Mortality Risk Conferred by Small Elevations of Creatine Kinase-MB Isoenzyme After Percutaneous Coronary Intervention

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OBJECTIVES
The aim of this study was to assess whether small creatine kinase-MB isoenzyme (CK-MB) elevations after percutaneous coronary intervention (PCI) affect the subsequent mortality risk.

BACKGROUND
Several studies have evaluated the relationship of CK-MB levels after PCI with the subsequent risk of death. While there is consensus that elevations exceeding 5 times the upper limit of normal increase mortality significantly, there is uncertainty about the exact clinical impact of smaller CK-MB elevations.

METHODS
We performed a meta-analysis of seven studies with CK-MB measurements and survival outcomes on 23,230 subjects who underwent PCI. Data were combined with random effects models.

RESULTS
Mean follow-up was 6 to 34 months per study. By random effects, 19% (95% confidence interval [CI], 16% to 23%) had one- to five-fold CK-MB elevations, while only 6% (95% CI, 5% to 9%) had >5-fold elevations. Compared with subjects with normal CK-MB, there was a dose-response relationship with relative risks for death being 1.5 (95% CI, 1.2 to 1.8, no between-study heterogeneity) with one- to three-fold CK-MB elevations, 1.8 (95% CI, 1.4 to 2.4, no between-study heterogeneity) with three- to five-fold CK-MB elevations, and 3.1 (95% CI, 2.3 to 4.2, borderline between-study heterogeneity) with over five-fold CK-MB elevations (p < 0.001 for all).

CONCLUSIONS
Any increase in CK-MB after PCI is associated with a small, but statistically and clinically significant, increase in the subsequent risk of death. (J Am Coll Cardiol 2003;42:1406–11)

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Microvascular coronary embolization, either spontaneous or iatrogenic, is now a well-recognized clinical entity (1). Creatine kinase-MB isoenzyme (CK-MB) elevation is common after percutaneous coronary intervention (PCI) and, if sought, can be detected in up to 25% of cases (2) or even a larger percentage if more sensitive markers, such as troponin T or I, are used (3,4). Extensive cardiac enzyme release after PCI has been correlated with late mortality in several studies (5,6). Still, however, the amount of increase that is clinically relevant and the threshold level of CK-MB that has prognostic significance remain elusive (7). Post-PCI CK-MB isoenzyme increases up to 5 times the upper limit of normal have typically not been found to be statistically significant for predicting survival, and their clinical meaning has been questioned (7,8). Nevertheless, the majority of post-PCI CK-MB elevations are in this range; most are actually in the range of 1 to 3 times the upper limit of normal (5). Previous studies have had inadequate power to evaluate the exact impact of such enzyme elevations on the subsequent risk of death. Thus, we performed a comprehensive meta-analysis of all pertinent studies to clarify the clinical significance of small CK-MB elevations after PCI.

METHODS
Eligibility and search strategy. The meta-analysis included studies reporting data on post-PCI CK-MB values in relationship to the subsequent risk of death during follow-up. Abstracts were not eligible. All types of PCI were eligible including percutaneous transluminal coronary angioplasty (PTCA), stent placement, atherectomy (directional, rotational, extraction), and excimer laser. Whenever study reports included both patients with and without PCI, only the first group was used. The meta-analysis focused on the strata of one- to three-fold elevation and three- to five-fold elevation compared with normal CK-MB, but also examined data on subjects with over five-fold CK-MB elevations to address whether there is a clear dose-response relationship. Because it is unclear whether the potential prognostic effect of CK-MB elevations may change in the very long-term due to competing causes of death or may be affected by extensive missing information and censoring, we

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focused on studies with mean follow-up between three months and three years; whenever reports with different follow-up were available from the same study, we selected the data closest to six months. We excluded studies with CK data without additional information on deaths according to MB isoenzyme strata. Potentially eligible studies were carefully scrutinized for overlap of subjects. Reports providing information on a subgroup of a larger population described in another report were excluded, while, in cases of considerable partial overlap of subjects between reports, we generally retained only the largest study with available data to avoid double counting.

We identified eligible studies in MEDLINE and EMBASE (last search updated February 2003) using the keywords creatine kinase AND angioplasty or stent. We also screened bibliographies of retrieved studies and communicated with experts.

