Variability in response to clopidogrel: where is the threshold for 'low response'? reply

We appreciate to read Dr Komócsi comments to our article entitled ‘Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation’.

He critically remarked the mortality rate in our study. Indeed, we found an all-cause mortality of 5.2% within 3 months (cardiovascular mortality: 3.9%). However, it is worthy to note that we investigated an unselected patient collective with moderate- to high-risk patients. In this context, around 45% of the initially enrolled patients were admitted with acute coronary syndromes and 21% had a STEMI.

The quoted meta-analysis of randomized stent trials by Nordmann et al. that was recently published in European Heart Journal provides a systematic overview mainly over trials that excluded patients with acute myocardial infarction like the RAVEL-trial. In fact, in studies describing a strictly elective setting the mortality is lower. To our opinion the mortality-rate observed in our patient cohort lies within the range reported in previous multicentre PCI studies including a similar risk collective. In trials with acute interventions, the mortality is comparable with or even higher than the mortality in our patient cohort. In PCI-CURE, 2658 patients with NSTEMI-ACS were enrolled, 4.5% had suffered a cardiovascular death after 30 days (all-cause mortality was even higher) and 6.0% at the end of follow-up (mean follow-up period 8 months). In ISAR-REACT II of 2022 patients with NSTEMI-ACS, around 1.4% of the patients (1.6% in the placebo group) had died after 30 days. Given the heterogeneity of the setting of our study including an important number of high-risk patients, and considering the follow-up period of 3 months, the mortality we reported is therefore reasonable and to our opinion in agreement with the literature. Besides, in many studies, the adoption of rigid criteria for randomization resulted in the exclusion of many patients at high risk of adverse events.

In addition, Dr Komócsi remarked the possible bias of acute coronary syndromes on the worse cardiovascular outcome of low responders to clopidogrel in our study. Concerning the prognostic influence of acute coronary syndrome in the low-responder group, we cannot neglect that patients with ACS show an increased a priori risk for recurrent cardiovascular events. However, when compared with other relevant factors in multivariable Cox regression analysis, low response and left ventricular dysfunction were independently associated with composite events within 3 months. Future trials will have to show that response to antiplatelet therapy has an essential impact on the prognosis of ACS patients. In this context, Cuisset et al. observed a significantly higher rate of cardiovascular events in NSTEMI-ACS patients who had a residual platelet aggregation of >70%. Furthermore, the author of the letter raised the question concerning the proper cut-off value. In the past, multiple definitions on the basis of different methods have been adopted to characterize response to antiplatelet therapy with clopidogrel (difference of pre- and post-treatment platelet activity <10%, platelet aggregation in the upper quartile, residual platelet activity >70%). However, there is a growing agreement that independently from definition, a high degree of remaining platelet activity has a relevant impact on cardiovascular outcome of coronary stent patients. Since we learn more and more about the importance of antiplatelet drug response, it should be the aim to develop a consensus method that on the one hand is practicable in clinical routine and on the other hand helps to identify patients at increased risk for cardiovascular events. Our aim was to evaluate the risk in patients with very high residual platelet aggregation (late ADP 20 μmol/L induced platelet aggregation >70%). It might be for the patients’ sake to lower this cut-off value (median) to segregate low responders from responders. However, if around half of the patients are not optimally treated and therefore might benefit from an intensified antiplatelet therapy in terms of better clinical prognosis has to be critically evaluated.

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

We are frankly disappointed by the recent article by Holmes et al.1 appraising the risk of death in patients randomized to sirolimus-eluting (Cypher) vs. bare-metal stents, which amounts to a missed opportunity. Indeed, analysis and reporting are clearly inadequate to provide a reliable answer to the scientific question posed.
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). 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.

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. Unfortunately, a lacunary ‘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. 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. A famous example of such biased reviews increasing the ‘smoke’ and hiding the ‘fire’, to use Wijns and Krucoff’s metaphor, are actually the many dozens produced in the past by authors affiliated with tobacco companies in support of cigarette smoking. These issues are also relevant to the recent so-called ‘independent physician-led patient-level analyses’ on sirolimus- and paclitaxel-eluting stents presented at the 2006 Transcatheter Cardiovascular Therapeutics, whose findings still await peer-review.

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. It is thus pivotal to follow strict quality criteria whenever systematic reviews and meta-analysis are performed, reported, peer-reviewed, and read. 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. 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