Does creatinine kinase-MB elevation after percutaneous coronary intervention predict outcomes in 2005?

Periprocedural Cardiac Enzyme Elevation Predicts Adverse Outcomes

Deepak L. Bhatt, MD; Eric J. Topol, MD

Excessive clinical investigation throughout the 1990s validated periprocedural myonecrosis as a powerful predictor of adverse outcomes, so it is surprising that this remains a contentious point. Originally derided as “enzyme leaks” or “myocardial infarctlets,” periprocedural myocardial infarction (MI) has now been definitively linked in large data sets to long-term adverse outcomes, most notably mortality. It is not, however, always directly contributory or causative. For example, a large creatine kinase (CK) elevation caused by closure of a major side branch resulting in chest pain and development of new Q waves is obviously undesirable and causally related to the interventional procedure. Alternatively, even small, asymptomatic CK elevations have been clearly associated with worse long-term outcome, and although this may in part be causally related to the procedure, it is more likely that the relationship is caused by the underlying predisposing factors that led to the periprocedural MI, such as arterial inflammation predisecting to the occurrence of embolization or to a large degree of atheroma burden leading to more myonecrosis. Under these circumstances, it is likely that the heightened inflammatory state and the diffuse disease that is present are the real causative factors for worse long-term outcomes. Recently, aspirin resistance has been demonstrated to predict periprocedural myonecrosis. Thus, both through direct causation and also as an epiphenomenon, embolization and attendant periprocedural myonecrosis are associated with short, intermediate, and long-term adverse outcomes (Table 1). This review details this evolution in thought.

Periprocedural Myonecrosis and Outcome

Periprocedural myonecrosis is a frequent occurrence in percutaneous coronary intervention (PCI). CK or CK myocardial band (CK-MB) elevation occurs in ≥25% of patients undergoing PCI. With the advent of sensitive troponin measurements, it is clear that at least 50% of patients undergoing PCI have postprocedural troponin elevation, reflecting the frequency with which embolization occurs. However, troponin offers relatively poor specificity for prognosis. In contradistinction, CK elevation has been validated as a marker of prognosis, perhaps due to a threshold phenomenon – that is, a certain degree of embolization may be necessary to be clinically relevant. The most common definition of periprocedural MI is a CK elevation ≥3 times the upper limit of normal (ULN), although this is obviously an arbitrary cut-off. Numerous studies have corroborated the frequency with which periprocedural myonecrosis occurs, even in elec-
Several other studies have corroborated the relationship between periprocedural MI and intermediate- and long-term outcome (Table 2). In a study of 15,637 patients undergoing elective PCI, mortality at 10 years was significantly higher in those with CK elevations >3 times the ULN. After excluding in-hospital and 30-day deaths, this degree of CK elevation remained an independent predictor of death. Even CK elevation 1.5 to 3.0 times the ULN is associated with higher mortality, with each 100 U/L increment of CK associated with a relative risk of cardiac mortality of 1.05. In fact, a meta-analysis of 7 studies with 23,230 patients undergoing PCI found that any CK elevation was associated with a small but statistically significant increase in mortality. Even troponin elevation in the setting of elective PCI has been linked to higher mortality, although this has been an inconsistent finding. Although 1 study did find that CK elevations <8 times the ULN were not associated with increased 2-year mortality, it is likely that with longer-term follow-up, there would have been an observed increase in mortality with even lower degrees of CK elevation, as seen in most other studies.

How, then, can one reconcile the fact that there are large studies that find an association between CK elevation and mortality and others that do not (Table 2)? Several analyses that did find a positive association did not exclude patients with procedural complications and did not stratify patients with varying degrees of postprocedural CK elevation. That is, an association between CK elevation >3 times the ULN may overestimate the strength of the relationship with mortality than if CK 3 to 5 times the ULN were compared with >5 times the ULN, if it is really just the large CK elevations that affect the mortality risk. A common thread among the negative analyses is a shorter duration of follow-up. In general, the longer the follow-up, the more likely the CK threshold associated with increased mortality drops. Perhaps, then, large CK elevations caused by complications from the procedure itself manifest as an increased mortality on a shorter time frame, whereas the associated mortality hazard from smaller CK elevations manifest only after longer-term follow-up through mechanisms described below (Figure 2).

### Table 1. Mechanisms Behind Periprocedural Myonecrosis

<table>
<thead>
<tr>
<th>Procedure-related complications</th>
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<tbody>
<tr>
<td>Side branch occlusion</td>
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<tr>
<td>Flow-limiting dissection</td>
</tr>
<tr>
<td>Abrupt closure</td>
</tr>
<tr>
<td>Macroscopic embolization</td>
</tr>
<tr>
<td>No reflow</td>
</tr>
<tr>
<td>Atheroablative techniques</td>
</tr>
<tr>
<td>Lesion-specific characteristics</td>
</tr>
<tr>
<td>Large thrombus burden</td>
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<tr>
<td>Plaque volume</td>
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<tr>
<td>Plaque vulnerability</td>
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<tr>
<td>Patient-specific characteristics</td>
</tr>
<tr>
<td>Arterial inflammation</td>
</tr>
<tr>
<td>Aspirin resistance</td>
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<tr>
<td>Genetic predisposition</td>
</tr>
</tbody>
</table>

Some mechanisms are clearly related to the interventional procedure, whereas some clearly are not but are caused by lesion or patient characteristics.

