EVENT sites, there was substantial variability in the value of CK-MB that was considered to represent the ULN at each site’s clinical laboratory (Figure 2). The reference values ranged from 2.6 ng/mL to 10.4 ng/mL, with a median of 5.0 ng/mL and an interquartile range of 4.9 ng/mL to 7.0 ng/mL. Based on the universal definition of periprocedural MI (peak CK-MB > 3× ULN), there was an inverse relationship between the reference value at a site and the proportion of patients that would be considered to have had a periprocedural MI (P < 0.001; Figure 3).

Association Between Peak CK-MB Levels and Mortality

In unadjusted analyses, there was a graded association between the peak CK-MB level after PCI and subsequent 1-year mortality (Figure 4). The association was particularly striking for patients with the highest levels of postprocedure CK-MB (≥ 50 ng/mL) for whom the curves diverged early (within the first month), and 1-year mortality was 12.0% as compared with 2.0% among patients with peak CK-MB < 5 ng/mL. In multivariable analyses using CK-MB < 5 ng/mL as the reference group, only CK-MB ≥ 50 ng/mL was independently associated with increased 1-year mortality (adjusted HR, 4.71; 95% CI, 2.42 to 9.13; P < 0.001). Although there were trends toward increased mortality among patients with lesser degrees of CK-MB elevation, the degree of excess risk was modest, and none of these differences were statistically significant in the risk-adjusted analyses (Figure 5). In a sensitivity analysis in which post-PCI bleeding was excluded as a covariate from the risk-adjustment model, the results were virtually identical (data not shown).

The association between the peak level of CK-MB elevation and subsequent mortality was also evaluated on a continuous basis using restricted cubic spline regression (Figure 6). Graphical inspection of the model demonstrated a nonlinear relationship with a gradual increase in the hazard ratio beginning at very low levels of CK-MB (3 to 5 ng/mL) and a prominent inflection point at peak CK-MB levels of ≥ 30 ng/mL. This was confirmed by a significant nonlinear effect in the cubic spline model (P < 0.001).

Discussion

In this study, we used data from more than 6000 unselected PCI patients treated between 2004 and 2007 to assess the frequency of CK-MB elevation after nonemergent PCI and to determine the prognostic significance of various degrees of elevation of CK-MB. In addition, we assessed how variability in the ULN of CK-MB at each participating center influenced the apparent frequency of periprocedural MI across centers.

We found that despite recent advances in adjunct pharmacology and device technology, CK-MB elevation remains common after nonemergent PCI, with levels > 15 ng/mL (corresponding to an approximate ratio of 3 × ULN) occurring in 7.8% of patients and levels > 25 ng/mL in 3.9%. Indeed, the frequency of CK-MB elevation ≥ 3 × ULN (using site-specific reference levels) in our unselected population (6.5%) was very similar to the 8% rate recently reported among patients who underwent routine assessment of postprocedure cardiac enzymes in the ACC-NCDR Cath-PCI Registry and serves to highlight the potential role of such surveillance for both monitoring and improving the quality of PCI procedures. Because assessment of CK-MB after PCI was mandated by the EVENT registry (and was available for 90% of study participants), it is likely that the prevalence of CK-MB elevation in the present study is reflective of the “real-world” practice of contemporary PCI, and it is unlikely that we have underestimated the frequency of CK-MB elevation after PCI.

