Editorial

Drug-eluting stents versus bare-metal stents for saphenous vein graft interventions

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Provenance: This is a Guest Editorial commissioned by the Section Editor Huiping Zhang, MD (Department of Cardiology, Beijing Hospital, the Fifth Affiliated Hospital of Peking University, Beijing, China).

Comment on: Brilakis ES, Edson R, Bhatt DL, *et al.* Drug-eluting stents versus bare-metal stents in saphenous vein grafts: a double-blind, randomised trial. Lancet 2018;391:1997-2007.

Submitted Nov 25, 2018. Accepted for publication Jan 30, 2019.
doi: 10.21037/jtd.2019.02.50
View this article at: http://dx.doi.org/10.21037/jtd.2019.02.50

Currently, the use of drug-eluting stents (DESs) for native coronary artery intervention is the standard of care. This is because robust evidence based on high-quality trails support the superior efficacy of DES compared to bare-metal stents (BMSs) (1,2). Additionally, observational studies have shown improved outcomes with DESs compared to BMSs for saphenous vein graft (SVG) intervention (3-5). However, randomized clinical trials (RCTs) frequently exclude patients with SVG stenoses and interpretation of observational studies is limited by multiple biases (6). At this time, the superiority of DESs relative to BMSs for SVG lesions has not been well-established. In fact, the reduction of restenosis in SVGs with cypher sirolimus-eluting stent (RRISC), which was the first reported RCT in this field, suggested that the sirolimus-eluting first-generation stents might be harmful for SVG intervention as those were associated with increased all-cause death at long-term follow-up compared to BMS (7,8). Following the RRISC trial, several additional trials have shown that for SVG intervention, DESs are not only as safe as BMSs, but more efficacious compared to BMSs (9-12). Unfortunately, most of these trials are small and used first-generation DESs. Given the current DESs used in practice, the generalizability of these prior studies to current practice is limited. To address this, the drug-eluting tents versus bare metal stents in saphenous vein graft angioplasty (DIVA**)** trial was undertaken and results have recently been published (13,14).

The DIVA trial was a double-blind, RCT conducted at multiple Veterans Affairs hospitals across the United States (14). Patients were eligible to participate if they were at least 18-year-old and were found to have at least one significant lesion in the SVG. Patients were not eligible if they presented with an acute coronary syndrome with ST-segment elevation, if the stenotic graft was supplying the last remaining vessel, if they had percutaneous coronary intervention (PCI) on the target graft within the last year, if bleeding disorder was present or if the patient had an indication for oral anticoagulant and thought not to be a candidate for triple antithrombotic therapy. Patients enrolled in the study were assigned randomly via a phone randomization system, to receive either DESs or BMSs. Patients were assigned to each group in a 1:1 ratio. The primary endpoint was the 1-year incidence of target vessel failure (TVF), which was defined as a composite of target vessel revascularization (TVR), target vessel myocardial infarction (MI), or cardiac mortality. Periprocedural MI was not included in the primary endpoint. Due to the lower than expected rates of TVF, after 384 patients were randomized, the target sample size was increased to 762 patients. However, after premature termination of the study, the final analysis included 597 patients.

In the DIVA trial, the baseline clinical and angiographical characteristics of the two groups were well-balanced, apart

from a higher average age of grafts in the DES group. In this trial, almost all patients were men with a mean age of 68.6 years. The minimum, median, and maximum follow-ups were 1 year, 2.7 years, and 5 years, respectively. Second-generation DESs were used in 88% of cases. At 1 year, there was no significant difference in the primary endpoint when comparing DESs and BMSs (17% versus 19%; P=0.70). Similarly rates of MI (6% versus 4%), TVR (12% versus 11%), TLR (8% versus 9%), stent thrombosis (1% in each group), and all-cause mortality (5% in each group) were not significantly different between the BMS and DES groups.

