Prognostic significance of creatine kinase release after percutaneous coronary intervention

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In the last 10 years a large number of studies have clearly shown that mild-to-moderate elevations of biochemical markers of myocardial damage are frequently detected after percutaneous coronary revascularization, but the clinical significance of these findings is still debated. Side branch occlusion, abrupt vessel closure and major dissection are the factors most frequently responsible for myocardial damage after stent implantation. However even in the case of a successful and uncomplicated procedure, enzyme leak may occur as a result of coronary microembolization. Post-procedural creatine kinase (CK)-MB rise is detected in 10 to 20% of the cases and is associated with a higher risk of death; the level of risk seems to increase linearly with any elevation of the marker, with no obvious threshold effect or cut-off value. Post-procedural elevations of cardiac troponins, occurring in almost 50% of the cases, do not seem to predict long-term mortality and do not add any prognostic information to that offered by CK-MB.

Potential mechanisms responsible for adverse prognosis after CK-MB elevation include increased susceptibility to ventricular arrhythmias via microreentrant circuits, compromise of coronary collaterals, and microvascular circulation dysfunction.

Although a cause-and-effect relationship between CK-MB elevation and adverse outcome has not been clearly demonstrated, post-procedural myonecrosis should be prevented, systematically sought for and, if detected, always reported in order to define the patient's risk profile more precisely.

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Percutaneous coronary intervention (PCI) has become a widely used and effective therapy for ischemic 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.

The epidemiological relevance of this phenomenon has become evident after the publication of glycoprotein IIb/IIIa inhibitor-PCI trials: by using a core laboratory that adjudicated the clinical events with the markers of myocardial damage systematically collected at pre-specified intervals, the incidence of creatine kinase (CK) and CK-MB isoenzyme periprocedural elevation ranged from 10 to 20% of the cases of successful and apparently uncomplicated procedures[1]; this rate turned out to be much higher (30-50%) when a more sensitive and specific marker of myonecrosis, such as cardiac troponins, was used[2,3].

These findings rapidly lead to the introduction of terms such as "enzyme leak", "infarctlets", "CK bumps", "CK efflux" or "microinfarcts" and set off a debate as to whether there was any clinical significance associated with these biochemical data. The interest for this topic is relevant, in that it is at the basis of some controversial points that frequently recur in daily clinical practice: the opportunity to recommend a wide use of expensive drugs or devices that have shown to reduce the risk of myonecrosis; the safety of an early discharge of the patients after PCI regardless of the post-procedural biochemical data; the diagnosis with which patients experiencing mild CK-MB elevations should be discharged.

In this debate even the position of scientific societies or expert committees is discordant: the Joint *ad hoc* Committee of the European Society of Cardiology and American College of Cardiology for the redefinition of myocardial infarction has defined any elevation in the markers of myocardial damage in the setting of coronary

interventions such as myocardial infarction[4]; yet, the new American Heart Association Diagnostic and Interventional Catheterization Committee recommendations raised the CK-MB diagnostic threshold for the diagnosis of myocardial infarction from 5 to 8 times the upper limit of normal (ULN) of the marker[5].

To elucidate the clinical significance of myonecrosis after PCI we will now discuss five questions that summarize most of uncertainties that still surround this topic: 1) does procedural enzyme release actually represent myocardial necrosis? 2) how is it induced? 3) can CK-MB release after successful PCI influence long-term mortality? 4) what are the mechanisms involved in poorer clinical outcomes? 5) do PCI-related and spontaneous microinfarcts have a similar prognostic significance?

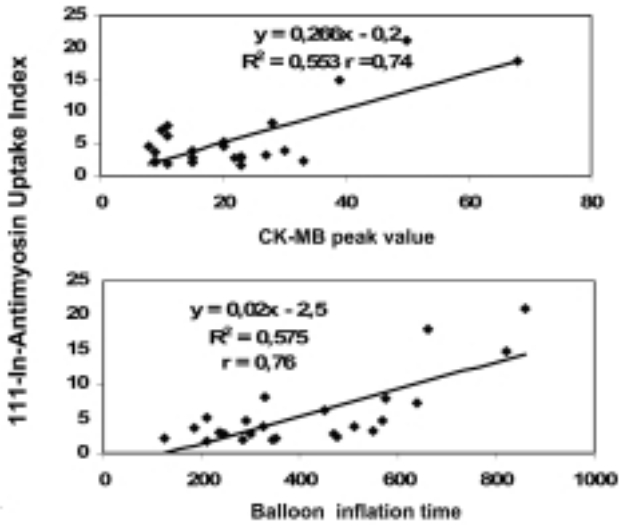

Figure 1. *Relationship between the indium-111 uptake index, total ischemic burden (balloon inflation time) and post-procedural creatine kinase (CK)-MB peak values. From Verna et al.[7], modified.*

Do procedural enzyme releases actually represent myocardial necrosis?