We also found that although there were trends toward increased mortality with even small elevations of CK-MB after PCI, only elevations ≥ 50 ng/mL (which corresponds roughly to ≥ 10 × ULN) were independently associated with increased 1-year mortality in our categorical analyses. Although any single threshold value of CK-MB is an arbitrary choice that represents a tradeoff between sensitivity and specificity in predicting subsequent mortality, such thresholds are nonetheless important because they are frequently used as end points for clinical trials of both cardiovascular drugs and devices. The fact that our spline analysis of CK-MB demonstrated a nonlinear relationship also supports the relevance of a threshold-based approach while demonstrating that peak CK-MB levels of 30 to 50 ng/mL may be clinically meaningful as well.
<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Overall Study Population (n=6347)</th>
<th>CK-MB &lt;5 ng/mL (n=4726)</th>
<th>CK-MB 5 to &lt;15 ng/mL (n=1123)</th>
<th>CK-MB 15 to &lt;25 ng/mL (n=247)</th>
<th>CK-MB 25 to &lt;50 ng/mL (n=158)</th>
<th>CK-MB ≥50 ng/mL (n=93)</th>
<th>P Value*</th>
</tr>
</thead>
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<td>Age, y</td>
<td>64.5±11.3</td>
<td>64.1±11.2</td>
<td>65.6±11.3</td>
<td>66.5±11.0</td>
<td>66.1±11.5</td>
<td>66.9±11.4</td>
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<td>Men, %</td>
<td>68.8</td>
<td>68.7</td>
<td>69.6</td>
<td>68.8</td>
<td>67.7</td>
<td>62.4</td>
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<td>30.2±6.8</td>
<td>30.4±7.0</td>
<td>29.8±6.3</td>
<td>29.2±5.7</td>
<td>29.4±6.9</td>
<td>30.2±6.3</td>
<td>0.61</td>
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<td>Diabetes mellitus, %</td>
<td>36.3</td>
<td>35.8</td>
<td>36.3</td>
<td>32.9</td>
<td>27.2</td>
<td>31.2</td>
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<td>79.9</td>
<td>80.2</td>
<td>81.2</td>
<td>76.0</td>
<td>70.3</td>
<td>78.5</td>
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<td>78.0</td>
<td>74.4</td>
<td>71.9</td>
<td>74.7</td>
<td>72.8</td>
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<td>23.2</td>
<td>23.2</td>
<td>23.9</td>
<td>18.0</td>
<td>29.1</td>
<td>16.3</td>
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<td>Congestive heart failure, %</td>
<td>9.4</td>
<td>9.0</td>
<td>11.5</td>
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<td>8.2</td>
<td>12.1</td>
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<td>Previous MI, %</td>
<td>32.9</td>
<td>31.6</td>
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<td>29.7</td>
<td>45.2</td>
<td>0.002</td>
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<td>Previous PCI, %</td>
<td>39.6</td>
<td>40.7</td>
<td>38.5</td>
<td>29.1</td>
<td>34.2</td>
<td>32.3</td>
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<td>GFR†</td>
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<td>&lt;30 mL/min</td>
<td>2.8</td>
<td>2.5</td>
<td>3.9</td>
<td>2.4</td>
<td>2.5</td>
<td>2.2</td>
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<td>30–59 mL/min</td>
<td>19.1</td>
<td>18.1</td>
<td>21.7</td>
<td>25.9</td>
<td>20.3</td>
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<td>&gt;60 mL/min</td>
<td>78.1</td>
<td>79.4</td>
<td>74.4</td>
<td>71.7</td>
<td>77.2</td>
<td>75.3</td>
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<td>Stable angina or + ETT</td>
<td>55.9</td>
<td>57.4</td>
<td>52.9</td>
<td>49.0</td>
<td>50.0</td>
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<td>Unstable angina</td>
<td>36.4</td>
<td>34.8</td>
<td>39.4</td>
<td>45.3</td>
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<td>Other</td>
<td>7.7</td>
<td>7.8</td>
<td>7.7</td>
<td>5.7</td>
<td>5.7</td>
<td>8.6</td>
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<tr>
<td>Lesion complexity (worst), %</td>
<td>13.1</td>
<td>14.1</td>
<td>9.9</td>
<td>11.3</td>
<td>10.2</td>
<td>7.7</td>
<td>&lt;0.001</td>
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<td>A</td>
<td>33.4</td>
<td>35.0</td>
<td>30.2</td>
<td>26.3</td>
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<td>41.5</td>
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<td>B2</td>
<td>26.7</td>
<td>25.3</td>
<td>32.0</td>
<td>28.7</td>
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<td>0.002</td>
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<td>C</td>
<td>14.7</td>
<td>12.5</td>
<td>20.5</td>
<td>25.1</td>
<td>20.3</td>
<td>18.5</td>
<td>&lt;0.001</td>
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<td>Maximum stenosis, %</td>
<td>85.8±10.5</td>
<td>85.5±10.6</td>
<td>86.4±10.1</td>
<td>86.8±9.5</td>
<td>87.3±9.0</td>
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<td>Multivessel PCI, %</td>
<td>14.7</td>
<td>12.5</td>
<td>20.5</td>
<td>25.1</td>
<td>20.3</td>
<td>18.5</td>
<td>&lt;0.001</td>
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<td>Bifurcation lesion, %</td>
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<td>10.9</td>
<td>14.2</td>
<td>15.4</td>
<td>16.5</td>
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<td>&lt;0.001</td>
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<td>No. of stents</td>
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<td>Drug-eluting stent</td>
<td>29.7±19.8</td>
<td>27.6±18.4</td>
<td>34.1±21.7</td>
<td>39.7±23.9</td>
<td>40.2±22.7</td>
<td>38.3±25.9</td>
<td>&lt;0.001</td>
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<td>Bare metal stent</td>
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<td>88.3</td>
<td>87.5</td>
<td>87.4</td>
<td>89.2</td>
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<tr>
<td>No procedural complications, %</td>
<td>11.9</td>
<td>11.7</td>
<td>12.5</td>
<td>12.6</td>
<td>10.8</td>
<td>13.2</td>
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<td>Antithrombotic therapy, %</td>
<td>94.2</td>
<td>96.3</td>
<td>92.2</td>
<td>82.3</td>
<td>78.7</td>
<td>69.3</td>
<td>&lt;0.001</td>
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<td>Heparin alone</td>
<td>21.5</td>
<td>20.8</td>
<td>24.5</td>
<td>23.1</td>
<td>17.7</td>
<td>21.5</td>
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<td>Heparin and GPI</td>
<td>27.6</td>
<td>26.4</td>
<td>30.8</td>
<td>29.6</td>
<td>35.4</td>
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<td>Other†</td>
<td>36.6</td>
<td>38.8</td>
<td>30.7</td>
<td>28.7</td>
<td>25.9</td>
<td>31.2</td>
<td></td>
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<tr>
<td>Therapeutic clopidogrel load, %</td>
<td>14.3</td>
<td>14.0</td>
<td>14.0</td>
<td>18.6</td>
<td>21.0</td>
<td>21.5</td>
<td></td>
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</tbody>
</table>