The findings of the DIVA trial were unexpected and were contradictory to those found in five previous RCTs, which individually showed that compared with BMSs, DESs decrease the TVR rate in the short term (median 12 months) (8-12). Small sample size can exaggerate the therapeutic effect, which might account for the discrepant results, given the small sample size of prior RCTs (15). However, findings of the DIVA study also contradict the drug-eluting-stenting associated with the improved results in coronary artery bypass Grafts (ISAR-CABG) study, which is the largest RCT to date on this topic and included 610 patients (11). In the ISAR-CABG trial, the major adverse cardiac event (MACE) rate was 15% in the DES group, which was significantly (P=0.02) lower than the 22% in the BMS group. The lower rate of MACE in the DES group was driven primarily by lower TVR rates (10% versus 16%). The rate of TVR at 1-year in the DIVA trial, compared with that in the ISAR-CABG trial, was lower in the BMS group (11% versus 16%), which could have resulted from the use of the new-generation BMSs (with thinner struts) in the former. However, despite the use of the new-generation DESs (with thinner struts compared to older-generation DESs used in the ISAR-CABG trial) in the DIVA trial, the TVR rate (12%) for the DES group remained higher compared to that in the ISAR-CABG trial (9.6%).

One major criticism and limitation of the DIVA study was its premature termination due to slow enrollment-enrolling only 599 of the planned 762 patients. This premature termination might have resulted in an underpowered study (16). Alternatively, the difference in the average ages of the grafts in the two stent groups could have introduced a bias favoring the BMS arm: as the grafts of the DES group were significantly older than the BMS group. Additionally, routine follow-up angiographies were not allowed in the DIVA trial, but in the ISAR-CABG trial, they were part of the study protocol. Two-thirds of the patients underwent routine follow-up angiographies. Thus, the lower rates of TVRs with DESs in the ISAR-CABG trial could have been driven by angiographically stenotic (but clinically asymptomatic) lesions. A recent meta-analysis of six RCTs, with 1,582 patients–including the DIVA study–showed that SVG interventions with DESs significantly decrease the MACE rate by 40% and TVR rate by 48% compared to BMSs, at a median follow-up of 12 months (17). No differences were seen in the rates of stent thrombosis, MI, all-cause death or cardiac death between the two stent groups.

The pathophysiology of atherosclerosis in the SVGs is different than to native coronary arteries (14,18). Atherosclerosis is known to be accelerated and more diffuse in SVG; thus, the durability of reduced rates of TVR with DESs is of great clinical interest. In the RRISC (first reported RCT), a significantly lower TVR rate at 6 months with the sirolimus-eluting stent (8) was lost at 3 years follow-up (7). Conversely, in the stenting of saphenous vein grafts (SOS) and Basel Kosten-Effektivitäts Trial, as well as the saphenous venous graft angioplasty using glycoprotein 2b/3a receptor inhibitors and drug-eluting stents (BASKET-SAVAGE) trials, the early benefits (decrease rate of revascularization) with DES persist at long term follow-up (up to 3 years) (12,19). However, these findings are confounded in the SOS trial by small sample size (80 patients), and in the BASKET-SAVAGE trial by high attrition rates, with only one-third of patients completing 3 years of follow-up. Recently, the long-term follow-up results of the ISAR-CABG trial with 5 years data showed that the advantage demonstrated for DESs at 1 year, was lost at 5 years follow up (18). The long-term results of the ISAR-CABG trial and the DIVA trial are consistent. In the long-term follow-up of the DIVA study, with a median follow-up of 2.7 years, there was no significant difference in TVF (37% versus 39%; P=0.44) between the DES and BMS groups (14). Additionally, there was no significant difference in the rates of TVR, TLR, MI, stent thrombosis, and all-cause death between the two stent groups. Recent meta-analyses are consistent with the findings of these studies. Using the longest available follow-up data from RCTs (including the DIVA trial), these meta-analyses showed no statistically significant differences in efficacy or safety outcomes between DESs and BMSs for SVG intervention, in the long term (>3 years) (20,21).

In conclusion, current evidence seems to suggest that SVG intervention with DESs might improve the short term

(1 year) outcomes compared to BMSs. Conflicting findings from the DIVA trial might be the result of any of its major limitations, which include the possibility of a type II error (16). On the other hand, current evidence is consistent, showing that in the long term (>3 years), DESs are not superior to BMSs for SVG intervention. In those parts of the world where the cost of DESs is of major concern, BMSs seem to be a reasonable option for SVG interventions (particularly in larger caliber SVGs), given that the lower cost is not accompanied by compromises in long term safety or efficacy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Shah R, Hesterberg K. Drug-eluting stents versus bare-metal stents for saphenous vein graft interventions. J Thorac Dis 2019;11(Suppl 9):S1257-S1260. doi: 10.21037/jtd.2019.02.50