There are consistent data showing that an increase in CK or CK-MB plasma levels is associated with an irreversible myocardial damage.

In animal models Ishikawa et al.[6] studied the histopathological and biochemical effects of coronary occlusion. They found that a transient interruption of coronary flow (< 15 min in the dog) led to reversible myocardial injury (cell swelling and depletion of glycogen, with integrity of the cellular membrane) that was never associated with any increase in CK plasma activity. On the contrary, when coronary occlusion was maintained for a longer period (> 20 min), irreversible myocardial injury (disruption of the mitochondrial membrane) was induced, and this was systematically associated with an increase in CK plasma activity.

Verna et al.[7] studied the myocardial uptake of indium-111 antimyosin (a specific tracer for irreversibly injured myocytes) in a group of patients who underwent balloon angioplasty. They found that indium uptake index did correlate with the total ischemic burden (expressed by the balloon inflation time) and with the post-procedural CK-MB peak (Fig. 1). When the inflation time lasted > 500 s, myocardial damage was systematically detected at scintigraphy, even in cases of uncomplicated procedures. These data indirectly support the concept that indium uptake index and degree of CK-MB elevation are two different aspects of the same phenomenon: procedural-induced myonecrosis.

Recently Ricciardi et al.[8] studied with magnetic resonance imaging a group of patients undergoing PCI; they found that new small areas of myocardial necrosis were frequently detected in the territory of distribution of the treated coronary artery. Interestingly, these areas of myonecrosis were observed only in patients showing increases in CK-MB plasma levels after the procedure, whereas they were systematically absent in patients without post-PCI CK-MB elevation. Finally a linear relationship between the area of hyperenhancement at magnetic resonance imaging and peak CK-MB was found, thus providing an anatomic correlate with biochemical evidence of myonecrosis.

How periprocedural myocardial damage can be induced?

Quite rarely procedural complications can be invoked to explain periprocedural CK-MB elevations. The time of ischemia during balloon inflation, device manipulation, or stent deployment is generally too short to result in myocardial necrosis. Side branch closure is very infrequent, being < 3% in recent trials. Transient or abrupt closure occurs only in < 1% of patients, and the actual time of ischemia is usually limited to a few minutes. Without alternative explanations, the differential diagnosis identifies embolization with microvascular obstruction as the leading cause. Intravascular iatrogenic manipulation of the coronary plaque can induce detachment of atherosclerotic debris and disruption of the fibrous cap with exposure of subendothelial matrix elements. Accordingly, plaque and vessel wall constituents, including lipid, endothelial cells, and platelet thrombus, can embolize, leading to microvascular obstruction[9,10]. Consistent with this hypothesis is the observation that the extent of atherosclerotic disease and the invasiveness of the revascularization technique are the two dominant risk factors in the development of periprocedural myocardial damage. In fact, the rate of infarction appears to be high in case of diffuse atherosclerotic involvement[11] as reflected by long lesions, multivessel disease, or degenerated saphe-

nous vein graft, and is different with respect to the percutaneous technique employed: the risk is high with directional[12] or rotational atherectomy, intermediate with stenting, and low with balloon angioplasty[1,13]. Moreover, the well-known effect of glycoprotein IIb/IIIa inhibitors in limiting the rate of periprocedural CK-MB elevation[14-16] can be explained by the reduced burden of leukocyte and platelet aggregates in the treated segment and, consequently, by a reduced risk of embolization[17]. Finally a relationship has recently been observed between the rate of CK-MB elevation and the quality of myocardial perfusion in the territory of distribution of the treated vessel. In patients who did not experience procedural complications, Gibson et al.[18] showed that a post-PCI suboptimal (0-2) TIMI myocardial perfusion grade was associated with a higher incidence of CK-MB elevation (Fig. 2). Similarly Bolognese et al.[19], in a group of high-risk patients with acute coronary syndrome undergoing PCI, reported that post-procedural cardiac troponin I (cTnI) elevation was associated with an abnormal tissue-level perfusion, as assessed with TIMI myocardial perfusion grade and myocardial contrast echocardiography. These data enforce the hypothesis that myonecrosis and microvascular dysfunction might be linked by the same pathophysiologic substrate, i.e. microembolization.