CK-MB indicates creatine kinase-MB; MI, myocardial infarction; PCI, percutaneous coronary intervention; GFR, glomerular filtration rate; + ETT, positive stress test; LMCA, left main coronary artery; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; SVG, saphenous vein graft; and GPI, glycoprotein IIb/IIIa inhibitor.

*P value based on linear regression trend tests for continuous variables and the Cochran-Armitage trend test for categorical variables.

†Calculated by the Cockcroft-Gault equation.

‡Other includes low-molecular-weight heparin alone or in combination with glycoprotein IIb/IIIa antagonists, glycoprotein IIb/IIIa antagonists alone, and various combinations (ie, bivalirudin with glycoprotein IIb/IIIa antagonists).
Comparison With Previous Studies
Although numerous previous studies have reported an association between elevated levels of CK-MB after PCI and long-term mortality, only a few have attempted to define a threshold for a clinically-important periprocedural MI. In a meta-analysis of 7 studies evaluating the prognostic importance of CK-MB elevation after PCI, Ioannidis et al found that there was a stepwise increase in the risk of death with increasing CK-MB levels, with the greatest risk of death among those with CK-MB >5× ULN. It is difficult to directly compare these results with our findings, however, because of differences in the CK-MB ULN both across sites and studies.

In a single-center study of more than 7000 patients undergoing PCI between 1994 and 1999, Stone et al found that only CK-MB elevations >8× ULN (corresponding to an absolute value of 32 ng/mL using their local reference level) were independently associated with increased 2-year mortality. Brener et al evaluated the association between periprocedural CK-MB elevation and long-term mortality among 3478 patients who underwent PCI at a single center between 1992 and 2000. Although any elevation in CK-MB was associated with increased mortality in univariate analyses, after multivariable adjustment, only CK-MB elevation >10× ULN (corresponding to 80 ng/mL at their center) was associated with increased risk.

Our findings thus extend these previous single-center results by demonstrating similar results across more than 50 US PCI centers when analyzing peak CK-MB levels both in a categorical as well as a continuous fashion. Moreover, these previous studies were largely performed in an era when the dominant forms of PCI were balloon angioplasty and athero-ablation, anticoagulation was predominantly unfractionated heparin, and use of aggressive and prolonged oral and parenteral antiplatelet therapy were uncommon. The current study thus demonstrates that despite substantial changes in PCI technology and pharmacology—with resulting shift in the mechanism of ischemic complications from dissection and abrupt vessel closure to microembolization and side branch occlusion—only large periprocedural infarcts are unequivocally associated with an important (ie, more than 2-fold) increase in long-term mortality.