Figure 1. Data from EPIC study demonstrated relationship between even moderate degrees of periprocedural myonecrosis and subsequent mortality. Reprinted with permission from Journal of the American Medical Association. Copyright 1997, American Medical Association. All rights reserved.
<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Design</th>
<th>Maximum Follow-up Duration</th>
<th>CK-MB Threshold</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelmeguid et al¹</td>
<td>4664</td>
<td>Consecutive patients</td>
<td>4.8 y</td>
<td>&gt;2× ULN</td>
<td>CK elevation associated with procedural complications (eg, embolism, transient vessel closure, hemodynamic instability, vein graft intervention, large dissections)</td>
</tr>
<tr>
<td>Akkerhuis et al⁶</td>
<td>8838</td>
<td>Pooled data from 5 RCTs</td>
<td>6 mo</td>
<td>&gt;1× ULN</td>
<td>CK elevation post-PCI associated with stepwise increased mortality rate; similar relationship seen in de novo ACS, although absolute mortality risk higher with de novo ACS</td>
</tr>
<tr>
<td>Baim et al⁵¹</td>
<td>1000</td>
<td>RCT of DCA versus PTCA</td>
<td>1 y</td>
<td>None</td>
<td>CK elevation more common after DCA, but no relationship to 1-y mortality, although low mortality rate in each arm</td>
</tr>
<tr>
<td>Brener et al⁵²</td>
<td>3573</td>
<td>Consecutive PCI patients</td>
<td>~4.5 y</td>
<td>&gt;1× ULN</td>
<td>Increased risk of mortality with graded elevations in CK strata</td>
</tr>
<tr>
<td></td>
<td>3812</td>
<td>Consecutive CABG patients</td>
<td></td>
<td>&gt;10× ULN</td>
<td>Increased risk of mortality only above threshold of 10× ULN</td>
</tr>
<tr>
<td>Dangas et al⁵³</td>
<td>4085</td>
<td>Consecutive uncomplicated PCI patients</td>
<td>1 y</td>
<td>&gt;5× ULN</td>
<td>Increased mortality observed in patients with normal and abnormal LV function</td>
</tr>
<tr>
<td>Ghazzal et al⁷</td>
<td>15 637</td>
<td>Consecutive elective PCI patients before GP IIb/IIIa era</td>
<td>10 y</td>
<td>&gt;3× ULN</td>
<td>Angiographic complication rates also higher in patients with CK elevation</td>
</tr>
<tr>
<td>Harrington et al⁵⁴</td>
<td>1012</td>
<td>RCT of DCA versus PTCA</td>
<td>1 y</td>
<td>&gt;3× ULN</td>
<td>DCA associated with higher rate of periprocedural MI than PTCA; in both procedures, periprocedural MI correlated with mortality</td>
</tr>
<tr>
<td>Hong et al⁵⁵</td>
<td>1056</td>
<td>Consecutive patients</td>
<td>1 y</td>
<td>&gt;1× ULN</td>
<td>Increased mortality in patients with periprocedural MI, even in patients without procedural or in-hospital complications</td>
</tr>
<tr>
<td>Jeremias et al⁵⁵</td>
<td>5850</td>
<td>Pooled analysis of patients from coronary stent trials</td>
<td>1 y</td>
<td>&gt;8× ULN</td>
<td>No effect of periprocedural MI on 1-year mortality if unsuccessful procedures excluded</td>
</tr>
<tr>
<td>Kini et al⁵⁶</td>
<td>1675</td>
<td>Consecutive patients</td>
<td>1.5 y</td>
<td>&gt;5× ULN</td>
<td>CK elevation common, even in those without procedural complications, especially in patients with diffuse disease</td>
</tr>
<tr>
<td>Kini et al⁵⁷</td>
<td>2873</td>
<td>Consecutive patients</td>
<td>~3 y</td>
<td>&gt;5× ULN</td>
<td>Troponin elevation did not predict mortality</td>
</tr>
<tr>
<td>Kong et al⁸</td>
<td>373</td>
<td>Case-control</td>
<td>&gt;3.5 y</td>
<td>&gt;1.5× ULN</td>
<td>Relative risk for cardiac mortality was 1.05 per 100 U/L increase in CK</td>
</tr>
<tr>
<td>Kugelmass et al⁵⁸</td>
<td>565</td>
<td>Consecutive DCA or stent patients</td>
<td>&gt;2 y</td>
<td>&gt;5× ULN</td>
<td>Trend toward decreased survival with elevation &gt;5× ULN</td>
</tr>
<tr>
<td>Saucedo et al⁵⁹</td>
<td>900</td>
<td>Consecutive stent patients</td>
<td>1 y</td>
<td>&gt;5×ULN</td>
<td>Association between periprocedural MI and mortality also holds true for stenting, not just PTCA or atherectomy</td>
</tr>
<tr>
<td>Stone et al¹²</td>
<td>7147</td>
<td>Consecutive patients</td>
<td>2 y</td>
<td>&gt;8× ULN</td>
<td>Development of Q wave MI most powerful predictor of mortality; CK elevation more common after atheroablation and stenting than PTCA, but did not correlate with either development of Q wave MI or 2-y mortality</td>
</tr>
<tr>
<td>Tardiff et al⁶⁰</td>
<td>3535</td>
<td>RCT of eptifibatide versus placebo</td>
<td>6 mo</td>
<td>&gt;1× ULN</td>
<td>Increased risk of death, MI, or revascularization with any elevation in CK</td>
</tr>
<tr>
<td>Topol et al¹¹</td>
<td>2099</td>
<td>RCT of abciximab versus placebo</td>
<td>3 y</td>
<td>&gt;1× ULN</td>
<td>Increasing mortality rate in patients with progressively higher cutoffs of CK elevation</td>
</tr>
</tbody>
</table>

RCT indicates randomized clinical trial; ACS, acute coronary syndrome; PTCA, percutaneous transluminal coronary angioplasty; all other abbreviations as in text.
Thus, it is likely that with long enough follow-up, in a large enough cohort, any degree of CK elevation or troponin elevation would be associated with worse outcome. The incremental clinical utility and cost effectiveness of preventing small degrees of periprocedural embolization in patients with perceived low risk may not be attractive, however. Furthermore, it would likely be impractical to design a single long-term large-scale randomized study to determine the value of preventing common low-level troponin elevations after PCI. Fortunately, as a generalization, therapeutic modalities to reduce periprocedural infarction apply to both large and small degrees of CK elevation.

**Mechanisms Underlying the Risk of Periprocedural MI**

Although it is obvious that large periprocedural myocardial infarctions, such as those caused by occlusion of a large side branch, flow-limiting dissection, or distal embolization of a large thrombus, would be undesirable and associated with worse subsequent cardiac outcomes, it is possible that even lower levels of periprocedural embolization may lead to microvascular obstruction and necrosis. Even this degree of necrosis may serve as a future nidus for arrhythmogenesis or may lower the arrhythmic threshold. Both the number of particles and their size affect the response of the microvasculature to embolization. Endogenous release of a vasodilator such as adenosine is able to compensate up to a point. A small number of large particles or a large number of small particles, if enough to exceed a certain threshold, may then lead ultimately to degradation of microvascular flow. Microembolization may also diminish ischemic tolerance and hence increase subsequent infarction size. Importantly, even careful angiographic assessment cannot fully predict which patients will ultimately develop myonecrosis from these “invisible showers.”

Tissue level perfusion, as measured by the tissue myocardial perfusion grade (TMPG), also reflects the degree of myonecrosis detected by CK elevation. TMPG has been found to correlate with mortality in the setting of myocardial infarction, including in patients with Thrombolysis in Myocardial Infarction (TIMI) III flow. Even during elective stent implantation, CK elevation and impaired TMPG have been correlated with one another as well as with infarct mass on contrast-enhanced MRI. Thus, it appears that embolization may lead to impaired tissue perfusion and myonecrosis.

**Devices and Periprocedural MI**

Through what has been termed the “cheese grater effect,” stents always lead to some degree of embolization, more so than does balloon angioplasty (Table 3). High-pressure stent implantation or purposeful stent overexpansion are also associated with increased rates of CK elevation. This effect is amplified in lesions containing thrombus, such as in acute MI. Initial trials of stenting in acute MI showed worrisome trends toward increased ischemic events; however, incorporation of appropriate periprocedural antithrombotic therapy appears to ameliorate any hazard caused by stenting. In fact, the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial supports the synergy of stenting with potent antiplatelet blockade across a wide variety of patient and lesion subtypes. Specifically, the EPISTENT trial demonstrated a reduction in periprocedural MI and 1-year mortality with the use of glycoprotein (GP) IIb/IIIa inhibitors. Of note, the majority of late mortality was caused by sudden cardiac death. Whether these deaths were the result of arrhythmia or de novo plaque rupture is unknown.
Directional coronary atherectomy (DCA) is associated with increased rates of periprocedural MI compared with angioplasty/stenting. Randomized clinical trials such as Coronary Angioplasty versus Excisional Atherectomy Trial (CAVEAT) have demonstrated this and meta-analyses have confirmed it.20 Furthermore, the 1-year data from CAVEAT demonstrated a significant increased out-of-hospital death rate in patients who had been randomized to DCA versus percutaneous transluminal coronary angioplasty (2.2% versus 0.2%, \( P < 0.01 \)).21 This analysis provides direct supportive evidence that devices that increase periprocedural MI may also increase mortality.

