

EDITORIAL COMMENT

## Head-to-Head Randomized Comparisons of Limus-Eluting Coronary Stents

### Pursuing Excellence or Flying Too High?\*

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Drug-eluting stents (DES) have become the primary treatment modality for patients with coronary artery disease requiring revascularization (1). The attractiveness of DES involves their dramatic ability to inhibit neointimal proliferation leading to a marked reduction in the clinical need for reinterventions (2). Since their first clinical use a decade ago, DES have experienced a major evolution. Recent generation devices have improved platforms facilitating their unrestricted use as a workhorse strategy in increasingly challenging anatomic scenarios. In addition, they incorporate advanced polymers with the aim of avoiding any potential untoward stimulus for late inflammatory reactions. Finally, currently available DES elute highly attractive drugs (2–4). Notwithstanding the value of

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these advances, a critical question remains unsolved, namely whether the potent antiproliferative properties of DES may be dissociated from a delayed vessel healing response (5). Indeed, delayed endothelialization has been considered as the unavoidable price to pay to benefit from their unique antirestenotic efficacy (5). Accordingly, prolonged dual antiplatelet therapy is recommended after DES implantation, as a safety net, during the period required for complete vascular wall restoration. Nevertheless, despite all technological advancements and improvements in concomitant medical therapy, the risk of very late DES thrombosis remains an issue of special concern (6). Fortunately, this feared complication is very rare, even in the

real-world clinical setting, and recent registry data suggest that its incidence may be declining (7,8).

Recent head-to-head randomized comparisons of first-generation DES with newer generation devices strongly suggest that new DES appear to be not only more effective but also safer (2–4). Surprisingly, however, in most of these studies only paclitaxel-eluting stents (PES) have been used as a comparator in the control arm. This action is worrisome because classical reports and meta-analysis suggest that sirolimus-eluting stents (SES) are actually more effective and safer than contemporary PES (9). From this perspective, the real clinical value of second-generation DES remains unsettled. Likewise, comparisons of current results with historical series are likely flawed by various chronological biases. Therefore, it remains possible that the improved current results may actually be secondary to a longer experience with the use of DES, resulting in better patient selection, improved deployment strategies, superior antithrombotic regimens, and closer clinical surveillance, rather than to superior performance of the new DES (2,7,8).

In this issue of the *Journal*, Park et al. (10) present the results of the first head-to-head randomized comparison of everolimus-eluting stents (EES) with SES in relatively unselected patients. This trial would be considered by many as another second- versus first-generation DES-to-DES contest. Notably, however, compared with SES, EES were unable to provide superior results in any of the pre-established clinical or angiographic outcome measures (10). Many clinicians and researchers would consider these results to be puzzling or even disappointing.

Are second-generation DES superior to first-generation DES? Is this classification meaningful or rather over-simplistic and arbitrary? Are all limus DES equally safe and effective? Are we pushing the envelope too early or too far? Are we just flying too high?

**Present study.** The EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial (10) included 1,443 patients randomized (3:1) to receive EES (n = 1,079; 1,459 lesions) or SES (364 patients; 468 lesions) in 19 Korean centers. The trial had a noninferiority design and was powered for its primary angiographic endpoint. Based on previous studies, a late loss of 0.2 mm was anticipated for both arms, and a noninferiority margin of 0.1 mm was predefined. The primary endpoint, the in-segment late loss at 9-month angiographic follow-up, was similar in both arms (EES  $0.11 \pm 0.38$ ; SES  $0.06 \pm 0.36$  mm), with the upper confidence interval (0.096 mm) just falling within the pre-specified noninferiority margin (p for noninferiority = 0.0382). Importantly, however, late angiographic follow-up was only obtained in ~67% of patients. This finding is lower than expected for a randomized trial with an angiographic primary endpoint (the trial design anticipated 80% of angiographic follow-up) and, actually, might jeopardize the value of the selected noninferiority margin because dropouts may dilute potential differences between treatments.