Practical Implications
The results of our study have important implications both for clinical practice and for future research studies. First, the fact

<table>
<thead>
<tr>
<th>Peak CK-MB (ng/mL)</th>
<th>Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - &lt;15</td>
<td>1.16 (0.77, 1.75)</td>
</tr>
<tr>
<td>15 - &lt;25</td>
<td>1.22 (0.58, 2.56)</td>
</tr>
<tr>
<td>25 - &lt;50</td>
<td>1.69 (0.81, 4.39)</td>
</tr>
<tr>
<td>≥50</td>
<td>4.87 (2.51, 9.44)</td>
</tr>
</tbody>
</table>

Figure 5. Adjusted hazard ratio for 1-year mortality according to level of postprocedure creatine kinase-MB fraction (CK-MB) elevation. A level of <5 ng/mL served as the reference value for all comparisons. Hazard ratios were calculated using Cox proportional hazards regression and adjusted for other independent correlates of mortality (age, sex, history of heart failure, peripheral arterial disease, glomerular filtration rate, previous coronary artery bypass surgery, prior myocardial infarction, and major bleeding during the index hospitalization).
that variations in site-specific reference values for CK-MB can influence the apparent frequency of periprocedural MI after PCI implies that benchmarking rates of MI across hospitals is not a reliable measure of hospital quality at the present time. If cross-hospital benchmarking of MI rates is to become an important tool for PCI-related quality assurance and improvement, it will therefore be important to use either absolute CK-MB levels or other biomarkers with standardized reference levels for such comparisons. In recognition of these and other challenges related to ascertainment bias, quality improvement initiatives such as the ACC-NCDR Cath PCI registry have recently abandoned the use of pMI as a quality indicator.21

Although pMI rates are not routinely assessed in PCI practice, such assessment remains commonplace in clinical trials of antithrombotic and antiplatelet agents in the PCI setting for which periprocedural myocardial infarction represents a key component of the primary study end point.22–24 Historically, such studies have used local laboratory assays for CK-MB levels and defined a periprocedural MI as a peak CK-MB level $>$3× ULN—now widely considered the “universal” definition of a pMI.11 Our findings suggest that use of absolute (rather than relative) CK-MB levels and a higher threshold for defining a pMI (eg, 30 to 50 ng/mL) would enhance both the ability to compare results across studies and the clinical relevance of any observed therapeutic differences. To further enhance precision of end point determination, use of a centralized core laboratory for CK-MB assessment would be optimal.

Limitations
The current study has several limitations. First, although we attempted to adjust for possible confounders, there is a possibility that unmeasured confounders could explain our results. Second, our assessment of mortality was restricted to 1-year events (the maximum duration of follow-up in EVENT). Thus, the prognostic impact of post-PCI elevations of CK-MB on longer-term mortality cannot be evaluated in the present study. However, recent studies have suggested that most of the prognostic impact of pMI after PCI is manifest in the first few months of follow-up.25

Third, we excluded STEMI patients from the current analysis; consequently, our results apply only to patients undergoing either nonemergent PCI in either the elective or unstable angina/non–ST-elevation–MI setting. Fourth, we were unable to reliably ascertain the mechanism of CK-MB elevation whether it was due to side branch compromise or due to distal microembolization—factors that have been previously suggested to alter the prognostic impact of pMI.26 Finally, although CK-MB was routinely measured in almost all patients after PCI, it is impossible to know whether the true peak value of CK-MB was recorded for all patients because many patients may have been discharged before reaching their peak CK-MB levels if they lacked signs or symptoms of myocardial ischemia. This could lead to an incorrect categorization of the severity of CK-MB elevation with a tendency to underestimate its severity.

Conclusions
In this large, real-world population of patients undergoing PCI with drug-eluting stents and contemporary antithrombotic therapy, only large CK-MB elevations (30 to 50 ng/mL) were independently associated with increased 1-year mortality. Variability in site-specific reference levels for CK-MB contributed importantly to apparent variation in rates of pMI across clinical sites. These findings suggest that future studies should consider the use of absolute (rather than relative) CK-MB levels for assessment of pMI (or optionally, the use of a central core laboratory) and raising the threshold for the definition of pMI—particularly when pMI is used as an end point for studies comparing revascularization with conservative therapy or as a quality-of-care metric for PCI.

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References


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