Creatine Kinase-MB Elevation Following Stent Implantation

We read with interest the study by Jeremias et al. (1) published in the Journal. The investigators claim that creatine kinase-MB fraction (CK-MB) elevations following stent deployment portend an unfavorable prognosis only for patients with unsuccessful procedures. Although this finding may be true, we have several reservations.

The researchers do not provide the absolute number of deaths; however, it can be indirectly inferred from the presented total number of patients and event rates that their entire study includes only 10 deaths among patients with an unsuccessful procedure and about 100 more deaths in patients with successful procedures. The main inferences are practically based on 10 deaths. Such small numbers do not allow any meaningful modeling in CK-MB strata or multivariate analyses.

Furthermore, the use of percentages is misleading here; for example, the 5% death rate on patients with type 2 myocardial infarction (MI) and unsuccessful procedure is based on a single death, and the 9.1% death rate on patients with type 1 MI is based on only two deaths! Even the unadjusted analyses are based on extremely thin information. The successful procedure data are also limited: the observed differences of 0.4% to 0.7% excess death rate with small CK-MB elevations are certainly not statistically significant given the small number of events, but they may be clinically important when extrapolated to the millions of patients who undergo "successful" procedures.

Moreover, the overall one-year death rate in the study by Jeremias et al. is only 2%, whereas it has been about 4% in other studies evaluating peri-procedural MI (2). The same relative risk increase would have a larger absolute magnitude in a population at higher baseline risk of death.

We are also concerned that the details of the study protocols and justification of data pooling as described in the study by Jeremias et al. (1) are not fully described in the cited reference (see reference 8 in their report). The definition of "unsuccessful" procedure is not standardized in the published data. The definition of Jeremias et al. comprises five different elements (stenosis, flow grade, dissection, repeat revascularization, stent thrombosis). Each of these may be selected with different cutoffs (e.g., stenosis grade, dissection, repeat revascularization, stent thrombosis). Each reference 8 in their report). The definition of "unsuccessful" and justification of data pooling as described in the study by Jeremias et al. is only 2%, whereas it has been about 4% in other elective stent populations (5) and was essentially flat for other criteria. Some investigators have published a meta-analysis of gastric interventions (treated by a mixture of stent, directional coronary atherectomy, and balloon angioplasty over a decade, showing a one-year mortality risk of 3.5% with normal CK-MB, rising to 5.2%, 6.3%, and 10.9% for CK-MB 1 to 3, 3 to 5, and >5 times normal, respectively (2). What such meta-analyses gain in numbers of patients and events may be lost in lack of detail about those patients—for instance, whether the effect holds true for stenting (as used in 90% of current interventions), and whether it applies equally to incidental CK-MB elevations seen after otherwise successful procedures. Our study is actually one of the largest reports after elective stenting, with nearly 6,000 patients and over 100 death events, and includes data pooled at the patient-by-patient level, so that it could look into the question with greater granularity. The pooling of the trials was fully justified based on the nearly identical inclusion criteria and baseline clinical and angiographic characteristics (3,4). The one-year mortality was similar to other elective stent populations (5) and was essentially flat for normal-to-moderate level CK-MB elevations among successful procedures, whereas mortality was over six times higher in patients with unsuccessful procedures and any elevation in CK-MB.

REFERENCES


REPLY

We thank Dr. Ioannidis and colleagues for their interest in our study (1), in which we hypothesized that procedure success would have a significant effect on the reported association between mortality and peri-procedural creatine kinase-MB fraction (CK-MB) elevation. Dr. Ioannidis and colleagues have raised concerns regarding insufficient numbers of patients and events to adequately address the question, justification for pooling of the clinical trial data, interpretation of the small absolute risk difference, and a definition of procedure success that is not standardized in the published data.

