Impact of the elevation of biochemical markers of myocardial damage on long-term mortality after percutaneous coronary intervention: results of the CK-MB and PCI study

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Received 4 September 2004; revised 11 January 2005; accepted 20 January 2005; online publish-ahead-of-print 1 March 2005

Aims Retrospective studies and post hoc analyses have suggested that mild elevations in the creatine kinase-MB (CK-MB) isoenzyme following percutaneous coronary intervention (PCI) may be associated with an increased risk of death in the long term. However, this finding is still controversial, and the prognostic significance of elevations of more sensitive markers of myocardial damage, such as the cardiac troponins, has not been established. In this multicentre prospective cohort study, we evaluated the influence of post-procedural elevations of CK-MB and troponin I (cTnI) on long-term mortality.

Methods and results The CK-MB and PCI study included 3494 consecutive patients undergoing PCI from February 2000 to October 2000 in 16 Italian tertiary centres. Blood samples were collected at baseline, and at 8–12 and 18–24 h after the procedure, and were analysed in a core biochemistry laboratory. CK-MB elevation was detected in 16% of the patients, and was associated with increased 2-year mortality (7.2 vs. 3.8%; odds ratio (OR): 1.9; 95% confidence interval (CI): 1.3–2.8; \( P = 0.001 \)). The degree of CK-MB elevation (peak CK-MB ratio) independently predicted the risk of death (adjusted OR per unit: 1.04; 95% CI: 1.01–1.07; \( P = 0.009 \)). A cTnI elevation was detected in 44.2% of the cases and was not associated with a significant increase in mortality (4.9 vs. 4.0%; OR: 1.2; 95% CI: 0.9–1.7; \( P = 0.2 \)).

Conclusion Post-procedural elevations of CK-MB, but not cTnI, influence 2-year mortality.

Introduction

In patients with ischaemic heart disease, slight elevations in the biochemical markers of myocardial damage are frequently detected after percutaneous coronary revascularization, but their clinical significance is still uncertain.1 A few studies have reported a progressive increase in the risk of late death at any elevation in creatine kinase-MB (CK-MB) isoenzyme levels,2–6 whereas others have found a non-linear relationship, with an excess risk being limited to the patients showing major enzyme release (more than five to eight times the upper reference limit).7–10 However, most of the available data describe retrospective evaluations of single-centre registries or subgroup analyses of selected populations enrolled in clinical trials, and no specifically designed prospective study has been carried out. Furthermore, the significance of increases in more sensitive markers of myocardial damage in conjunction with percutaneous coronary intervention (PCI), such as the cardiac troponins (cTn), has not been adequately assessed.11–14

The CK-MB and PCI study was a multicentre prospective cohort study of a consecutive series of patients undergoing PCI, which was designed to evaluate the influence of procedural elevations in CK-MB and cTnI on long-term mortality.
Methods

Patient selection

All patients with ischaemic heart disease undergoing PCI at 16 Italian hospitals between February and October 2000 were considered eligible for the study. The consecutive nature of the enrolment was constantly evaluated by monitoring every centre for the percentage of patients included in the study against the total number of patients treated; an enrolment rate of <90% was considered a cause of study termination in that centre. In order to avoid any exclusion criteria, patients with persistent (lasting >30 min) ST-segment-elevation acute coronary syndrome (ACS) who were prospectively identified by the local investigators were also enrolled in the study but, as specified by the protocol, were not considered in the present analysis. The study complied with the Declaration of Helsinki; the protocol was approved by the Institutional Review Boards of the participating hospitals, and the patients gave their written informed consent.

Study protocol

Three blood samples were drawn: the first immediately before the beginning of the percutaneous intervention (baseline), and the second and third at 8–12 and 18–24 h, respectively, after the end of the procedure. Four millilitres of blood was collected in an anticoagulant-free vial and centrifuged at 3000 r.p.m.; after being separated from the red cells, the serum was stored at $-70\degree C$ and regularly shipped to the core biochemistry laboratory, where CK-MB and cTnI levels were measured. The selection of medications, devices, degree of revascularization, and subsequent hospital care was left to the discretion of the treating physician and was recorded in the case report forms. The patients’ vital conditions were assessed after 6, 12, and 24 months by means of clinical examinations, predated questionnaires, or telephone interviews. An independent clinical event committee verified the source data in a randomly selected sample of 10% of the patients and in all of those who died.