Data. For each study we recorded study design, the types of PCI employed, and the number of subjects in CK-MB strata (normal, 1- to 3-fold elevation, 3- to 5-fold elevation, >5-fold elevation). The outcome of interest was mortality during the available follow-up, excluding acute events during the PCI. Deaths were recorded per stratum. Whenever exact numbers were not provided, we approximated risk ratios and 95% confidence intervals (CI) from Kaplan-Meier curves and other presented information. Two independent investigators extracted data, and discrepancies were resolved with consensus.

Analysis. Proportions of the subjects in each CK-MB stratum across studies were synthesized with random effects models. We evaluated separately the risk ratio for mortality with one- to five-fold, one- to three-fold, three- to five-fold, and >5-fold elevation versus normal CK-MB. Risk ratios for mortality were estimated in each study, and between-study heterogeneity was estimated using the Q statistic (significant for p < 0.10) (9). Risk ratios were then combined using the general variance method, weighting each log-transformed risk ratio by the inverse of its variance (fixed effects model) or by the inverse of the sum of its variance plus the between-study variance (random effects model) (9). In the absence of between-study heterogeneity, the two models coincide, while random effects are more appropriate when there is between-study heterogeneity.

Absolute risk differences for mortality across different CK-MB strata were calculated by multiplying the random effects relative risk increase (risk ratio – 1) times the observed death rates in the stratum of subjects with normal CK-MB after PCI. Typical observed death rates were based on Kaplan-Meier estimates at one and two years of follow-up in studies that provided such information.

Analyses were conducted in SPSS 10.0 (SPSS Inc., Chicago, Illinois) and in Meta-Analyst (Joseph Lau, Boston, Massachusetts). The p values are two-tailed.

RESULTS

Eligible studies. We identified 23 potentially eligible reports (5, 6, 8, 10–29). Fifteen were excluded up front (CK-based strata [n = 4] [15–18]; entirely included in larger studies [n = 6] [19–24]; partial overlap with other larger studies with available data [n = 5] [25–29]). Another large study (8) provided neither separate information for all the pertinent CK-MB strata nor absolute numbers of deaths, and it largely overlapped with another study that provided detailed pertinent data for the meta-analysis. We were unable to obtain additional clarifications from the primary

Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>n*</th>
<th>Age (yrs)</th>
<th>Male (%)</th>
<th>Procedures Involved (% of Total Number)</th>
<th>Reported Protocol for Obtaining CK-MB Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brener (2002)</td>
<td>3,573</td>
<td>64 (mean)</td>
<td>71</td>
<td>Various (not specified)</td>
<td>At 8 h, next morning and with suspected ischemia</td>
</tr>
<tr>
<td>Akkerhuis (2002)</td>
<td>8,383</td>
<td>60 (median)</td>
<td>69</td>
<td>PTCA (81%), stent (8%), DCA (6%), other (5%)</td>
<td>Variable, used peak value within 48 h</td>
</tr>
<tr>
<td>Stone (2001)</td>
<td>7,147</td>
<td>64 (mean)</td>
<td>70</td>
<td>Stent (37%), atheroablation (37%), both (17%), PTCA (9%)</td>
<td>At baseline, 8–12 and 16–24 h; if abnormal, also every 8–12 h until normalized</td>
</tr>
<tr>
<td>Kini (1999)</td>
<td>1,675</td>
<td>64 (mean)</td>
<td>68</td>
<td>Stent (29%), HRSA (25%), both (32%), PTCA (10%), other (4%)</td>
<td>At baseline, 6–8 and 16–24 h</td>
</tr>
<tr>
<td>Baim (1998)</td>
<td>956</td>
<td>58 (mean)</td>
<td>79</td>
<td>DCA (50%), PTCA (50%)</td>
<td>At baseline, 4–6 h, and hospital discharge or 24 h</td>
</tr>
<tr>
<td>Harrington (1995)</td>
<td>483</td>
<td>60 (mean)</td>
<td>79</td>
<td>DCA (58%), PTCA (42%)</td>
<td>At 12 and 24 h and with suspected ischemia</td>
</tr>
<tr>
<td>Kugelmas (1994)</td>
<td>558</td>
<td>60 (mean)</td>
<td>82</td>
<td>Stent (51%), DCA (49%)</td>
<td>At baseline and 24 h; if abnormal, repeated until peak</td>
</tr>
</tbody>
</table>

*With available CK-MB data; †composite data from five trials (PURSUIT, IMPACT-II, EPIC, EPLOG, CAPTURE).