It is important to note that intravenous antiplatelet therapy appears to be able to diminish the impact of embolization in all of these settings, perhaps most prominently with the techniques that lead to the most embolization, such as rotational and directional atherectomy. Indeed, rotational atherectomy may serve as the best in vivo model of embolization. Koch et al demonstrated that rotational atherectomy may produce a transient myocardial perfusion defect but that pretreatment with abximab abolished this response.22,23 Indeed, the benefit of abximab in PCI is evident across all of the devices used, including directional atherectomy. Thus, the sequelae of embolization—myocardial ischemia and necrosis—can be attenuated by potent antithrombotic therapy.

In the setting of ST elevation MI, where periprocedural embolization is most likely, the benefits of GP IIb/IIIa inhibition during PCI are most pronounced. On the opposite end of the risk spectrum, GP IIb/IIIa inhibition seems to be unnecessary in low-risk elective PCI, at least if patients are adequately pretreated with aspirin and a large enough loading dose of clopidogrel.

Aspirin Resistance and Periprocedural Myonecrosis

In an interesting analysis, Chen et al found that patients undergoing elective PCI who were classified as aspirin resistant at baseline using the VerifyNow™ (Accumetrics) point-of-care platelet function assay were likely to develop periprocedural myonecrosis (Figure 3).24 Indeed, 66% of the patients categorized as aspirin resistant had a postprocedural troponin elevation as compared with 39% of the aspirin-sensitive patients.24 This study did not use GP IIb/IIIa inhibitors and used only a 300-mg loading dose of clopidogrel. Perhaps a significant degree of periprocedural myonecrosis that is linked to aspirin resistance can be decreased by more potent oral and intravenous antiplatelet and anticoagulant therapy.25 Other studies have demonstrated an association between aspirin resistance and long-term cardiac outcomes.

### TABLE 3. Proven Interventions to Increase or Decrease Risk of Periprocedural MI With PCI

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenting versus PTCA</td>
<td>GP IIb/IIIa inhibitors</td>
</tr>
<tr>
<td>DCA or Roto versus stenting</td>
<td>Aspirin</td>
</tr>
<tr>
<td>High-pressure versus low-pressure stenting</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>SVG interventions</td>
<td>Embolic protection devices</td>
</tr>
<tr>
<td>Elevated hsCRP</td>
<td>Statins</td>
</tr>
<tr>
<td>Aspirin resistance</td>
<td>( \beta )-Blockers</td>
</tr>
<tr>
<td>p38 MAP kinase inhibition</td>
<td></td>
</tr>
</tbody>
</table>

Roto indicates rotational atherectomy; SVG, saphenous vein graft; MAP, mitogen-activated protein; all other abbreviations as in text or Table 2.

**Figure 3.** Patients with evidence of aspirin resistance at baseline are much more likely than patients without evidence to have periprocedural myonecrosis during elective PCI. This tendency would likely be even greater in patients presenting for PCI with acute coronary syndromes. Reprinted with permission from *Journal of the American College of Cardiology.*24 Copyright 2004, American College of Cardiology Foundation.
events. Thus, if aspirin resistance is linked to periprocedural MI and aspirin resistance is linked to long-term adverse cardiovascular outcome, then some of the association between periprocedural MI and long-term outcome may be mediated by aspirin resistance. Of note, in the study by Chen et al, even the aspirin-sensitive patients had a significant rate of periprocedural myonecrosis; therefore, aspirin resistance is only part of the story.

Clopidogrel pretreatment (ie, before PCI as opposed to afterward) was initially understood to decrease periprocedural ischemic events in observational registries. Subsequently, the concept of pretreatment was validated in the Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) study and the Clopidogrel for the Reduction of Events During Observation (CREDO) study. Although antiplatelet effects of pretreatment are the obvious explanations for the benefit from clopidogrel, anti-inflammatory effects have also been postulated. Recent data suggest that clopidogrel lowers CD40 expression and high-sensitivity C-reactive protein (hsCRP) levels. These potential anti-inflammatory effects are more expeditiously achieved by higher loading doses.

Advanced anticoagulants such as the low-molecular-weight heparin enoxaparin or the direct thrombin inhibitor bivalirudin decrease platelet reactivity and may have some enhanced role in aspirin-resistant patients. These observations may explain the benefits of enoxaparin over unfractionated heparin in acute coronary syndromes and of bivalirudin over unfractionated heparin in PCI.

Atheroma Burden and Embolization

An interesting analysis of preinterventional intravascular ultrasound (IVUS) found several important determinants of subsequent periprocedural myonecrosis. The amount of plaque burden, lesion site calcification, cross-sectional narrowing at the lesion and reference sites, and positive remodeling all were associated with higher CK elevation. In addition, atheroablative techniques were also associated with an increased incidence of myonecrosis.

It also appears that purposeful IVUS-guided stent overexpansion, in an effort to reduce restenosis, is associated with higher degrees of CK elevation. In a study of 989 consecutive patients, progressively greater degrees of CK elevation were seen with more aggressive stent-to-artery ratios. One-year mortality did not increase in parallel with the degrees of CK elevation observed in this study, however, again suggesting that at least some part of the association between CK elevation and longer-term mortality may be caused by the underlying plaque burden. Similarly, in an analysis of 1226 consecutive patients, longer stent implantation as compared with shorter stent implantation was associated with more periprocedural myonecrosis but no observed effect on 1-year mortality.

Plaque vulnerability may also be linked to periprocedural MI; that is, plaque that contains rich lipid pools may be most friable. This, too, may explain part of the association of periprocedural embolization and late outcome, inasmuch as the patient with lipid-rich plaque is the one who is most likely to have future ischemic events. Although PCI-induced embolization is the focus of this review, spontaneous embolization is also caused by plaque that is vulnerable. Indeed, this is the basis of the majority of acute coronary syndromes. Interestingly, this phenomenon of spontaneous embolization has also been demonstrated in saphenous vein grafts. It is likely that this explains in part the greater proclivity of unstable thrombotic coronary plaque and vein graft atheroma to embolize during PCI.