Biochemical analyses

Mass CK-MB and cTnI levels were analysed using a Dimension RxL/HM analyser (Dade Behring, Glasgow, DE, USA). The upper reference limit for CK-MB was 5.0 ng/mL; the upper reference limit for cTnI was 0.15 ng/mL, which represented the 99th percentile of the distribution of a reference control group with an analytical imprecision of no more than 10%.15

Definition of CK-MB and cTnI elevation

If the baseline CK-MB level was below the upper reference limit, a CK-MB elevation was defined as a level above the upper reference limit in at least one of the two post-procedural samples. If the baseline level was above the upper reference limit, a CK-MB elevation was defined as an increase of 50% above the baseline level in both post-procedural samples. The same criteria were used to define cTnI elevation. The degree of CK-MB or cTnI elevation was expressed as the CK-MB or cTnI peak ratio, which was calculated by dividing the maximum post-procedural level of the marker by its upper reference limit, or by its baseline value if the baseline value was above the upper reference limit.

Outcome

The outcome of interest was 2 year all-cause mortality, defined as the number of deaths that occurred from the time of the second blood sample up to 24 months thereafter.

Statistical analysis

Continuous variables are expressed as mean ($\pm$ standard deviation) or median values (interquartile range); the categorical variables are expressed as proportions. Assuming a 15% incidence of CK-MB elevation and 8% mortality after 2 years in patients without elevation, it was calculated that a sample size of 3850 patients was required to detect a risk ratio of 1.5 with a power of 80% and a two-tailed significance level of 0.05. This sample size was increased to 4000 patients to allow for patients with ST-segment-elevation ACS who were enrolled but prospectively excluded from the analysis. Logistic regression (SAS version 8.0, SAS Institute) was used to calculate the ORs and the corresponding 95% CIs.

A multivariable logistic regression analysis was performed to ascertain whether CK-MB levels independently predicted the risk of death and included the variables known to influence mortality in this population. These were age, diabetes, previous coronary artery bypass graft surgery, chronic renal insufficiency (serum creatinine $>2.0 \text{ md/dL}$), peripheral arterial disease, the presence of non-ST-segment elevation ACS, the presence of multivessel disease, left ventricular ejection fraction, an unsuccessful procedure [a residual coronary lumen narrowing of $>50\%$ or a Thrombolysis in Myocardial Infarction (TIMI) grade flow of $<3$ in one attempted coronary lesion], and the CK-MB peak ratio. The quartiles of the distribution of age, ejection fraction, and CK-MB were determined. Two analyses were performed considering the quartiles as qualitative and quantitative variables. The difference in deviance between these two models was then used to decide whether the effects were linear.

Additional analyses excluding patients with high baseline CK-MB levels or procedural complications were also made, in order to investigate further the role of high cardiac markers before PCI and the potential confounding factors between CK-MB elevations and procedural complications (side branch closure, transient abrupt vessel closure, distal thromboembolism, and transient slow flow). A two-sided P-value of 0.05 was considered statistically significant.

Results

Patients

4017 consecutive patients undergoing PCI for ischaemic heart disease were enrolled, i.e. 98% of the eligible patients. A complete set of serum samples was available from 3911 patients. Given that 417 patients with persistent ST-segment elevation ACS were prospectively excluded as per protocol, the study population consisted of the remaining 3494 patients, for all of whom 2 year mortality data were available. One hundred and fifty-three patients (4.4%) died: 15 during index hospitalization and 138 after hospital discharge (median 233 days: interquartile range 47–452).

CK-MB elevation and mortality

CK-MB elevation was detected in 559 patients (16.0%): 496 with a normal baseline level and 63 with a baseline level above the upper reference limit. The distributions of the clinical, angiographic, and procedural variables in patients with and without CK-MB elevation are shown in Table 1.

Two year mortality was significantly higher in patients with CK-MB elevation (40/559 or 7.2%) than in those without (113/2935 or 3.8%; OR: 1.9; 95% CI: 1.3–2.8; $P < 0.001$). A multivariable logistic regression analysis showed that the CK-MB peak ratio independently predicted the risk of death (adjusted OR per unit: 1.04; 95% CI: 1.01–1.07; $P = 0.009$, Table 2), with a linear relationship between it and the adjusted probability of death (Figure 1). When the patients with baseline CK-MB levels above the upper reference limit ($n = 104$) or procedural complications ($n = 334$) were removed from the analysis, the CK-MB peak ratio retained a similar independent
predictive value (adjusted OR per unit: 1.04, \( P = 0.01 \) and 1.03, \( P = 0.04 \), respectively).

cTnI elevation and mortality

cTnI elevation was detected in 1544 patients (44.2%): 1055 with a normal baseline level and 489 with a baseline level above the upper reference limit. The distributions of the clinical, angiographic, and procedural variables in the patients with and without cTnI elevations are shown in Table 1.

Two year mortality was not significantly higher in patients with cTnI elevations (75/1544 or 4.9%) than in those without (78/1950 or 4.0%; OR: 1.2; 95% CI: 0.9–1.7; \( P = 0.2 \)). The relationship between the cTnI peak ratio and the adjusted probability of death is shown in Figure 2.