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We should keep in mind that noninferiority trials have particular methodological issues regarding design, conduct, analysis, and interpretation (11). In these studies, the null and alternative hypotheses are reversed and, therefore, a type II error is the erroneous rejection of a truly noninferior treatment. Furthermore, the selected noninferiority margin should be the smallest value that would be considered a “clinically relevant” effect. Finally, in noninferiority trials, intention-to-treat analyses may increase the risk of falsely claiming noninferiority (type I error). Therefore, in these trials, “non-intention-to-treat” analyses are particularly important as a protection from this problem. The EXCELLENT investigators selected the per-protocol analysis for the primary angiographic endpoint. In this regard, although probably not affecting the main study findings, the trend for a higher device success rate in the EES arm (10)—possibly resulting from its superior deliverability—should be also kept in mind.

Both groups were well balanced for baseline characteristics, although a higher number of stents was required in the EES arm (10). The investigators suggest that the trial was designed to reflect “real-life” clinical practice. From the clinical standpoint, many patients with unstable disease were enrolled and only patients with cardiogenic shock, recent myocardial infarction, and “severe” left ventricular dysfunction/renal failure were excluded. From the anatomic perspective, vessel size, lesion length, and the presence of multiple lesions were not exclusion criteria although, again, highly complex anatomic settings were not included. Although these criteria are rather inclusive for a randomized trial, caution is required before extrapolating the study findings to truly unselected real-world patients seen in daily practice. Likewise, nearly one-half of the patients (44%) received intravascular ultrasound-guided stenting. This is not standard practice in most institutions and should also be considered before current results are generalized to settings in which angiography alone is used to optimize procedural results.

Multivessel intervention was also allowed in this trial (10). Considering that multiple lesions could be targeted with the allocated DES, generalized estimating equations were required to statistically account for potential clustering effects. Notably, when all lesions eventually treated were compared (i.e., not only the “index” lesion selected for the primary endpoint), the in-segment late loss ( $0.10 \pm 0.36$  mm vs.  $0.05 \pm 0.34$  mm) tended to be higher ( $p = 0.05$ ) after EES (10).

