Editorial

Second-generation drug-eluting stents versus bare-metal stents in saphenous vein grafts: is the choice more complicated than before?

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Saphenous vein grafts (SVGs) are still commonly used for surgical revascularization of coronary arteries although are related to poor long-term patency rates (1-4). "Full arterial" revascularization in coronary artery bypass graft (CABG) procedures, despite related to an improved clinical outcome, is still seldom achieved (5-7). For this reason, percutaneous coronary intervention (PCI) of SVGs is being routinely performed in daily practice, accounting for approximately 6% to 10% of total PCI volume (8), with a clinical outcome that remains suboptimal if compared with that of PCI of native coronary arteries given the higher rates of in-stent restenosis (ISR), target vessel revascularization (TVR), myocardial infarction (MI), and death (9-11). In this unfavorable scenario the choice of the drug-eluting stent (DES) rather than the bare-metal stent (BMS) remains a matter of discussion, especially in light of the paucity of long-term clinical outcome data. However, following the findings of PCI in native coronary arteries, the most recent randomized clinical trials (RCTs) comparing DES and BMS in SVGs PCI have evermore shown favorable outcomes for DES regarding angiographic and clinical restenosis at short and mid-term follow-up (12-16). Nevertheless, all these studies are related to several limitations, like small size (12,14,16), absence of blinding design (14-16), routine angiographic follow-up (12-14), low use of embolic protection devices (15) and use of first-generation DES (12,14-16).

In the DIVA trial (17), recently published in "*The Lancet*", Brilakis and colleagues investigated the safety and efficacy of DES versus BMS implantation in de-novo SVG lesions, without a mandatory routine angiographic follow-up. A total of 599 patients with previous CABG with at least one significant de-novo SVG lesion requiring PCI, were randomized in a 1:1 ratio to receive a DES or BMS. Finally, the data of 597 patients were used. Relevant exclusion criteria were: ST-segment elevation acute myocardial infarction (STEMI) as a clinical presentation; a target SVG as last remaining vessel or left main equivalent; a warfarin administration for the following 12 months and the high bleeding risk profile with the need of a triple anticoagulation/antiplatelet therapy. Although the interventional cardiologist was not blinded to the result of randomization, patients, referring physicians, primary study coordinators, and outcome assessors, were masked to group allocation. For the blinding aim and in order to avoid bias between the group in terms of events at 12 months follow-up, patients randomized to BMS, requiring clopidogrel for only 1 month, who did not present with an acute coronary syndrome (ACS), were treated with clopidogrel or placebo after the first month for the following 11 months. At 1-year follow-up the incidence of target vessel failure (TVF) (primary endpoint composite of cardiac death, target vessel MI, or TVR), was not different between the two groups

(17% DES group versus 19% BMS group; HR 0.92, 95% CI: 0.63–1.34, P=0.70). These results were consistent during the entire follow-up (median 2.7 years), with a TVF incidence of 37% in the DES group and 34% in the BMS group (HR 1.10, 95% CI: 0.84–1.43, P=0.44). Log-rank tests unstratified by diabetes mellitus and one versus two or more SVG stenoses were not significant as well as no difference between-group in the primary endpoint after adjustment for baseline imbalance in SVG age (median <13.5 *vs.* ≥13.5 years) were detected. Moreover, no significant differences between the two groups in rate of all-cause death, MI, stent thrombosis, stroke, bleeding or other secondary outcomes were observed. The two main causes of repeat revascularizations were ACS [70% (133 of 191)] and stable angina [24% (46 of 191)].