Discussion

Percutaneous coronary revascularization has become a widely used and effective therapy for ischaemic heart disease, with almost 1.7 million procedures being performed annually and an immediate success rate of >90%.

Severe acute complications are rare, but a mild and asymptomatic release of the biochemical markers of myocardial necrosis is frequently observed after otherwise technically successful interventions. A recent magnetic resonance imaging study has shown that such increases in the CK-MB isoenzyme are due to detectable myocardial necrosis, and the Joint Ad Hoc Committee of the European Society of Cardiology and American College of Cardiology for the Redefinition of Myocardial Infarction has taken an unequivocal position by defining any elevation in the markers of myocardial damage in the setting of coronary

### Table 1 Distribution of clinical, angiographic, and procedural characteristics in the patients with and without CK-MB or cTnI elevations

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CK-MB elevation (n = 559)</th>
<th>No CK-MB elevation (n = 2935)</th>
<th>C-TnI elevation (n = 1544)</th>
<th>No C-TnI elevation (n = 1950)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 10</td>
<td>63 ± 10</td>
<td>65 ± 10</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>22.5</td>
<td>21.3</td>
<td>22.5</td>
<td>20.7</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>20.6</td>
<td>19.0</td>
<td>19.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>53.8</td>
<td>58.9</td>
<td>54.0</td>
<td>61.4</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>14.7</td>
<td>10.1</td>
<td>11.8</td>
<td>10.0</td>
</tr>
<tr>
<td>Chronic renal insufficiency (%)</td>
<td>5.4</td>
<td>4.0</td>
<td>4.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>49.9</td>
<td>50.8</td>
<td>52.0</td>
<td>49.6</td>
</tr>
<tr>
<td>Prior coronary bypass surgery (%)</td>
<td>10.7</td>
<td>10.3</td>
<td>11.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Non-ST elevation ACS (%)</td>
<td>57.4</td>
<td>49.6</td>
<td>54.1</td>
<td>48.2</td>
</tr>
<tr>
<td><strong>Angiographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>45.8</td>
<td>38.8</td>
<td>43.7</td>
<td>37.0</td>
</tr>
<tr>
<td>B2/C coronary lesion type (%)</td>
<td>58.7</td>
<td>51.4</td>
<td>56.0</td>
<td>44.8</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>56 ± 12</td>
<td>57 ± 11</td>
<td>57 ± 12</td>
<td>57 ± 11</td>
</tr>
<tr>
<td><strong>Procedural</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment with thienopyridines (%)</td>
<td>52.8</td>
<td>61.7</td>
<td>57.1</td>
<td>62.8</td>
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<tr>
<td>Glycoprotein IIb/IIIa-Inhibitors (%)</td>
<td>30.8</td>
<td>18.2</td>
<td>23.1</td>
<td>17.9</td>
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<tr>
<td>Multivessel procedure (%)</td>
<td>39.0</td>
<td>27.7</td>
<td>36.8</td>
<td>23.7</td>
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<tr>
<td>Vein graft intervention (%)</td>
<td>3.6</td>
<td>2.8</td>
<td>3.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Stent use (%)</td>
<td>82.6</td>
<td>77.1</td>
<td>80.7</td>
<td>75.9</td>
</tr>
<tr>
<td>Mean fluoroscopy time (min)</td>
<td>15.8 ± 11</td>
<td>11.9 ± 8</td>
<td>14 ± 10</td>
<td>11 ± 8</td>
</tr>
<tr>
<td>Procedural complications (%)</td>
<td>18.4</td>
<td>7.9</td>
<td>12.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Unsuccessful procedure (%)</td>
<td>7.6</td>
<td>4.6</td>
<td>5.2</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*Plus–minus values are mean ± standard deviation.*

*According to the American College of Cardiology/American Heart Association Classification.

The occurrence of one or more of the following periprocedural events: side branch closure, transient abrupt vessel closure, distal thromboembolism, and transient slow flow.

*A residual coronary lumen narrowing of >50% or a TIMI grade flow of <3 in one attempted coronary lesion.

### Table 2 Multivariable predictors of death after 2 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal insufficiency (yes vs. no)</td>
<td>2.29 (1.32–3.95)</td>
<td>0.003</td>
</tr>
<tr>
<td>Unsuccessful angiographic procedure (yes vs. no)</td>
<td>2.13 (1.14–3.96)</td>
<td>0.017</td>
</tr>
<tr>
<td>Peripheral vascular disease (yes vs. no)</td>
<td>1.78 (1.14–2.77)</td>
<td>0.010</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs. no)</td>
<td>1.50 (1.01–2.23)</td>
<td>0.045</td>
</tr>
<tr>
<td>Age (per 1 year)</td>
<td>1.07 (1.05–1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK-MB peak ratio (per 1 unit)</td>
<td>1.04 (1.01–1.07)</td>
<td>0.009</td>
</tr>
<tr>
<td>Ejection fraction (per 1% decrease)</td>
<td>1.03 (1.01–1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior coronary bypass surgery (yes vs. no)</td>
<td>1.47 (0.91–2.369)</td>
<td>0.109</td>
</tr>
<tr>
<td>Non ST-elevation ACS (yes vs. no)</td>
<td>1.31 (0.90–1.91)</td>
<td>0.155</td>
</tr>
<tr>
<td>Multivessel disease (2,3 vs. 1)</td>
<td>1.148 (0.79–1.665)</td>
<td>0.467</td>
</tr>
</tbody>
</table>

