

EDITORIAL COMMENT

Optimal Coronary Interventions in Small Vessels



Is Size All That Matters?*

Fernando Alfonso, MD, PhD, Marcos García-Guimaraes, MD

Coronary interventions on small vessels, representing up to 30% to 40% of procedures, are challenging and often disappointing because of suboptimal acute results and high restenosis rates (1,2). In this setting, bare-metal stents (BMS) proved to be superior to balloon angioplasty (BA), with the greatest benefit encountered in patients with smaller vessels and suboptimal BA results (1,2). Because late luminal loss resulting from neointimal proliferation is relatively independent of vessel size, late angiographic findings after BMS implantation are poorer in small vessels (1,2). Drug-eluting stents (DES) drastically inhibit neointimal proliferation and are especially attractive in these patients. However, even with the advent of new-generation DES, small vessel disease remains a powerful predictor of restenosis (3). More recently, drug-coated balloons (DCB) have been incorporated into our armamentarium for lesions in small vessels, with promising results (4,5).

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In this issue of *JACC: Cardiovascular Interventions*, Siontis et al. (6) report a comprehensive and exhaustive network meta-analysis that summarizes all the evidence currently available from randomized clinical trials on the relative safety and efficacy of different coronary interventions in small vessels. This group from the University of Bern previously reported several elegant network meta-analyses disclosing relevant evidence on the relative efficacy

of different interventions in distinct anatomic and clinical scenarios (7). The statistical approach used in network meta-analyses is able to incorporate, to the classic evidence derived from direct comparisons, information from the indirect evidence emerging from interventions that have never been directly compared (8). This methodology not only estimates the relative effectiveness between interventions never compared in head-to-head studies but also provides a hierarchy analysis ranking interventions (8). All available information is eventually synthesized to increase precision in the selected outcome estimates.

The present work addresses the conundrum of interventions in small coronary vessels. A total of 19 randomized clinical trials, including 5,072 patients, were analyzed (6). The primary angiographic outcome measure was percentage diameter stenosis at follow-up. This represents a well-accepted surrogate angiographic endpoint to compare different (namely, balloon vs. stent based) interventional modalities. Long-term angiographic data were available from 16 trials including 4,349 patients. Five interventions (sirolimus-eluting stents [SES], paclitaxel-eluting stents [PES], BMS, DCB, and BA) were evaluated. However, no trial evaluating new-generation DES could be identified. SES provided the best clinical and angiographic results and were ranked as the most effective treatment regarding diameter stenosis, followed by PES and DCB. Both BMS and BA provided poorer clinical and angiographic results. Considering binary restenosis rates, SES remained the best-ranked intervention, and SES, PES, and DCB were significantly better than BMS and BA. Importantly, clinical outcomes were also improved after SES implantation, driven by a significant reduction in the need for target lesion revascularization. Finally, regarding myocardial infarction, DCB were ranked first, followed by

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From Hospital Universitario de La Princesa, Madrid, Spain. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

PES and then SES, but only SES compared with BA significantly reduced infarction rates (6).

The investigators should be commended for selecting this sound methodology to unravel the best evidence currently available from randomized clinical trials comparing coronary interventions in small vessels. An editorial is not a license to preach, but we intend to provide some perspective to help with the interpretation of the results and highlight their potential clinical implications. Actually, most caveats pertain to the original individual trials or to the assumptions required to lump them together rather than to the present study per se.

First, vessel size is of paramount importance in this scenario, yet the criteria to define small vessels diverged across studies. Nine randomized controlled trials analyzed results in vessels with reference diameters <3 mm. Many investigators, however, will agree that vessels >2.5 mm should not be considered small vessels. In this regard, data on final stent or balloon size would have been of interest. In addition, as patient-level data were not available, the potential interaction of vessel size with the relative efficacy of different interventional modalities could not be analyzed. This remains critical, as it is likely that the relative effect of these competing interventions will depend on vessel size. Likewise, assessing the potential interaction caused by strut thickness, particularly relevant in small vessels, would have been of additional value.