Inflammation and Periprocedural MI

It appears that baseline inflammatory marker status can predict the occurrence of periprocedural myonecrosis. Several studies have established the prognostic value of baseline hsCRP in patients undergoing PCI. In a study of elective PCI patients, Saadeddin et al found that patients with elevated baseline levels of CRP were more likely to sustain periprocedural troponin elevation. Thus, it is the patient with arterial inflammation at baseline who is most likely to be the embolizer; this is a key point. Perhaps this is why statin treatment before PCI has been demonstrated to improve outcomes, including periprocedural MI and mortality, so dramatically. Initially, observational studies linked pretreatment with statins (ie, statins before the procedure as opposed to only afterward) with a decreased rate of ischemic events, including mortality (Figure 4A). A lipid-lowering effect is unlikely in the time frame examined, but an anti-inflammatory mode of action may influence PCI-related events and reduce periprocedural MI (Figure 4B). In fact, it appeared that the bulk of the benefit of statin pretreatment was confined to those patients in the highest quartile of baseline hsCRP (Figure 4C). A randomized trial, ATORvastatin for Reduction of Myocardial Damage during Angioplasty (ARTMYDA), prospectively validated the observations regarding the benefit of statin pretreatment, demonstrating a significant reduction in periprocedural MI. Studies such as Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) and Pravastatin Or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) lend additional credence to the powerful relationships among plaque burden, inflammation, CRP reduction, and statin therapy.

Beyond statins, other targeted anti-inflammatory agents may be useful to diminish periprocedural myonecrosis. The use of such drugs before, during, and/or after PCI may diminish myonecrosis and improve clinical outcomes. In addition to anti-inflammatory medications, drugs that affect vascular tone such as adenosine may be proven to be useful in decreasing periprocedural myonecrosis. 40 β-blockers have been shown in some analyses to reduce periprocedural MI, whereas other analyses have disputed this finding. Although markers of inflammation such as hsCRP appear capable of predicting embolization and myonecrosis, other
inflammatory markers such as soluble CD40L or myeloperoxidase may prove to be of greater utility. More likely, panels of inflammatory markers measured before PCI would provide greater incremental prognostic ability. Ultimately, the characterization of single-nucleotide polymorphisms (SNPs) and haplotypes may allow more precise prediction of an individual patient’s likelihood of periprocedural myonecrosis and may facilitate the development of strategies to minimize its occurrence. Polymorphisms have already been identified that affect levels of inflammatory markers and mediators.

Devices to Reduce Periprocedural MI
Pharmacotherapy, such as the use of antiplatelet drugs, can reduce the impact of embolization. Preventing embolization in the first place would be even better. Embolic protection devices (EPD) capitalize on this approach. Interestingly, periprocedural MI was the end point principally affected in the embolic protection trials, similar to the initial data with GP IIb/IIIa inhibitors. Indeed, there is no direct evidence from a single trial that the EPD significantly reduce mortality. Nevertheless, controversy over the validity of periprocedural MI as an end point in the setting of EPD did not erupt. Unlike the debate over platelet GP IIb/IIIa blockade in the 1990s, concerns about cost are not voiced as often in this setting.

The Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial put mechanical embolic protection on the map. This trial demonstrated a significant reduction in periprocedural MI in patients undergoing PCI of bypass grafts, although it was not powered to look at reductions in mortality (Figure 5). Although SAFER investigators used a distal occlusion balloon, distal filters have also been validated as effective in reducing myonecrosis. Interestingly, the use of GP IIb/IIIa inhibitors have not convincingly been shown to be beneficial in patients undergoing bypass PCI, perhaps because the volume of emboli generated overwhelms the ability of antiplatelet therapy to “soften the blow” to the myocardium. Although EPD have not directly been proved to decrease mortality, other studies have shown that periprocedural MI is common in saphenous vein graft PCI, with CK elevation occurring in roughly 15% of cases. Even in patients without angiographic or in-hospital complications, elevated CK was associated with increased mortality, including CK elevations 1 to 5 times the ULN. Therefore, it is logical to believe that because EPD have been demonstrated to decrease periprocedural MI that occurs with vein graft PCI, and because periprocedural MI appears to be associated with increased mortality, EPD should reduce mortality, assuming a large enough study with long-term follow-up were ever to be performed.

Embolic protection has also been used in acute MI. The Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberalized Debris (EMERALD) trial examined the use of the Medtronic GuardWire in patients presenting with acute ST-segment elevation MI. This is the area where embolic protection should seemingly shine. It is surprising that this trial did not demonstrate any clear advantage in patients who were randomized to this device. It is conceivable that the optimal end points were not examined; however, ST-segment resolution is generally believed to be a sensitive marker of the degree of successful tissue level reperfusion. Also, nuclear perfusion scans may not be the best marker in the PCI setting. In fact, the studies of nuclear perfusion in primary PCI versus fibrinolytic trials did not show clear benefit, although it is generally agreed that PCI yields superior clinical benefit as compared with fibrinolytics. Also, the benefit of embolic protection may not manifest without longer-term follow-up, for example, to detect an improvement in LV func-

Figure 4. Treatment with statins before the procedure appears to reduce the rate of mortality (A) in patients undergoing PCI. Reprinted with permission from Circulation. Copyright 2002, Lippincott Williams & Wilkins. Rate of periprocedural MI (B) is also reduced. Apparent benefit in 1-year mortality (C) is most notable in patients with elevated baseline hsCRP. Reprinted with permission from Circulation. Copyright 2003, Lippincott Williams & Wilkins.
tion. Continued recovery of myocardial function after primary PCI has been documented to occur up through 3 months, so it is possible that it would take at least this long to detect any additional incremental benefit from a reduction in embolization; however, this recovery of LV function is at least somewhat dependent on the time to treatment. Another possibility has to do with the specific device. Unlike in a saphenous vein graft, a native coronary artery has branches, so a distal occlusion device may prevent embolization down the parent vessel but still permit some degree of embolic shunting down other branches; filter-based devices would help address that limitation. Of course, the embolic protection device itself may generate some degree of embolization as it initially passes through the lesion.

Newer-generation, lower-profile filters such as the Rubicon filter are much less likely to cause embolization when compared with the available, bulkier devices. This device, planned for evaluation in acute MI, may yet find clinical benefit. Proximal emboli protection devices such as the Kerberos Proximal Solutions Rinspirator or Velocimed Proxis systems may also further decrease the potential for embolization with passage of the device through the lesion and allow more complete aspiration of embolic debris. Mechanical protection may be of greatest utility in large vessels such as a vein graft or a carotid artery, where plaque volume and embolic burden are greatest, and perhaps in smaller vessels, such as coronary arteries. Here, the actual volume of debris is not as large in relationship to the distal circulation, and in this setting, pharmacotherapy is relatively more important. A final, more disturbing possibility for the lack of a positive finding in EMERALD is that in acute MI the window of time in which embolic protection may be useful may be more narrow than originally imagined. By the time most patients have reached the interventional suite, the “horse is out of the barn” and prevention of additional embolization is of minimal clinical consequence. If this were true, then it would mean that time to treatment is even more crucial and that initial pharmacological pretreatment will be necessary and, indeed, complementary to PCI with embolic protection (a strategy of facilitated primary PCI). Therefore, there may yet be a role for EPD in acute MI (Figure 6) and for EPD in high-risk non–ST-segment elevation acute coronary syndromes. Additional trials of embolic protection devices should sort out these important issues.