These same investigators have published a meta-analysis of ACS [acute coronary syndrome] and vein graft interventions) treated by a mixture of stent, directional coronary atherectomy, and balloon angioplasty over a decade, showing a one-year mortality risk of 3.5% with normal CK-MB, rising to 5.2%, 6.3%, and 10.9% for CK-MB 1 to 3, 3 to 5, and >5 times normal, respectively (2). What such meta-analyses gain in numbers of patients and events may be lost in lack of detail about those patients—for instance, whether the effect holds true for stenting (as used in 90% of current interventions), and whether it applies equally to incidental CK-MB elevations seen after otherwise successful procedures. Our study is actually one of the largest reports after elective stenting, with nearly 6,000 patients and over 100 death events, and includes data pooled at the patient-by-patient level, so that it could look into the question with greater granularity. The pooling of the trials was fully justified based on the nearly identical inclusion criteria and baseline clinical and angiographic characteristics (3,4). The one-year mortality was similar to other elective stent populations (5) and was essentially flat for normal-to-moderate level CK-MB elevations among successful procedures, whereas mortality was over six times higher in patients with unsuccessful procedures and any elevation in CK-MB.
As we stated in our discussion, the 0.4% absolute difference in mortality between patients with and without myocardial infarction (MI) after successful intervention could still be clinically meaningful. But we must reject the other criticisms of Dr. Ioannidis and colleagues regarding the limitations of our study. The inferences are not based on a small number of unsuccessful procedures, but on an analysis of 5,850 patients with over 100 deaths, for which an unsuccessful procedure was one of the most significant independent predictors of one-year mortality. Most importantly, we are concerned with the misinterpretation of our identification of successful and unsuccessful procedures. We were careful to select unsuccessful procedures using criteria on which most operators would concur in the context of current stenting techniques. We agree many would choose to broaden these criteria and thus further purify the successful group. Regardless of where this line of success is drawn, however, it is clear that the effect of CK-MB elevation among truly successful procedures in this patient cohort would be small to nonexistent.

We also agree that this finding is worth validating in larger numbers of patients. Doing so will require access to databases where the pre-procedure risk and results of successful and unsuccessful procedures are clearly identified, thereby avoiding unnecessary panic among patients and their physicians when small elevations in CK-MB are detected following an otherwise successful procedure.

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REFERENCES

Cardiac Rehabilitation Following Myocardial Infarction

In an observational study Witt et al. (1) report a striking survival advantage among patients attending cardiac rehabilitation. They employ a rather unusual adjustment to compare patients of very different ages, a “propensity to attend cardiac rehabilitation” rather than the more usual inclusion of prognostic risk factors in multivariate analyses.

Their findings are not borne out by randomized trials. In discussion, they comment that early (small) trials may not be generalized to contemporary practice. Too true. Pooling of all trials undertaken since the World Health Organization European collaborative (but excluding ours, see the next sentence) show collectively no significant effect on mortality (2). The only multicenter trial undertaken since widespread use of thrombolysis, aspirin, beta-blocker, angiotensin-converting enzyme inhibitor, and statin shows no effect on mortality (3).

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REPLY

We appreciate the interest of Dr. West in our work (1). We respectfully take issue with the statement that the use of propensity-score methodology is unusual. Indeed, the use of propensity score is a commonly used, well-accepted method of statistical adjustment (2,3). It is considered by many to be preferable to conventional regression analysis to adjust for differences in baseline characteristics and control for confounding by indication. As in any observational study, however, we cannot rule out residual confounding related to unmeasured characteristics. This point, which was emphasized in our report, is important to underscore in the interpretation of our data.

As underscored by Dr. West, and as stated in our study, randomized controlled trials constitute the methodological gold standard to test the effect of an intervention. Dr. West quotes one meta-analysis of four trials (4) and one multicenter randomized trial (4). Both of these are published only in abstract format, and neither one provides sufficient information to interpret the findings. For example, the trial inclusion criteria or components of the rehabilitation programs may be substantially different from what is reported in our community-based myocardial incidence cohort (1). These differences could, in turn, explain the observed differences in survival. More importantly, the duration of follow-up in the randomized trial is only 12 months (5), shorter than in our published follow-up of 6.6 years (1). Finally, the apparent age and gender disparities in the delivery of care noted in our analysis could...