Second, the analysis of the nodes and edges of the “network graph” is highly illustrative. Of the 19 randomized trials, most (12 studies) directly compared (head to head) BMS with BA, precisely the less effective strategies. Direct comparisons of other therapeutic modalities were relatively limited. This was expected considering the relatively large number of competing interventions. There were 4 studies comparing SES with BMS but only 1 comparing SES with PES. Because no closed loops were obtained, the potential differences between direct and indirect comparisons could not be ascertained (8). Inconsistency refers to differences between the treatment effects provided by direct and indirect comparisons (8). Poorly connected networks depend excessively on indirect comparisons and are less reliable than networks in which most treatments have been directly compared against each other (8). However, the present study suggested a nicely balanced distribution of potential effect modifiers (transitivity indicates comparable patient characteristics across studies), thus increasing the plausibility of obtaining reliable findings from the indirect comparisons.

Third, only 2 randomized studies evaluated the efficacy of DCB in small vessels, both versus PES. A close scrutiny of these trials reveals that they were relatively small ($n = 182$ and $n = 60$, respectively). In the BELLO (Balloon Elution and Late Loss Optimization) trial (5,9) statistically significant smaller late luminal loss (the primary endpoint of the trial) was found with DCB compared with PES. However, results for diameter stenosis and minimal luminal diameter at follow-up, were similar (5,9). The PICCOLETO trial (10) included only 60 patients, as the study had to be prematurely discontinued because the very early generation DCB used proved to be unable to reduce neointimal proliferation. This is relevant because a class effect cannot be considered for all DCB. DCB with coated technologies different from those used in the present meta-analysis (iopromide vs. urea or shellac) have consistently demonstrated efficacy in patients with in-stent restenosis (7). Accordingly, it seems that “definitive” evidence on the relative efficacy of DCB cannot be obtained from these studies. Furthermore, no trial provided a direct comparison between SES and DCB. Whether novel DCB, including the recently released sirolimus-eluting DCB, will be more effective in patients with small vessels, warrants further investigation.

Fourth, trials allowing a mixture of interventions in the same arm were excluded, and this appears reasonable to better delineate the results of individual interventions. However, provisional stenting has been classically considered an acceptable strategy in small vessels restricting the use of stents to patients with suboptimal results or significant dissections after BA (1,2). Therefore, additional information on the results of trials allowing a more liberal bailout strategy could have been of value.

Last but not least, none of the analyzed trials included new-generation DES. This cannot be considered a limitation of the present study but rather of the currently available evidence. In fact, it is difficult to understand why no randomized trial exists assessing the value of new-generation DES in small vessels. The investigators suggest that the benefit may be greater with novel-generation DES, but data in this regard could not be obtained.

In closing, this study provides robust evidence demonstrating the superiority of first-generation SES compared with other classic coronary interventions in patients with small vessels (6). However, from a practical standpoint, the optimal strategy for the current treatment of these lesions cannot be inferred from the present study, as new-generation DES were not included and first-generation SES and PES are no

longer available. A large body of evidence suggests that new-generation DES are safer and more effective than first-generation DES (11), and this benefit appears to be even more evident in complex anatomic scenarios. Vessel size is probably no more relevant than other important clinical (diabetes) or anatomic (lesion length) factors to predict outcomes of interventions—but size matters indeed! New-generation DES, with thinner polymer and platform architecture, should outperform older DES in small vessels. Therefore, we are more than ready for

dedicated head-to-head randomized clinical trials aimed to confirm the expectations generated by novel DES and novel DCB in this challenging anatomic scenario.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Fernando Alfonso, Department of Cardiology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria, IIS-IP, Universidad Autónoma de Madrid, c/ Diego de León 62, Madrid 28006, Spain. E-mail: falf@hotmail.com.

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KEY WORDS drug-coated balloon(s), drug-eluting stent(s), restenosis, small vessels