Can mild creatine kinase-MB release after successful percutaneous coronary intervention negatively influence the long-term outcome?

Many studies have analyzed the prognostic impact of post-procedural enzyme infarction, with conflicting results.

Abdelmeguid et al.[20] analyzed 4484 patients whose post-procedural maximal CK level was < 2 ULN. Recent myocardial infarction (< 36 hours), "salvage" atherectomy for failed coronary angioplasty and chronic total occlusion procedures were excluded. Within this restricted group, a continuous relationship was also found between the degree of CK-MB elevation and the risk of death at follow-up, with no evident threshold.

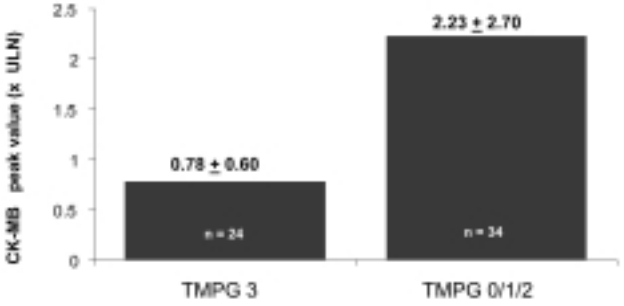

Figure 2. *Relationship between the TIMI myocardial perfusion grade (TMPG) e post-procedural creatine kinase (CK)-MB peak values after stent implantation. ULN = upper limit of normal. From Gibson et al.[18], modified.*

Harrington et al.[21] reported on findings in 1012 patients enrolled in the randomized Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT) comparing excisional atherectomy with angioplasty. Atherectomy was associated with a greater incidence of enzyme-positive events, and a ≥ 3-fold increase in CK-MB levels was associated with a higher rate of repeat revascularization, longer hospital stay, and greater costs. These enzyme rises were also associated with a higher rate of 1-year mortality.

Kong et al.[22], in a single-center analysis, evaluated 253 consecutive patients with elevated CK-MB levels and 120 control patients in a case-control study. Elevation of CK-MB was a significant independent predictor of cardiac mortality, even after considering coronary anatomy and left ventricular function, and this relation did not have an obvious threshold (Fig. 3).

Topol et al.[23] published the long-term outcomes of patients entered into the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial as a function of CK-MB elevation. A stepwise increase in the 3-year rise of death was observed, ranging from a risk ratio of 1.47 (CK-MB 1-2× ULN), to a risk ratio of 2.40 (for patients with an elevation > 10× ULN) (Fig. 4).

Similar results were obtained in a *post-hoc* analysis among patients enrolled in the Integrilin (eptifibatide) to Minimize Platelet Aggregation and Prevent Coronary Thrombosis-II (IMPACT-II): the likelihood of death/myocardial infarction at 30 days, and of death/myocardial infarction/surgical revascularization at 6 months did correlate with post-procedural CK-MB peak value. The predictive value of enzyme data was maintained after adjustment for the variables known to influence the outcome[24].

Recently Ioannidis et al.[25] in a large meta-analysis combined the results of seven published studies that included a total of 23 230 patients. These studies were reported between 1994 and 2002 and involved the use of a wide variety of devices, with variable assays and protocols for the measurement of CK-MB after PCI. Overall, the authors found the incidence of periprocedural CK-MB elevation to be 31%, with the risk of late mortality rising proportionately with increasing biomarker elevations. Importantly, this risk was present even when the degree of CK-MB elevation was only 1 to 3× ULN, suggesting a "dose-response" relationship between biomarker release and subsequent mortality. In this study, however, the risk estimates reported were unadjusted for the influence of confounding factors.

In other recent papers this association between mild periprocedural myocardial damage and long-term mortality was less evident.

