Outcomes with short-term versus long-term antiplatelet dual therapy after drug-eluting stenting: Quantifying the equivalence margins

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**Letters to the Editor**

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In evaluating short-term versus long-term antiplatelet dual therapy after drug-eluting stenting, the efforts of many researchers worldwide have permitted us to generate a sufficiently large body of evidence-based data. The two most recent meta-analyses in this area have been focused, respectively, on the information obtained from randomized controlled trials [1] and from all types of clinical studies [2]. While the best quality of evidence is likely to derive from the first meta-analysis, two randomized studies (namely, the RESET [3] and the OPTIMIZE [4] trials) were too recent for being examined by Valgimigli and co-workers [1].

On the other hand, an increasing amount of evidence-based research [5] has recently been aimed at differentiating between no proof of difference (i.e., failed demonstration of superiority) and proof of no difference (demonstration of non-inferiority/equivalence or futility where futility is essentially represented by equivalence with no treatment). Clearly, proof of no difference is a much more informative result than no proof of difference: the former however requires that an equivalence (or non-inferiority margin) is incorporated in the analysis.

To study the differences between short-term versus long-term antiplatelet dual therapy, we re-analyzed the meta-analytical results published by Valgimigli and co-workers [1] by incorporating the data of both the RESET [3] and the OPTIMIZE [4] trials. Then, we carried out a formal equivalence test based on confidence intervals (CIs). All of our analyses evaluated the same composite end-point originally measured in the clinical trials. Since our objective was to determine to what extent short-term and long-term dual antiplatelet therapies are equivalent regarding the incidence of the composite end-point, our analysis was carried out as a meta-analysis of equivalence [6,7]. Our design was of equivalence and not of non-inferiority, mainly because the end-point was a mixture of effectiveness and safety, and so we could not exclude results in either direction. The incidences of the above-mentioned end-point were estimated by a standard (random-effect) meta-analysis in which the results were firstly expressed as risk difference (RD) and

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then as relative risk (RR), both with 95%CIs. Finally, to carry out the equivalence test, we did not declare any pre-specified margin of equivalence, but we preferred to carry out a post-hoc analysis in which we determined which equivalence margins were compatible with the conclusion of equivalence. The techniques for equivalence testing were those previously published in specialized papers [6].

Fig. 1 summarizes the results of our meta-analysis. Panel A shows the study-specific crude rates and the pooled (meta-analytical) value of RD, which was characterized by no heterogeneity (according to the I² index). Panel B shows the equivalence graph that allowed us to identify the post-hoc equivalence margins.

Overall, these results indicate that the equivalence between short-term and long-term dual treatments can be considered demonstrated by setting the equivalence margin at RD = ±1.1%. This margin proves to be largely acceptable from a clinical standpoint particularly if one recalls that, as pointed out by Feres et al. [4], previous research in this area adopted margins of about 2.7%.

Finally, if one repeats a meta-analysis of the same data using RRs rather than RDs (data not shown in detail), the equivalence margin, determined post-hoc, can be calculated at a percent relative risk increase of 30%; in fact, the meta-analytical RR for short-term vs long-term treatment is at 1.073 with 95%CI from 0.889 to 1.296. Interestingly enough, the exclusion of this trial from the meta-analysis markedly strengthened the equivalence between the two treatments (pooled RD = −0.03% with 95%CI from −0.9% to 0.8%). Another limitation is that the end-points were also slightly different across the trials. Despite these limitations, our conclusion is that, in patients receiving drug-eluting stenting, the equi-effectiveness of short duration vs long duration dual antiplatelet therapy seems to be supported not only by no evidence of difference, but also by a quite strong evidence of no difference.

References

[2] Zhang T, Shen L, Hu L, He B. Optimal duration of dual-antiplatelet therapy: the RESET Trial (REAL Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implanta-