CK-MB = creatine kinase-MB isoenzyme; DCA = directional coronary atherectomy; HSRA = high-speed rotational atherectomy; PTCA = percutaneous transluminal coronary angioplasty.
investigators. Nevertheless, this study was included in a sensitivity analysis for the comparison of one- to five-fold CK-MB elevation versus normal controls.

The seven eligible studies with complete pertinent data (5,6,10–14) totaled 23,230 subjects (Table 1). Four of the eligible studies clearly stated that they excluded patients with major complications during catheterization (6,10,11,13), while three studies (5,12,14) did not comment on whether any such patients were included. All studies included a preponderance of males with a mean or median age between 58 to 65 years. A variety of PCI types had been employed in each study (Table 1). The protocol for measuring CK-MB in each study is shown in Table 1.

The seven eligible studies included 16,133 subjects with normal CK-MB, 3,981 subjects with one- to three-fold, 1,124 subjects with three- to five-fold, and 1,992 subjects with over five-fold CK-MB elevations (Table 2). The percentage of subjects with one- to five-fold CK-MB elevation (range, 8.6% to 27.7%) exceeded the percentage of subjects with larger CK-MB elevations (range, 2.4% to 11.8%) across all studies. By random effects, the overall percentage was 19% (95% CI, 16% to 23%) for one- to five-fold CK-MB elevations versus 6% (95% CI, 5% to 9%) for CK-MB elevations exceeding five-fold the upper limit of normal.

Meta-analysis. There was no significant between-study heterogeneity in the risk ratio estimates in any of the contrasts of CK-MB strata (p > 0.10), with the exception of the comparison between subjects with over five-fold CK-MB elevations against subjects with normal CK-MB where borderline between-study heterogeneity was seen (p = 0.10). One- to five-fold CK-MB elevations conferred a significant increase in the risk of mortality with an overall risk ratio of 1.5 (95% CI, 1.3 to 1.8, p < 0.001; Fig. 1A). There was a dose-response: the summary risk ratio was 1.5 for one- to three-fold elevation (95% CI, 1.2 to 1.8, p < 0.001; Fig. 1B) and 1.8 for three- to five-fold elevation (95% CI, 1.4 to 2.4, p < 0.001; Fig. 1C). Fixed and random effects coincided, and the results were very consistent across studies. The dose-response was also clear when subjects with over five-fold CK-MB were considered. Their risk ratio compared with normal CK-MB subjects was 3.1 (95% CI, 2.3 to 4.2, p < 0.001) by random effects calculations (Fig. 1D). There was a suggestion that for this contrast the risk ratio estimates tended to be higher in three (5,10,12) of the four (5,10,12,14) studies with relatively shorter follow-up.

A sensitivity analysis including Ellis et al. (8) in the one- to five-fold versus normal CK-MB analysis yielded similar results (summary risk ratio 1.6, 95% CI, 1.3 to 1.8, p < 0.001). There was no significant difference in the risk ratio estimates of small versus larger studies or in early published versus recent studies in any of the considered contrasts (not shown).

Based on Kaplan-Meier plots, the one-year and two-year mortality risks among patients with normal CK-MB was 3% to 4% and 6% to 8%, respectively, in studies that provided such data (Table 2). For a cohort with a death rate of 3.5% per year among subjects with normal CK-MB, the absolute increase in the mortality risk among patients with one- to three-fold, three- to five-fold, and >5-fold CK-MB elevations after PCI would be 1.7%, 2.8%, and 7.4% per year, respectively.

**DISCUSSION**

This meta-analysis based on data from over 23,000 subjects clarifies the clinical significance of small CK-MB elevations after PCI. Any CK-MB increase is associated with a potential increase in the subsequent risk of death during follow-up. One- to three-fold CK-MB elevations increase the risk of death by approximately 50%. In a step-wise fashion, the risk is increased by 80% with three- to five-fold CK-MB elevations and is tripled with over five-fold CK-MB elevations.