Cutlip et al.[26] in a *post-hoc* analysis of 1865 patients enrolled in the Stent Anti-Thrombotic Regimen Study (STARS) and followed for a 6-12 month period,

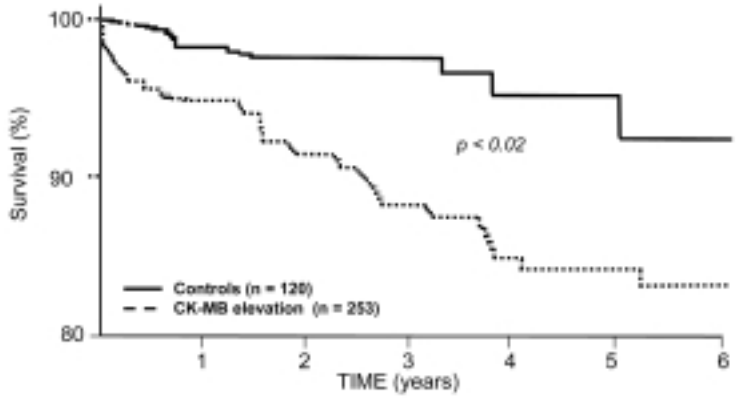

Figure 3. *Survival curves in patients with periprocedural creatine kinase (CK)-MB elevation and in a control group of patients without CK-MB elevation. From Kong et al.[22], modified.*

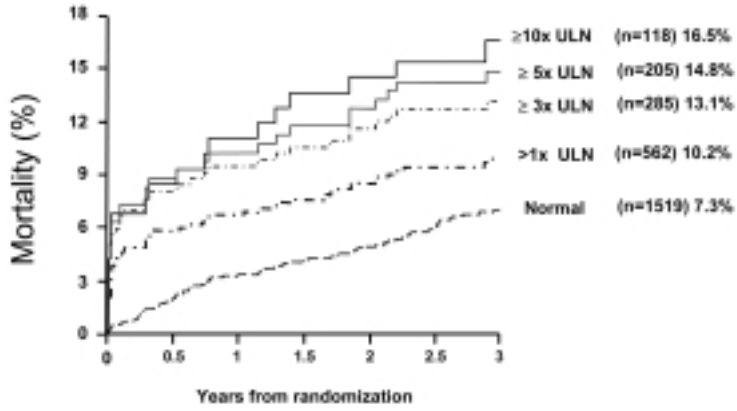

Figure 4. *Mortality curves in patients with different degrees of periprocedural creatine kinase elevation enrolled in the EPIC study. ULN = upper limit of normal. From Topol et al.[23], modified.*

did not found any relationship between CK-MB elevation and mortality. Similarly in the Balloon vs Optimal Atherectomy Trial (BOAT) in which 1000 patients were randomized to receive balloon angioplasty or coronary atherectomy, the incidence of non-Q wave myocardial infarction was higher in the latter group (14 vs 34%, respectively) but this was not associated with a different 12-month mortality[27]. In a more recent retrospective analysis involving 7147 patients treated with PCI at the Washington Hospital Center between 1994 and 1999, and followed for 1.4 ± 1.2 years, Stone et al.[28] found that an elevation of CK-MB above the ULN was present in 37.3% of patients. In most cases, the elevation was quite mild, peaking at between 1 to 3 times the normal values. The frequency of myocardial damage was found to correlate with the type of procedure (higher in case of atherectomy and stent implantation). However the development of new Q waves at ECG occurred very rarely with a frequency ranging from 0.4% following stenting to 0.8% following atherectomy. At multivariate analysis, the most important predictors of both the short- and long-term mortality were new Q waves on the ECG and CK-MB increases > 8× ULN (in the absence of Q waves on the ECG). On the other hand, lesser increases in CK-MB levels (5-8×, 3-5×, < 3× ULN) were not found to have any predictive significance. Finally in a study of Brener et al.[29] including 3478 patients undergoing stent implantation at the Cleveland Clinic between 1992 and 2000, CK-MB elevation was independently associated with an increased risk of death at 15 months, but this risk was confined to those patients with the highest post-procedural CK-MB values (> 10× ULN).

In conclusion, there is general agreement that large elevations in biomarker release (e.g., CK-MB release > 5-8× ULN) are independently associated with late mortality, whereas the prognostic significance of small elevations is still uncertain as they have been related with an increased risk of late death in some analyses, and with a benign long-term outcome in others.