Periprocedural Myonecrosis in the Setting of Bypass Surgery

CABG–related CK elevation is also associated with worse outcomes. This has not been an easy area to study because many cardiac surgeons are resistant to the idea of measuring myocardial necrosis after surgery. Nevertheless, a number of studies have found that elevations in CK after cardiac surgery are associated with worse outcome. The Guard During Ischemia Against Necrosis (GUARDIAN) study found a strong relationship between CK elevation >10 times the ULN and 6-month

**Figure 5.** Data from the SAFER trial demonstrated the value of embolic protection in saphenous vein graft intervention on periprocedural myonecrosis and a number of associated end points with the Medtronic GuardWire. Reprinted with permission from *Circulation.* Copyright 2002, Lippincott Williams & Wilkins.

**Figure 6.** A, Angiogram of occluded right coronary artery with large thrombus burden in patient with acute inferior MI complicated by hypotension and complete heart block. B, Angiogram after placement of TAXUS drug-eluting stent with Boston Scientific FilterWire in off-label fashion. C, Large amount of atherothrombotic material captured by filter. D, Material largely thrombotic in nature, although there is also some atheroma.
mortality. Although lower degrees of CK elevation were not associated with mortality in that study, with a longer follow-up, a relationship may have emerged. Other studies have found a graded increase in mortality across the full spectrum of CK elevation, including CK-MB >3 times the ULN. In a mechanistic study of 23 patients without previous MI who underwent CABG, infarctions were found in 18 patients. Contrast-enhanced MRI corroborated the occurrence of infarction in patients with elevated biochemical markers, especially those with CK-MB >5 times the ULN.

Conclusions

Periprocedural myonecrosis is associated with an increased risk of adverse outcomes, including mortality. Therapies that decrease periprocedural myonecrosis such as antithrombotic and anti-inflammatory medications also appear to yield clinical benefit. In part, this may be caused by the fact that antiplatelet resistance and heightened states of arterial inflammation each predispose to periprocedural embolization and necrosis but have also themselves been independently linked to worse long-term outcomes. In addition to pharmacological methods to mitigate the effects of embolization, to decrease periprocedural myonecrosis, and to improve clinical outcomes, mechanical approaches such as embolic protection appear to also diminish myonecrosis. Although these lessons have been demonstrated most elaborately about the coronary circulation, data are being amassed in the cerebral and peripheral circulations as well, although the optimal combination of specific drugs and devices may not be constant for different applications. Refinements in pharmacotherapy and ongoing developments in embolic protection will lead to additional decrements in macro- and microembolization, less periprocedural tissue necrosis, and associated improvements in short- and long-term clinical outcomes.

References


Cardiac Enzyme Elevation After Successful Percutaneous Coronary Intervention Is Not an Independent Predictor of Adverse Outcomes

Donald E. Cutlip, MD; Richard E. Kuntz, MD, MSc

The debate over the importance of periprocedural creatinine kinase-myocardial band (CK-MB) elevation after percutaneous coronary intervention (PCI) has captured the attention of cardiologists since the early days of balloon angioplasty, when the phenomenon was first recognized and reported to have no clear association with adverse clinical sequelae.1,2 These early reports were limited by the small numbers of patients and follow-up that extended only to hospital discharge. Since then there have been numerous published studies documenting the frequency and clinical outcomes of periprocedural CK-MB elevation, most of which have implicated it in a clear relationship to later adverse outcome including increased mortality.3–9 Multiple additional reports of this adverse association have been presented only in abstract form. Moreover, previous controversies about whether these enzyme elevations actually represent myocardial infarction (MI) have been dismissed by clear evidence demonstrating myocardial necrosis in the zones of the target vessel after PCI accompanied by CK-MB elevation.10 The consistency of these findings has led to widespread acceptance of a deleterious role for periprocedural MI,11 and moderate elevations of CK-MB (>3 times the upper limit of normal [ULN]) have been regarded by many as appropriate surrogate end points for studies of coronary interventional devices and antithrombotic drug therapy. Still, some investigators have not found an association or have reported adverse outcomes only after large MI (CK-MB >5 to 10 times the ULN) or with a concurrent procedural complication for which the survival consequences are not debated.12–15

The fact that the debate continues at national meetings and has been included here in this series of controversies in cardiovascular medicine points to a need for a critical reappraisal of this literature to determine a thesis that the available data can support, while providing a clear explanation for the discrepant findings of the opposing view. As in all analyses, the task must begin with a clear statement of the question, which we pose as “Does any elevation of CK-MB after an otherwise successful procedure have an independent association with subsequent mortality?” We frame our antagonist position within the following 3 arguments: (1) Many studies purporting a relationship between low-level CK-MB elevation and mortality have faulty designs that limit their conclusions; (2) the data do not support periprocedural CK-MB elevation as a surrogate end point for mortality; and (3) the definition of “otherwise successful” has been inconsistent and in many cases may not pertain to the current stent era.

Finally, we address specific situations in which the effect of periprocedural MI may be modified by higher baseline risk, such as saphenous vein graft intervention or patients with significant left ventricular systolic dysfunction.

Limitations of Previous Studies

The evaluation of late clinical outcomes after periprocedural CK-MB elevation is restricted to a study of potentially unmatched cohorts because it is by definition a post hoc event. As such, its occurrence selects groups that are likely to be heterogeneous for multiple baseline and procedural characteristics that influence not only the choice of the interventional procedure itself but also many pre- and post-treatment management decisions. Any of these measured or unmeasured confounding factors could contribute significantly to late outcome. Indeed, the postprocedure measurement of CK-MB itself may be based on other clinical concerns and thus adds selection bias as a limitation. Finally, many PCI populations on which previous reports have been based included patients presenting with acute coronary syndromes, and it is unclear to what degree so-called periprocedural CK-MB elevations actually represented events occurring preprocedure and thus were secondary to spontaneous MI.3–6 Efforts to reduce this limitation by merely excluding patients with periprocedural CK-MB elevation are incomplete given the inherent delay between time of MI and elevation of CK-MB.

Some of these limitations can be overcome by appropriate study design. For example, a prospective analysis within a clinical trial that has strict inclusion and exclusion criteria and a requirement for systematic collection of cardiac enzyme
data in all patients at specific time intervals should minimize the potential for major baseline differences between the MI and no MI groups and avoid bias caused by incomplete ascertainment. If acute coronary syndrome patients are included, then the protocol must either exclude these patients unless a normal CK-MB value is obtained &gt;8 hours after presentation and before PCI or require careful adjudication by an independent events committee to determine whether periprocedural CK-MB elevation is likely caused by a periprocedural spontaneous event.

Instead, most of the studies reporting an increased mortality risk for periprocedural CK-MB elevation after otherwise successful procedures have been retrospective reviews of single-center databases. It is not possible for any retrospective analysis to approximate equality between the study groups or to adequately control for all unmatched factors influencing outcome. Moreover, even slight deficiencies in ascertaining postprocedure CK-MB data that are invariably a part of retrospective analyses may significantly bias the results. In fact, such potential difficulties are clearly identified by the authors of these studies. In 1 study, patients who had CK &gt;2 times the ULN were also more likely to have had recent MI, unstable angina, thrombotic or complex lesions, vein graft intervention, and directional coronary atherectomy (DCA) procedures. It is not surprising that these risk factors may identify a group at higher risk for subsequent death. The same authors reported similar baseline differences as well as an increased risk for subsequent MI and revascularization in patients identified only by CK-MB elevation without elevated CK, further suggesting that CK-MB may be an epiphenomenon in otherwise identified high-risk patients.

