First, given the focus on randomized trials with sirolimus-eluting vs. bare-metal stents and the likely endorsement by Cordis (manufacturer of Cypher), it is unclear why other potentially eligible trials were not included (e.g. the SES-SMART or the DIABETES studies). This type of methodological error, potential harbinger of publication bias, is well known to authors and readers of systematic reviews (and indeed the work by Holmes et al. should be appraised as an individual patient data quantitative review).2

Secondly, the study was designed as a meta-analysis pooling separate data sets, but analysis is inappropriately conducted on a single data set (e.g. with Kaplan-Meier curves). Whether this choice was made by the authors or by an anonymous statistical reviewer is unclear. However, pooling all patients into a large group is incorrect and may lead to biased estimates. Other more valid approaches should have been used, which separately maintain the data sets of each individual study before pooling them.3

Thirdly, no data on conflicts of interest are reported. Several authors have received research grants, organized sponsored congresses, and/or are involved in contract research organizations for revenues likely amounting to millions of euros.4 Unfortunately, a laconic ‘Conflict of interest: none declared’ is posted at the end of the article, but this all-too-common practice is best seen as involuntary malpractice and should be discouraged.

We conversely praise Wijns and Krucoff for detailing in their accompanying editorial their conflicts of interest and the potential amount of money that is at the base of such conflicts.5 As even a layman can understand, we should always declare the rough estimate of a conflict of interest, as a 5000€ consultancy is much different from a 10 000 000 contract with a related research company. The implication of the previous point are all evident if we keep in mind that reviews from people strongly linked to involved companies are more likely to be biased.6,7 A famous example of such biased reviews increasing the ‘smoke’ and hiding the ‘fire’, to use Holmes’ metaphor, are actually the many dozens produced in the past by people strongly linked to involved companies and systematic reviews: reply

In conclusion, as enthusiastic supporters and practitioners of systematic reviews and meta-analyses, we are well aware of their inherent limitations and potential for biased conclusions.11,12 It is thus pivotal to follow strict quality criteria whenever systematic reviews and meta-analysis are performed, reported, peer-reviewed, and read.13 Otherwise the ‘smoke’ from conflicting meta-analysis on drug-eluting stents will only increase and might become overwhelming.

Conflicts of interest: Dr Biondi-Zoccai has consulted for Cordis, Italy and Boston Scientific Italy either directly or through a Milan-based contract research organization for a total amount of <20 000€ in the last 5 years.

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Keeping a high standard in quantitative analyses, meta-analyses, and systematic reviews: reply

I am certainly disappointed that Biondi-Zoccai et al.1 have been disappointed by the recent article, which assessed the risk and cause of death in patients in four pivotal randomized trials of drug-eluting stents (DES) vs. bare metal stents (BMS).

The letter raises some interesting issues. Although you state that this was a ‘meta-analysis’, the intent of the manuscript was not to be a meta-analysis. This manuscript included those trials in which the corresponding author (D.R.H.) had access to and was able to review the specific clinical patient notes on each death in these four trials. There was just one data set and that data set again was all deaths from each of the trials. It is of interest that these trials are the pivotal trials that were used for approval of this technology. There are clearly other studies in the field but...
these were the only studies that I had access to the clinical data on the deaths. The principle author (D.R.H.) reviewed each of the deaths and then came to a separate conclusion irrespective of what the DSMB, the CEC, or the sponsor might have wanted. There were no other deaths in these trials. Accordingly, the intent was not to be a meta-analysis of all trials; it was to evaluate the cause of death in those trials that I had access to and to gain insight into cardiac vs. non-cardiac death.

It is unclear what the authors of the letter mean by 'endorsement by Cordis'. I performed this analysis and did not receive any endorsement by the manufacturer for this work.

Dr Biondi-Zoccai’s comment on conflict of interest is of course extremely important. We have written about many of these issues in a conference that was held and reported in 2004. It is unclear where the ‘10 000 000€ contract figure’ mentioned by Dr Biondi-Zoccai comes from. Although, I was the local site principal investigator for the SIRIUS trial at the Mayo Foundation, I did not receive any direct compensation other than for nurse coordinator time. I have never been exposed to 10 000 000€ as the authors appear to impugn. Certainly, a figure like that is not germane from my standpoint as the principal author of this manuscript nor does it add much to a 'scientific' letter to the editor.

The issue of the effect of stent technology on clinical outcome in patients is of central importance of the field. We have previously identified in an analysis we performed that indeed stents do not improve survival compared with conventional dilatation at least in the trials that we studied. Nordman et al. came to a similar conclusion in their article when they found that DES do not decrease mortality in the current trials when compared with BMS. There are, certainly, limitations to studies such as these. They do, however, point the way towards the need for further analysis. Certainly, long-term follow-up in a wider group of patients and lesions will be required to continue to evaluate the issues of safety vs. efficacy for not only DES but also BMS.

References

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