The introduction of troponins as a more sensitive and specific marker of myocardial damage in the set-

ting of PCI has further increased this uncertainty since the conclusions of different studies are diverging. Bertinchant et al.[30] have shown that cTnI and troponin T (cTnT) increases following PCI are not associated with a worse long-term prognosis (mean follow-up 19 months). Fuchs et al.[31] on a series of 1129 patients reported an adverse in-hospital prognosis only for the 175 patients (15.5%) in whom a cTnI peak was > 15× ULN (mortality 1.6 vs 0.6%), but this increased risk was lost at the medium-term follow-up (8 months). Recently Cantor et al.[32], in a study concerning 481 patients with acute coronary syndrome, found that high post-PCI cTnI levels (> 10× ULN) were associated with a significant higher rate of death or (re)infarction at 90 days. Finally Kini et al.[33] in a more recent retrospective study involving 2873 patients, reported that cTnI elevations, detected in 38.9% of the cases, do not predict mid-term (12 months) mortality, whereas CK-MB elevations > 5× ULN do.

The potential methodological limitations of the published reports, such as study design (retrospective or *post-hoc* evaluation vs prospective studies), patient selection (selected subsets vs general population), long enrolment times (up to 6 or 8 years in single-center series), a lack of statistical power, and an inadequate follow-up duration may partially account for these inconsistent conclusions.

In order to provide some further insights into the significance of myonecrosis after PCI, two Italian scientific societies (the Atherosclerosis, Thrombosis and Vascular Biology Study Group and the Italian Society for Invasive Cardiology-GISE) sponsored the CK-MB and PCI study[34], the first prospective study specifically designed to assess the prognostic value of enzyme elevation after PCI. In this multicenter, prospective cohort study, a population of all almost 4000 all-comers treated with PCI in 16 Italian hospitals between February to October 2000 was enrolled and followed for 2 years. To avoid any exclusion criteria, the patients with acute myocardial infarction were also enrolled in the study, although, as pre-specified, were not considered in the final analysis. In all of the patients multiple blood samples were obtained: the first immediately before PCI and the second and third 8-12 and 18-24 hours after the end of the procedure; the serum was stored at -70°C and then shipped to a core biochemistry laboratory where CK-MB and cTnI levels were measured. At the end of the 2-year follow-up all-cause mortality was significantly higher in patients with CK-MB elevation than in those without (7.2 vs 3.8%, $p < 0.001$). A multivariate logistic regression analysis was performed to ascertain whether CK-MB elevation independently predicted long-term mortality, and included all the variables known to influence prognosis in this population. CK-MB peak ratio (calculated by dividing the maximum post-procedural level of the marker by its upper reference limit) proved to be an independent predictor of mortality (odds ratio per unit 1.04, $p = 0.009$), with a linear relationship between the CK-MB peak ratio and the adjusted probability of death. On the contrary the 2-year mortality was not significantly affected by cTnI elevations (4.9 vs 4.0%, $p = 0.2$). The conclusions of this prospective study were that procedural elevations in CK-MB can influence the 2-year mortality, and that there is a linear relationship between the degree of CK-MB elevation and the risk of death, regardless of other variables. Finally, an increase in cTnI does not influence long-term mortality and therefore does not add any prognostic information to that offered by CK-MB levels.

Mechanisms responsible for adverse clinical outcomes

It is only possible to speculate as to why periprocedural CK-MB elevation influences long-term mortality.

One potential mechanism may be related to myocardial damage *per se*, which leads to an increased mortality through electrical instability: microinfarcts can create zones of slow conduction that increase the susceptibility to ventricular arrhythmias via microreentrant circuits. Another potential mechanism is the compromise of coronary collaterals due to microembolization. The interruption of collateral blood flow has been shown to potentiate the ischemic effects of subsequent coronary occlusion. Consistent with these two hypotheses is the observation that antithrombotic drugs such as platelet glycoprotein IIb/IIIa receptor inhibitors, which have been shown to reduce microembolization and post-procedural myocardial damage, also reduce long-term mortality, especially in the high-risk subset of patients[35,36].

Another possibility is that elevated enzymes may identify a particular plaque characteristic otherwise unrecognized by means of other techniques. Such a plaque might be prone to embolic events at the time of the percutaneous procedure and might be associated with an adverse prognosis through a more frequent recurrence of spontaneous rupture and thrombosis and, therefore, of acute clinical events.

Finally, enzyme rises might occur predominantly in patients with more severe disease: from this viewpoint, CK-MB elevation might be a marker of a more active atherosclerotic process and associated with a poor outcome for reasons independent of the enzyme elevation itself[37]. Although in our and other studies the risk of death associated with CK-MB elevations was adjusted for clinical and procedural variables known to influence prognosis in these populations, we cannot exclude that other potentially confounding factors, of difficult evaluation and not taken into account in the analyses, could influence marker elevation and prognosis at the same time.