Prior investigations had clearly stressed the adverse prognosis of subjects with CK-MB increases exceeding 5 times (or even 8 times) the upper limit of normal (6,8). However, such CK-MB elevations are on average three times less frequent than elevations in the one- to five-fold range. Thus, the impact of “small” CK-MB elevations on excess mortality on a population basis is not negligible when
compared against the impact of the more unusual high-level increases.

Approximately one in five subjects undergoing PCI will have an elevation of CK-MB by one- to five-fold, and one in 15 subjects will have an even larger increase. Stent and atheroablative procedures may confer a higher risk of CK-MB release than PTCA (10,12,13), and combined procedures may increase the risk even further (6). Saphenous vein graft interventions may also have a higher risk of CK-MB release (27). In certain clinical settings, such as diabetes mellitus and states of elevated C-reactive protein or other inflammatory markers, patients are particularly prone to coronary microembolization, either spontaneous or iatrogenic (1). We could not address separately the risk of death in these subgroups according to CK-MB strata. However, it is possible that the absolute excess mortality may be even larger in high-risk subpopulations.

We should acknowledge that the studies included in the meta-analysis used a considerable variety of revascularization procedures. Even with 23,000 patients, the meta-analysis is not fully powered to examine whether there are any differences on what subclinical CK-MB elevations mean for different types of PCI. However, the absence of between-study heterogeneity in the risk ratios suggests that any such differences, if present, may not be very prominent. Another issue is whether the impact of the CK-MB elevations on mortality risk remains constant over long durations of follow-up. This seems to be the case at least for two to three years with minor CK-MB elevations; CK-MB may be an index of myocardial damage that carries prognostic information in the long-term even with small increases. For high CK-MB elevations, other investigators have noted a more prominent adverse prognostic impact in the early months after PCI (6), and our data, although not definitive, are also consistent with this perspective. Finally, it would be interesting to evaluate also with large-scale studies the ability of other myocardial enzymes (3,4) to predict long-term outcomes after PCI.

It has been speculated whether periprocedural embolization carries the exact same adverse prognostic implications as with spontaneous myocardial necrosis (5). Other investigators observed two- to five-fold increases in the risk of death with one- to five-fold CK-MB elevations after spontaneous infarction and suggested that iatrogenic and spontaneous CK-MB elevations may have similar implications (5). Although our risk ratio estimates are somewhat smaller,
and the CIs exclude a doubling in mortality risk with one-to-five-fold CK-MB elevations, any enzyme release post-PCI does seem to affect prognosis. The level of post-PCI CK-MB elevation that carries an adverse prognosis has been debated (7). Based on our findings and in concordance with the recent redefinition criteria of myocardial infarction (30), we conclude that any increase in CK-MB post-PCI is associated with a small, but significant, increase in the subsequent risk of death. Given that minor elevations are far more common than more pronounced CK-MB increases, their mortality impact may be considerable in the population of patients undergoing PCI.

We should acknowledge that our meta-analysis focuses on the importance of mostly asymptomatic elevations of CK-MB after PCI as contrasted to major symptomatic periprocedural myocardial infarctions. We have clearly documented an increasing long-term mortality risk with increasing levels of CK-MB elevation. Nevertheless, this risk would have to be weighed against the anticipated benefit of the PCI and should not lead to abandoning PCI, when this is clearly indicated. For example, the risk conferred from small CK-MB elevations may be negligible compared with the benefit obtained from revascularization in a patient with tight proximal left anterior descending stenosis with unstable angina and a positive stress test. Risks and benefits should be carefully weighed in each case. Moreover, we should caution that the observed association between CK-MB elevation and subsequent mortality risk does not necessarily prove causality for this relationship. The CK-MB elevation may indeed reflect direct myocardial damage in some cases. However, in other cases it may simply be a surrogate for more extensive disease or more vulnerable plaques, and the subsequent increased mortality may not be directly linked to the original PCI-related microinfarction. New strategies should be considered to try to minimize the risk of cardiac events and death after PCI. For example, use of platelet glycoprotein IIb/IIIa receptor antagonists has recently been shown to decrease the risk of death both in the short- and long-term in patients undergoing PCI (31).

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