Differences between the MI and no-MI groups of other studies have been even less subtle. In a report from the Coronary Angioplasty versus Excisional Atherectomy Trial (CAVEAT), 3 of 13 cardiac deaths were associated with abrupt closure during or shortly after the procedure and large Q-wave MI. These events represented 3 of the 6 deaths assigned to the group with elevated CK-MB, and contributed to the conclusion that elevated CK-MB was a significant predictor of 1-year mortality. In another study with a matched cohort design, the matching of groups with and without CK elevation based only on date of procedure and interventional device failed to account for significantly worse periprocedural success measures in the CK elevation group, including final diameter stenosis &gt;50% (15% versus 7%, $P = 0.003$) and final Thrombolysis in Myocardial Infarction (TIMI) grade flow &lt;3 (17% versus 3%).

Most evidence incriminating modest elevations of periprocedural CK-MB after otherwise successful procedures is derived from the aforementioned studies. Clearly, the concerns regarding the retrospective designs and other limitations of these studies should give investigators pause before accepting the conclusion that any level of CK-MB elevation after an otherwise successful procedure has subsequent mortality risk. Furthermore, as we address this question for 2005, it is important to consider that these studies are limited not only by inherent design flaws but also by data obtained from an era before the widespread use of coronary stents and other refinements of PCI technique. Before discussing the data from more current stent populations, however, we review the case for acceptance of elevated periprocedural CK-MB elevation as an appropriate surrogate end point for subsequent mortality.

### Elevated CK-MB as a Surrogate End Point for Mortality

The clinical benefit of PCI in most patient subsets is restricted to relief of angina with no clearly proven effect on mortality or subsequent myocardial infarction. Yet it is these major clinical complications of coronary artery disease that most concern cardiologists and their patients and represent the leading causes of morbidity and mortality in the Western world. Despite this apparent disconnect, the rate of PCI continues to increase, with &gt;800 000 procedures performed annually in the United States. If it is true that a procedure performed only for relief of symptoms actually has an increased mortality risk in at least 10% to 20% of the patients undergoing the procedure, then this topic should receive even greater attention and the continued performance of the procedure should be strongly questioned in all but a limited number of patient groups. Support for having not adopted this stance can be developed by an examination of the value of CK-MB elevation as a surrogate end point for cardiovascular mortality.

The significance of cardiovascular mortality for the public health has led to the performance of numerous interventional clinical trials aimed at preventing or delaying these events. Such trials require large numbers of patients and long periods of follow-up at considerable cost with the attendant potential pitfalls of lack of validity by the time results are available or serious delays in availability of efficacious therapies. Furthermore, as clinicians, we value reliable predictors of mortality to help guide treatment decisions for our patients. The availability of markers that are tightly linked to disease pathogenesis and outcome would be valuable as potential replacements for the hard clinical morbidity and mortality end points. Care must be exercised, however, to distinguish risk markers that are only statistically related to disease outcome from true surrogate end points. To meet the requirement for surrogate status, a marker must track with the frequency of disease both as an epidemiological risk factor and a therapeutic responder. That is, there must be a plausible cause-and-effect mechanism as well as evidence to support an equal directional effect on disease outcome for interventions that either increase or decrease the frequency of the surrogate marker. An intervention that decreases (or increases) the frequency of a surrogate marker for mortality should have a corresponding decrease (or increase) in mortality.
Studies reporting an association of CK-MB elevation and late mortality have argued, at least implicitly, for surrogate status for periprocedural CK-MB and have led to 2 significant modifications in the practice of interventional cardiology: demise of DCA as an alternative to balloon angioplasty and approval and widespread use of glycoprotein (GP) IIb/IIIa inhibitors during PCI. Although both of these judgments by the interventional community may have been correct choices from the perspective of the modern stent era, a surrogate role for periprocedural CK-MB elevation should not be credited with providing the convincing evidence. Indeed, it is worth considering the data from the major DCA studies and mortality data from GP IIb/IIIa clinical trials as antithetical arguments for CK-MB elevation as a mortality surrogate.

The CAVEAT study was the first large randomized trial of DCA versus balloon angioplasty and raised concerns regarding the continued use of DCA. The concerns were caused by the lack of efficacy in preventing restenosis and, more important, serious safety issues, including increased 1-year mortality in the DCA group. This 1-year mortality difference (2.2% versus 0.6%, \( P=0.035 \)) was attributed mostly to the increased frequency of periprocedural MI, defined as CK-MB elevation >3 times the ULN, after DCA (15.2% versus 6.8%, \( P=0.001 \)). If we apply the test for surrogacy based on these results, then we may conclude that because the potential surrogate (CK-MB elevation) is associated with increased risk of the outcome (mortality) and is increased in response to the intervention (DCA), the test criteria are fulfilled. A review of additional data proves this conclusion to be erroneous.

Of the 13 cardiac deaths in CAVEAT, 5 (36%) occurred in the group with CK-MB elevation. Of these, however, 3 were associated with large Q wave MI and major procedural complications, 2 of which were actually in the balloon angioplasty group. Whereas DCA was associated with increased mortality, only 2 of the 11 DCA deaths could be related to CK-MB elevation after otherwise successful DCA procedures.

Additional evidence against CK-MB as a surrogate marker after DCA comes from the Balloon Angioplasty versus Optimal Atherectomy Trial (BOAT). The BOAT investigators had the advantage of increased experience and knowledge of the potential complications of DCA from CAVEAT and other studies, resulting in many technical refinements to the procedure to achieve higher device success and fewer acute angiographic complications. Similar to CAVEAT, the frequency of CK-MB elevation was still significantly higher for DCA as compared with balloon angioplasty (16% versus 6%, \( P<0.01 \)). In sharp contrast, however, observed 1-year mortality was actually lower in the DCA group (0.6% versus 1.6%, \( P=0.14 \)). Taken together, the data from CAVEAT and BOAT argue convincingly against CK-MB elevation as a surrogate marker inasmuch as an intervention with a consistent response effect on the potential surrogate marker demonstrates variable association with the measured outcome.