Do percutaneous coronary intervention-related and spontaneous microinfarcts have a similar prognostic significance?

Theoretically the prognostic impact of spontaneous vs procedure-induced microinfarcts might be remarkably different: differently from the latter, the former may recur more frequently during the unstable phase of an acute coronary syndrome, leading to a longer lasting risk of hard events; furthermore, the potential negative prognostic impact associated with iatrogenic myocardial damage may be balanced by the positive influence of the revascularization procedure. In a recent paper Akkerhuis et al.[38] retrospectively compared the prognostic impact of spontaneous and periprocedural microinfarcts detected in a large cohort of patients enrolled in five clinical trials: CAPTURE (Chimeric c7E3 Antiplatelet Therapy in Unstable Refractory angina), EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications), EPILOG (Evaluation in PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa Blockade), IMPACT-II (Integrilin [eptifibatide] to Minimize Platelet Aggregation and Coronary Thrombosis-II) and PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy). They found that the absolute mortality rates were lower after procedure-related infarcts compared with spontaneous infarcts. Yet the relative increase (odds ratio) in the 6-month mortality at any level of increase of CK-MB peak value was similar, for both spontaneous and PCI-related enzyme elevations (Fig. 5). This seems to suggest that, regardless of the pathophysiological circumstances in which they develop, post-procedural and spontaneous CK-MB release tends to have a similar prognostic significance.

Conclusions and recommendations

Slight elevations in the biochemical markers of myocardial damage are frequently observed after percutaneous coronary revascularization. Elevations are detected in almost all of the patients with abrupt vessel closure, side branch occlusion, thrombus formation or major dissection, but even in case of successful and uncomplicated procedures an enzyme leak may occur as the result of coronary microembolization. Post-procedural CK-MB rise is associated with a higher risk of death; the level of risk seems to increase linearly with any elevation of the marker, with no obvious threshold effect or cut-off value. It is still controversial whether CK-MB elevation is associated with an adverse outcome in a cause-and-effect relationship or whether it simply represents a marker of the patient's worse underlying illness. Attempts to adjust for other prognostic factors seem to confirm that the enzyme rise is an independent predictor of late death. However, beyond the marker and causation theory, post-procedural myonecrosis should be prevented[14,39], systematically sought for and, if detected, always reported in order to better define the patient's risk profile. Ideally, a pre-procedural and post-procedural ECG and a routine measurement of CK-MB levels at baseline and 8 and 16 hours after the procedure should be obtained in every patient. Measurement of cardiac troponins, that do not seem to predict long-term mortality and do not add any prognostic information to that offered by CK-MB in this setting, could be avoided. Further investigations are warranted in order to define whether aggressive secondary prevention strategies[40,41] may improve the long-term outcome of patients with procedure-induced myocardial necrosis.

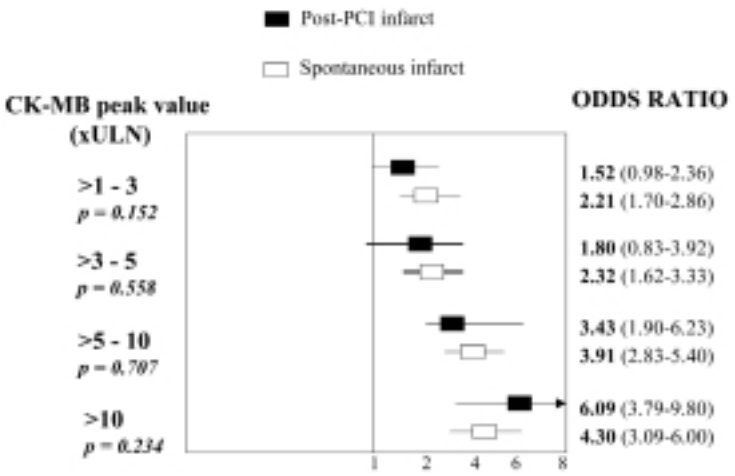

Figure 5. *Odds ratios (and confidence intervals) for the 6-month mortality associated with increasing creatine kinase (CK)-MB peak values in spontaneous and post-percutaneous coronary intervention (PCI) infarcts. ULN = upper limit of normal. From Akkerhuis et al.[38], modified.*

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