*A residual coronary lumen narrowing of >50% or a TIMI grade flow of <3 in one attempted coronary lesion.*
interventions as myocardial infarction. A few retrospective studies have suggested an association between CK-MB elevations after PCI and increased long-term mortality, whereas others have highlighted a higher risk only for major enzyme release (more than five to eight times the upper reference limit). The potential methodological limitations of the published reports, such as study design (retrospective or post hoc evaluations vs. prospective studies), patient selection (selected subsets vs. the general population), long enrolment times (up to 6 or 8 years in single-centre series), lack of statistical power, and inadequate duration of follow-up may partially account for these inconsistent conclusions.

The major findings of our prospective cohort study are that procedural elevations in CK-MB affect 2 year mortality and that there is a linear relationship between the degree of elevation and the risk of death, regardless of other variables. Finally, an increase in cTnI does not affect 2 year mortality and therefore does not add any further prognostic information to that offered by CK-MB levels.

It is only possible to speculate as to why procedural CK-MB elevations influence long-term mortality. One potential mechanism may be related to the myocardial damage per se, which leads to increased mortality as a result of reduced ventricular function or electrical instability. Alternatively, high CK-MB levels may be a sign of a more active atherosclerotic process and hence be associated with an adverse prognosis due to a more frequent recurrence of ischaemic events. However, regardless of the mechanism involved, it is interesting to note that antithrombotic drugs such as platelet glycoprotein IIb/IIIa receptor inhibitors, which have consistently been shown to reduce post-procedural myocardial damage, also reduce long-term mortality especially in the high-risk subset of patients. This observation indirectly supports the concept of an effect of CK-MB elevation on mortality.

The fact that slight increases in cTnI do not predict an increased risk of death may be due to the high sensitivity of this marker in detecting myocardial cell damage, as expressed by the high rate of cTnI elevations in this study. It is, therefore, possible to hypothesize that even the mild and potentially reversible myocardial injuries caused by transient procedure-induced ischaemia lead to troponin elevations, and that these do not influence the prognosis. Alternatively, the sensitivity of the test may reduce its ability to predict prognosis: the increased risk associated with troponin elevations could be so small that only studying a larger number of patients for a longer follow-up time would reveal any significant effect on survival.

Study limitations

First of all, as in other previous studies, no independent angiographic core laboratory analyses were performed, and the description of variables that are potentially relevant for prognosis, such as lesion morphology, the extent of coronary artery disease, the result of the procedure, and the degree of revascularization, were left to the operator’s evaluation. Secondly, serum samples were collected only in the first 24 h after the procedure, with the potential risk of underestimating the degree of marker elevation in cases of a delayed peak associated with large myocardial necrosis. Finally, post-procedural ECG was not considered in the analysis: Q-wave myocardial infarctions were not adjudicated nor was the prognostic impact of Q-wave vs. non-Q-wave myocardial infarction examined. However, the aim of the study was to assess the clinical relevance of minor marker elevations, which are usually characterized by a rapid return to normal values and not normally associated with significant ECG changes.

Another possible limitation of this study may be the infrequent use of GPIIb/IIIa antagonists (20%). These were more frequently used in the group of patients with CK-MB elevation; a difference that probably reflects their more frequent use in patients with high-risk clinical and angiographic characteristics, such as acute coronary syndrome or a complex anatomy, or in ‘bail-out’ situations after procedural complications have developed.
In conclusion, our results demonstrate that CK-MB elevations in patients undergoing PCI affect 2 year mortality and that the risk of death increases linearly with any elevation of the marker. Procedural CK-MB elevations should, therefore, be prevented, 19,20,22 systematically sought, and, if detected, always be reported in order to define the patient’s risk profile more precisely. Further evaluations are necessary to establish whether aggressive secondary prevention strategies 23,24 can improve the long-term outcome of patients with procedure-induced myocardial necrosis.

Acknowledgements
The authors have no conflicts of interest. This study was funded by the Italian Atherosclerosis, Thrombosis, and Vascular Biology Study Group. We thank Dr Giovanni Bader, MD, PhD, for his technical assistance in preparing the manuscript.

Appendix

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References