Similar conclusions can be derived from a review of GP IIb/IIIa inhibitor mortality data. The Evaluation of IIb/IIIa Inhibitor for Stenting (EPISTENT) trial was the first trial of a percutaneous revascularization strategy to show a beneficial effect on mortality with a 57% mortality reduction in favor of a group randomized to coronary stenting and the GP IIb/IIIa inhibitor abciximab compared with standard stenting without a GP IIb/IIIa inhibitor. Given that the only documented significant benefit of GP IIb/IIIa inhibitors had been a reduction in the frequency of periprocedural CK-MB elevation, many assumed that periprocedural CK-MB elevation represented a surrogate for late mortality. Subsequent data argue against that assumption. In a pooled analysis of abciximab PCI studies, Anderson et al reported that periprocedural CK-MB elevation explained only 18% of the abciximab mortality benefit (HR 0.71, \( P=0.003 \)). This is consistent with findings from the Do Tirofiban and Reopro Give Similar Efficacy Outcome Trial (TARGET), in which, despite significant reductions in frequency of periprocedural CK-MB elevation for abciximab compared with tirofiban, the 6-month outcomes were not different, and 1-year mortality rates among the high-risk patients with diabetes were identical. This dissociation between rates of periprocedural CK-MB elevation and reduced mortality not only fails to support CK-MB as a surrogate marker but also requires alternative mechanisms to account for the late mortality benefit of GP IIb/IIIa inhibitors that has now been demonstrated in 2 separate meta-analyses. These explanations may involve improved microvascular perfusion as demonstrated after stenting with adjunctive GP IIb/IIIa versus placebo, and potent antagonistic effects by GP IIb/IIIa inhibitors on platelet inflammatory mediators such as sCD40L.

It should be noted that the absence of surrogate status for CK-MB elevation does not reject the statistical association between reduced rates of periprocedural CK-MB elevation and mortality. CK-MB elevation may simply identify, albeit imperfectly, a group of patients who are at higher baseline risk and may be more likely to benefit from early aggressive antiplatelet therapy.

Such a role for CK-MB as a marker for higher risk rather than a cause of or surrogate for increased mortality has been suggested as a harmonious interpretation of the studies discussed above. Indeed, the finding by some studies that the largest mortality difference between groups with low-level CK-MB elevation and no elevation occurs >1 year after the procedure suggests the identification of a group with a confounding factor that is associated with worse late prognosis, such as more severe underlying atherosclerotic disease. Although earlier reports did not suggest that the prognostic significance of periprocedural CK-MB elevation was explained by greater underlying disease, more recent studies have found evidence for an association. Kini et al observed that diffuse coronary disease, determined by lesion length >20 mm or multiple single lesions in ≥1 vessels, and
systemic atherosclerosis, defined as a history of peripheral vascular, cerebrovascular, or aortic disease, were both independent predictors of periprocedural CK-MB elevation among 1675 consecutive patients. In a study of preintervention intravascular ultrasound analysis of 2780 lesions, Mehran et al reported increases in plaque volumes at both the reference segments and lesion sites for patients with progressively higher periprocedural CK-MB. Plaque volumes at the reference segments and lesion sites were both independently associated with periprocedural CK-MB elevation. To the extent that these studies identify more severe atherosclerosis associated with the probability of periprocedural CK-MB elevation, it is not surprising that a higher mortality risk may also exist.

The available data thus do not support a role for periprocedural CK-MB elevation as a surrogate marker for morbidity and mortality after PCI. There is a reported statistical association between elevated periprocedural CK-MB and late mortality, but there is no convincing evidence of a cause-and-effect relationship and the supposition is supported mostly by retrospective studies from the present era. It is likely that the relationship is explained in part by the identification of a group with baseline characteristics that increase both the risk for periprocedural CK-MB elevation and late mortality.

Previous reports have shown that the frequency and severity of periprocedural CK-MB elevation are strongly related to the choice of percutaneous device and that outcomes after serious procedure-related complications or Q wave MI are the choice of percutaneous device and that outcomes after PCI. Differences such as persistent dissections and acute vessel closure,4 CK-MB elevation after coronary artery stenting is most often thought to be the most common cause of periprocedural CK-MB elevation after stenting, which occurs in >20% of patients, including elevations >3 times the ULN in at least 8% of patients. Based on extrapolation of data from many of the studies of balloon angioplasty and atherectomy discussed above, periprocedural non-Q wave MI, defined as CK-MB elevation >3 times the ULN or total CK >2 times the ULN, has been included as a component of the primary safety end point for recent coronary stent clinical trials evaluated by the US Food and Drug Administration. Whether the findings from these studies of devices with differing pathogenesis of CK-MB elevations—even accepting their other limitations, can be applied to coronary stent patients has not been clearly demonstrated.

Several studies have provided some insight into this question. Saucedo et al studied 900 consecutive patients undergoing successful stenting at a single institution between 1994 to 1995 and noted large periprocedural CK-MB elevation (>5 times the ULN) in only 67 (0.7%) patients. These patients represented a uniquely high-risk group with significantly more complex lesion characteristics and increased in-hospital ischemic complications including subacute stent thrombosis and repeat revascularization as compared with patients without CK-MB elevation. In this small study, 1-year mortality was significantly higher for patients with CK-MB >5 times the ULN as compared with patients without CK-MB elevation (6.9% versus 1.7%, P=0.01) but was not different for patients with CK-MB elevation <5 times the ULN (1.2% versus 1.7%).

More recently, Stone et al reported a much larger series of 7147 consecutive patients treated from 1994 to 1999 including >3600 stent patients. Periprocedural CK-MB elevation >3 times the ULN occurred in 16.9% of patients and was >8 times the ULN or associated with Q wave MI in 7.8%. By 2 years, mortality was independently and significantly higher for patients with periprocedural Q wave MI (38.6%, HR 9.9, P<0.0001) or CK-MB elevation >8 times the ULN without Q waves (14.5%, HR 2.2, P<0.0001). Lesser degrees of periprocedural CK-MB elevation had no effect on 2-year mortality compared with no CK-MB elevation.

The Stone et al study has the strength of a consecutive series of patients with complete ascertainment of periprocedural CK-MB data and representing variable periprocedural risk and procedure outcomes. Although the authors excluded patients with recent MI (<72 hours) and those with subacute vessel closure or who required emergency bypass surgery within 24 hours, an accompanying editorial in Circulation speculated whether this study adequately addressed the question we have stated in this debate, namely whether there is an effect of periprocedural CK-MB elevation after an otherwise successful stent procedure. This raises the issue of how a successful stent procedure should be defined in 2005. In the previous studies described in this review, “otherwise successful” was broadly defined according to National Heart, Lung, and Blood Institute registry standards as <50% diameter.
stenosis without in-hospital death, Q wave MI, or emergency CABG. Even though some of the studies included procedures that were unsuccessful even by this definition, it can be argued that a more conservative definition should be adopted for stent procedures in which unstented dissections and final slow flow also connote failure. Furthermore, although the risk of emergent CABG has been reduced dramatically in concert with improved acute lesion outcomes and the near elimination of abrupt closure, stenting is associated with a unique risk of acute and subacute thrombosis. We have reported that in the modern stent era most of these thrombotic complications occur within the first 24 to 48 hours after the procedure and are associated with a 6-month mortality rate of 20%. Because this is the time interval during which postprocedure cardiac enzyme measurements are also determined, it is possible that enzyme levels caused by stent thrombosis may have been included among otherwise successful procedures. Obviously, it would be a mistake to equate the increased mortality related to stent thrombosis with outcomes of periprocedural CK-MB elevation after otherwise successful procedures.