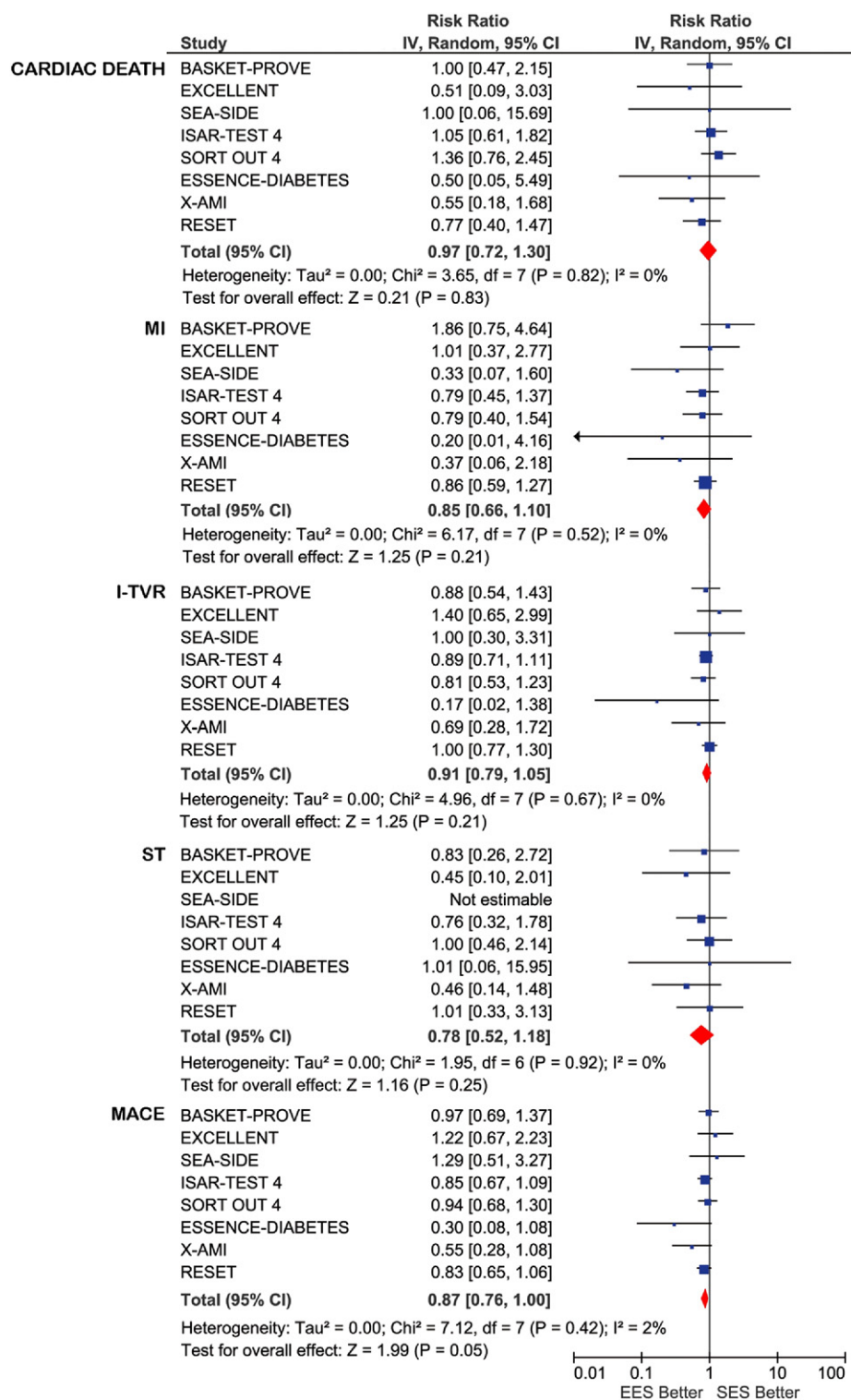
Secondary clinical endpoints, including death, target lesion/target vessel failure, myocardial infarction, and stent thrombosis, were equivalent in both arms. Although event rates were similar, “effectiveness” outcome measures were numerically higher whereas those related to “safety” were numerically lower after EES. As nicely acknowledged, however, the study was largely underpowered to detect differences in major clinical endpoints. From these unstable trends, the authors elegantly dare to suggest that EES might be safer than SES although perhaps slightly less effective. It was speculated that the latter might be a result of EES offering a potentially less effective drug at a lower concentration compared with SES (10,12). In addition, the EXCELLENT trial had a  $2 \times 2$  factorial design

and concomitantly evaluated the effect of the duration (6 months vs. 12 months) of the dual antiplatelet therapy (13). However, data on whether adjuvant long-term medical therapy unevenly affected safety results in the 2 arms were not provided in the present report.

Uneven randomization schemes (3:1 in this study) led to unstable outcome measure estimates in the smaller arm (i.e., SES group). This increases the risk of a play of chance in this arm, especially regarding the analysis of rare clinical endpoints. In the EXCELLENT trial, randomization was stratified for the presence of diabetes mellitus and long lesions. An interaction was detected in the diabetic cohort that showed a significantly larger late loss after EES, although this angiographic finding did not translate into diverging clinical endpoints. As discussed, a play of chance cannot be excluded considering the small diabetic cohort receiving SES. Actually, this small patient subset had a surprisingly low angiographic late loss (paradoxically lower than that seen in nondiabetic patients treated with SES), further preventing a satisfactory interpretation of this finding. Interestingly, in patients with diabetes mellitus, previous studies failed to demonstrate the superiority of EES over PES (3,4) whereas SES remain more effective than PES in this cohort (14).

