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 >50% or >30%; dissection ≥D or ≥C; Thrombolysis In Myocardial Infarction [TIMI] flow grade <3 or other criteria). Some investigators may use only some (3,4), but not all, of these criteria, or may add other parameters (5). In a database of 6,186 patients, it is almost certain that definition changes can always allow identification of a minuscule group of about 100 patients where 10 deaths have occurred and thus support a claim that this is the high-risk group par excellence.

Overall, such claims about high-risk groups are primarily hypothesis-generating speculations. It is important to try to replicate these findings in other patient cohorts using the exact same definitions. Chances are that the greater the degree of selection and strict data-fitting in the original investigation, the less likely the findings are replicated elsewhere (6). Nevertheless, given the great clinical importance of the observations made by Jeremias et al. (1), such validation is essential.

John P. A. Ioannidis, MD
Evangelia Karvouni, MD
*Demosthenes G. Katritsis, MD, PhD, FACC

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 and 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 23,230 patients (including 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.

*Athens Euroclinic
9 Athanassiadou St.
Athens 11521
Greece
E-mail: dkatrits@otenet.gr

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