We recently evaluated the differential impact on the 1-year mortality effect of periprocedural CK-MB elevation according to success or failure of the stent procedure in a pooled series of 5850 coronary stent patients from 6 coronary stent clinical trials. For this analysis, an unsuccessful procedure was defined as final diameter stenosis < 50%, final TIMI grade flow < 3, final dissection National Heart, Lung, and Blood Institute grade D or greater, or development of stent thrombosis or requirement for urgent target vessel revascularization within 24 hours. All clinical events and procedure failure criteria were adjudicated by an independent committee or angiographic core laboratory. The events committee also adjudicated MI events that were in progress at the time of the stent procedure leading to the exclusion of those patients from the analysis. The procedure was considered successful in 98% of patients. Periprocedural CK-MB elevation occurred in 20.4% of successful procedures but was not associated with an increase in 1-year mortality as compared with no CK-MB elevation (2.1% versus 1.7%, P > 0.20). CK-MB was elevated > 8 times the ULN or new Q wave MI was present after only 2% of successful procedures. In contrast, CK-MB was elevated after 70% of unsuccessful procedures including > 8 times the ULN or new Q waves in 32%, and was associated with a significantly higher risk of death in the first year as compared with no CK-MB elevation (13.1% versus 0%, P = 0.03). This included 19.7% mortality among patients with unsuccessful procedures and CK-MB > 8 times the ULN or new Q waves.

These studies demonstrate that periprocedural CK-MB elevation is common after coronary stenting but is limited to low-level elevations in most cases with infrequent occurrence of large non-Q wave and Q wave MIs. When these larger MIs do occur, they are almost always the result of procedural or early postprocedure serious complications, which would not indicate a successful procedure by most perceived standards. Regardless, these large MIs are consistently and uniquely associated with an increased mortality risk at 1 and 2 years, with no apparent significant increase in either short- or long-term mortality for low- and moderate-level (< 5 to 8 times the ULN) CK-MB elevation after successful coronary stenting.

Special High-Risk Subgroups

There are 2 groups of patients for whom periprocedural CK-MB elevation may carry an exceptional risk and the general comments and interpretations of previous studies we have included in this discussion may not apply. These groups include patients undergoing PCI within a degenerated saphenous vein graft and patients with significantly depressed baseline LV systolic function.

Hong et al reported periprocedural CK-MB elevation in 45% of patients undergoing saphenous vein graft PCI, including 30% with “minor” (CK-MB > 1 to 5 times the ULN) and 15% with “major” (CK-MB > 5 times the ULN) elevation. There was significantly increased 1-year mortality for minor (6.5%) or major (11.7%) levels of periprocedural CK-MB elevation as compared with no elevation (4.8%). Distal embolization is likely to be more severe during saphenous vein graft PCI and more likely to result in major reperfusion abnormalities, which may account for this observed increased risk. For this reason, we recommend routine use of embolic protection devices in the treatment of these lesions with a goal of avoiding these complications and associated periprocedural CK-MB elevation.

Ellis et al noted an increase in the magnitude of risk for periprocedural CK-MB elevation depending on the presence of LV systolic dysfunction. For patients with LV dysfunction, 4-month mortality rates increased from 1.9% to 14.0% if periprocedural CK-MB elevation > 5 times the ULN occurred. A smaller but important increase to 3.0% was approximated for patients with CK-MB elevation < 5 times the ULN. It is reasonable to suspect that patients with abnormal baseline LV function will have poorer tolerance of any additional insult and additional concern about periprocedural CK-MB elevation in this group is warranted.

Conclusions

Despite widespread acceptance of a direct association between any level of periprocedural CK-MB elevation and subsequent mortality, a critical review of the available studies does not support this position. Instead, most studies are seriously flawed on the basis of unavoidable retrospective design and failure to adequately account for significant other differences between patients with and without CK-MB elevation. Furthermore, there are convincing data that periprocedural CK-MB elevation is not an acceptable surrogate marker for later mortality, and that any true statistical association is most likely caused by the identification by periprocedural CK-MB elevation of a group with increased...
mortality risk before the PCI procedure was performed. In the current stent era, available studies suggest an increased risk only for large non-Q wave and Q wave MI, the occurrence of which is almost always caused by major procedure-related complications or early postprocedure clinical events rather than by unexpected events after otherwise successful procedures.

In 2005, low-to-moderate level CK-MB elevation does not predict outcomes. Similar to patients without CK-MB elevation, outcomes are determined by procedure-related complications or early postprocedure clinical events rather than by unexpected events after otherwise successful procedures.

References


Response to Cutlip and Kuntz

Deepak L. Bhatt, MD; Eric J. Topol, MD

Dr Cutlip and Kuntz make several valid points in their article; however, they have redefined the question that was posed. The point of contention was whether periprocedural MI predicts outcome, and several studies have demonstrated that it does, although the exact threshold has varied depending on the population examined, the sample size of the study, and the duration of follow-up. Therapies to reduce periprocedural MI, such as antithrombotic medications and statins, improve clinical outcomes. Thus, periprocedural MI is more than just a marker for risk—it is also a target for therapy. Therefore, measurement of CK-MB is worthwhile and clinically meaningful.

Furthermore, we agree with the excellent work by Cutlip and Kuntz regarding the benefits of embolic protection devices. In those articles, the end point they appropriately used incorporated CK-MB >3 times the upper limit of normal, even in the absence of angiographic complications, as part of the major adverse cardiac event rate. Indeed, up to the present, embolic protection devices have largely been associated with reduction in CK elevation, not in Q wave MI or mortality. Nevertheless, we concur with them that CK elevation is an end point worth preventing in the setting of vein grafts as well as in other settings by devices as well as by drugs.

In conclusion, we restate that the bulk of available evidence supports the importance of periprocedural myonecrosis as a clinical entity that is worthy of prevention, and we agree with the work of Drs Cutlip and Kuntz and others who have used and continue to use this end point in clinical investigation.

References

Response to Bhatt and Topol
Donald E. Cutlip, MD; Richard E. Kuntz, MD, MSc

We congratulate Drs Bhatt and Topol on their excellent review of the available data regarding the significance of CK-MB elevation after PCI. Although their review and ours reach different conclusions, it may be helpful to the clinician faced with this dilemma to consider the points on which the 2 articles seemingly agree. There is agreement that large CK-MB elevations, especially if associated with major procedure-related complications, increase mortality. Both articles also agree that lesser CK-MB elevations probably do not have a causal effect on mortality but may be a marker of other high-risk factors such as severity of disease or inflammatory status. It is also likely that we would agree on the inability to reliably predict serious procedure-related complications and on the notion that efforts to prevent these events should be fully used, including optimal technique and appropriate antiplatelet therapy.

The difference arises in the interpretation of low-level CK-MB elevation that occurs despite these efforts and the explanation that should be provided to the patient having this finding. In our view, CK-MB elevation in this setting is a statistical confounder rather than a predictor of outcome. After appropriate statistical testing, it appears to be at best a fairly weak marker of other high-risk factors. To assume otherwise means that both short- and long-term risk prevention strategies should be stratified by the presence or absence of postprocedure CK-MB elevation rather than by the underlying risk factors with which CK-MB may be associated. Such an approach not only causes undue alarm related to the procedure in the short term but may miss the opportunity to provide similar secondary prevention for patients with equally high-risk profiles but with a negative CK-MB marker.
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