**EES versus SES randomized trials in perspective.** SES provided a breakthrough in the prevention of restenosis. Second-generation DES were designed to improve long-term safety with similar—or even greater—antirestenosis efficacy than first-generation devices. Accordingly, direct comparisons of EES with SES remain of major interest to fully elucidate the potential advantages of novel DES (2). Indeed, SES appear to be the best possible first-generation DES to be used as a comparator and ideally suited for benchmark purposes (9).

To date, the final results of 8 randomized studies comparing head-to-head EES with SES are available (10,15–21). These studies are heterogeneous regarding: 1) the type of enrolled patients/lesions (unselected in 4 trials; focused in patients with diabetes mellitus, 1 trial; large vessels, 1 trial; bifurcations, 1 trial; or acute myocardial infarction, 1 trial); 2) primary endpoints (5 clinical outcomes, 3 angiographic surrogates [1 acute, 2 late]); 3) requirement of late angiography (3 trials); and 4) time of clinical follow-up (from 9 months to 2 years) (10,15–21). Furthermore, a third arm (different from EES vs. SES) was included in 2 studies, and 3 trials selected uneven (different from 1:1) randomization schemes. Finally, clopidogrel duration was also variable (from 6 months to 1 year), and slight variations in event definitions should be noted. Of these, 3 studies have been already published (10,15,16), and final data of 5 trials have been presented as official “late-breaking clinical trials” at major cardiovascular meetings (17–21). With these considerations in mind, the available data may be polled together in a new meta-analysis (Fig. 1). None of these 8 trials demonstrated superiority of EES over SES in combined or individual endpoints. The results of this meta-analysis, totaling 11,351 patients, suggest that EES and SES provide similar efficacy and safety outcome measures. No heterogeneity across trials was detected in relation to any event.



**Figure 1** Meta-Analysis of Randomized Trials Comparing EES With SES

Random-effects meta-analysis of the 8 randomized clinical trials comparing everolimus-eluting stents (EES) with sirolimus-eluting stents (SES) with final data available (BASKET-PROVE, EXCELLENT, SEA-SIDE, ISAR-TEST-4, SORT-OUT-4, ESSENCE-DIABETES, X-AMI, and RESET) (10,15–21). Forest-plot representation of risk ratios: the size of the blue squares is related to the powered weight of each individual trial, while red diamonds represent the overall effects. The horizontal axis has a logarithmic scale. CI = confidence interval; I-TVR = ischemia-driven target vessel revascularization (2 studies reported only total target vessel revascularization); MACE = major adverse cardiovascular events (death, myocardial infarction, and ischemia-driven target vessel revascularization [with individual event definitions slightly variable among trials]); MI = myocardial infarction; ST = definitive or probable stent thrombosis (Academic Research Consortium criteria).



There were, however, clear efficacy and safety “signals” favoring EES. These would require definitive confirmation in additional studies with longer clinical follow-up. If present, however, it remains questionable whether they will be considered as “clinically relevant” from a practical perspective.

**Final remarks.** Head-to-head randomized comparisons of different DES are required to substantiate superior results and potential changes in clinical practice. Park et al. (10) should be commended for their interesting, well-conducted study, and for enlightening our understanding of DES evolution. Many of these trials, however, represent a premature “photo finish” of the ongoing “Star Wars.” Ironically, manufacturing of the time-honored SES used in all these studies has been recently halted. It is clear that in our “galaxy,” scientific reasons are not the only gravitational forces. This piece may serve as a farewell tribute to this still-unbeaten first-generation SES.

Pushing the envelope provides new answers but also begets new questions. We need to keep on working to translate basic science discoveries from bench to bedside. Clinical “failures” should stimulate the reverse process, revisiting bench sources to come back to the clinical arena with novel solutions. The clinical and angiographic long-term results currently obtained with DES are, simply, superb. Nevertheless, scientific humbleness is always more rewarding than narcissism. Every single patient presenting to us with a DES failure (restenosis and, especially, thrombosis) should stimulate our passion to keep spinning the wheel of knowledge. We should never be scared of flying too high.

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**Key Words:** everolimus-eluting stents ■ percutaneous coronary intervention ■ sirolimus-eluting stents ■ stents.