The findings of DIVA trial are surprising as well as discordant with the results of previous RCTs, which have shown improved clinical outcome with DES implantation in de-novo SVG lesions, at least in the short- and mid-term follow-up. In RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher) trial, where 75 patients with de-novo SVG lesions were randomized in 1:1 fashion to receive Cypher™ sirolimus-eluting stents (SES) or BX-Velocity™ BMS, the ISR rate at 6 months follow-up with SES was significantly reduced, consistently with a significant drop of both TLR (5.3% SES versus 21.6% BMS; P=0.047) and TVR (5.3% SES versus 27% BMS; P=0.012) at 6 months follow-up, without difference in terms of death and MI (12). Similarly in the SOS (Stenting Of Saphenous Vein Grafts) trial, where 80 patients were randomly allocated 1:1 to Taxus™ paclitaxel-eluting stent (PES) or BMS, the lower ISR rate (51% BMS *vs.* 9% PES; P<0.0001) translated into a significant reduction of TLR (28% BMS *vs.* 5% PES; P=0.003) and TVR (46% BMS *vs.* 22% PES; P=0.03) over a median follow-up of 1.5 years, with a similar mortality between the two groups (13). Both RRISC and SOS trials, although limited by small sample size and the use of first-generation DES (Cypher™ SES in RRISC trial and Taxus™ PES in SOS trial), had angiographic follow-up (6 months in RRISC trial and 12 months in SOS trial) and showed a significant advantage of DES implantation in SVGs. However, their post-hoc analyses of 3-year clinical outcomes revealed conflicting results. The SOS trial reported significant reduction of major adverse cardiac events (MACE) in patients treated with DES at a median of 35 months, mainly due to a reduced rate of MI and TVR, without significant difference in mortality (14). The DELAYED RRISC trial showed, at a median follow-up of 32 months, a late "catch up" for repeat revascularization and a remarkable increase in mortality in patients treated with DES (29% *vs.* 0% with BMS) (18). Based on these results and on the above-mentioned limitations, Mehilli and colleagues performed a large RCT (four-times increase in sample size as compare to previous studies) in which 610 patients were randomly allocated (1:1:1:3) to receive either first-generation DES [1 of 3 types: permanent-polymer PES (Taxus™), permanent-polymer SES (Cypher™) or biodegradable-polymer SES (Yukon™)] or BMS. DES reduced the incidence of the primary endpoint (combined incidence of death, MI, and TLR at 1 year) compared with BMS (15% *vs.* 22%; HR 0.64, 95% CI: 0.44–0.94; P=0.02), mainly driven by a significant reduction in TLR (DES 7% *vs.* BMS 13%; HR 0.49, 95% CI: 0.28–0.86; P=0.01), without significant differences in all-cause mortality, MI and stent thrombosis as compared with BMS (15). The two main points of strength of the ISAR-CABG trial were the planned angiographic follow up at 1 year and a long-term clinical follow-up, recently reported. The advantage of first-generation DES over BMS observed at mid-term (1 year) was lost at 5 years follow-up, without different event rates in both groups. As in the DELAYED RRISC trial the late "catch up" phenomenon was the culprit in the ISAR-CABG. Between 1 and 5 years the TLR rate in the DES group was more than twice that in the BMS group, irrespectively of the DES type used (19). Newly the BASKET-SAVAGE (Basel Kosten Effektivitäts Trial-SAphenous Venous Graft Angioplasty Using Glycoprotein 2b/3a Receptor Inhibitors and Drug-Eluting Stents) trial, early interrupted due to the limited enrolment (173 patients), also demonstrated an advantage in clinical outcome at 1 year with first-generation DES (PES Taxus Liberté™), mainly driven by a 12% rate TVR in the BMS group compared with none in the DES group (HR 0.04; P<0.001), as well as a significantly higher rate of non-fatal MI in patients treated with BMS (12% *vs.* 2%, HR 0.24; P=0.025). In contrast with the previous mid- and long-term follow-up studies, in the BASKET-SAVAGE trial there was a significant lower rate of MACE in the DES group (30% *vs.* 12%, HR 0.33; P=0.0012) at 3 years follow-up, with a safety profile similar in both arms (16). Still in this trial only one-third of patients completed the follow-up to 3 years, which makes the advantage for first-generation DES over BMS in the long term questionable. The findings of DIVA trial remain unclear as well as difficult to explain. The higher use of embolic protection devices (69%) than any other previous SVG stenting trial could not justify a

possible prognostic impact on the reduction in peri-procedural MI at 1-year follow-up, since the latter was not different between the two groups as well as the adoption of embolic protection devices. Moreover, it seems particularly odd the absence of improved outcomes with DES in DIVA trial despite the use of second-generation DES in 88% of patients of DES group. One might speculate that in the unfavorable "SVG scenario" in which the atherosclerosis is more concentric, diffuse and aggressive over the time, the adoption of second-generation DES, which has a better stent platform and a more biocompatible profile than the first-generation DES, could play an important role like in native coronary arteries. The authors have hypothesized that the use of thin-strut BMS might have lower risk of ISR as compared with thicker strut BMS used in previous SVG PCI studies. The struts thickness seems to give a minimum rationale to the results of DIVA trial, not so much for the ISR, but rather for TVF rate driven by target vessel MI or TVR. Autopsy studies have demonstrated that SVGs plaques are typically fibroatheroma with large necrotic cores, generally accompanied by plaque hemorrhage and a disrupted fibrous cap (20). While stenting of such SVGs lesions has been associated with a roughly complete endothelialization by 3 to 4 months after BMS placement (21), DES implantation turns in a delayed healing, because of longer retention of lipophilic drug, with a consequent incomplete endothelialization. Even if focal stent struts penetration into this lipid core of SVGs lesions does not depend on the type of implanted stent (BMS or DES), the long-term (≥360 days) uncovered struts rate is much prominent with DES than BMS (20). This important discrepancy in endothelialization time after SVGs PCI (3–4 months for BMS *vs.* >1 year for DES) could partially explain the similar outcome at 1-year follow-up of patients treated with DES and BMS in the DIVA trial. Moreover the "non-additional advantage" of the second-generation DES in SVGs PCI is supported by long-term results, albeit coming from retrospective studies. In a series of 12,339 patients with SVGs lesions newer-generation everolimus-eluting stents (EES) showed similar safety and efficacy to early-generation SES and PES during long-term follow-up to four years (22). Similar results have been provided by Pokala and colleagues in a comparison between first-generation SES and PES and second-generation EES and zotarolimus-eluting stents (ZES) at two years follow-up (23). If the "non-additional advantage" of the second-generation DES in this setting might be a matter of drug is unclear. The hypothesis proposed by Jeger and Möbius-Winkler regarding the specific effect of paclitaxel, which might lead to an adequate treatment effect in SVG with first-generations PES (24), looks still speculative. In an experimental study of comparison between paclitaxel, sirolimus, everolimus, and zotarolimus on several endothelial progenitor cells (EPC) properties as a surrogate of vascular healing, paclitaxel treatment was associated with the greatest down-regulation of antithrombotic gene expression and up-regulation of prothrombotic gene expression. If paclitaxel blunts the proliferative and antithrombotic functions of EPC much more than the other drugs, could also contributes more to incomplete vascular healing and increase the risk of stent thrombosis (25). If on one hand all these controversial hypotheses do not clarify the results of DIVA trial, on the other they lead us to conclude that the clinical outcome after SVGs PCI is mainly related to the different pathobiology of SVG as compare to native coronary arteries, rather than the type of stent implanted. The atherosclerosis in SVGs is often concentric and diffuse, with a less well-defined fibrous cap, which is more vulnerable to rupture and thrombosis. Due to the aggressive progression of the plaque upstream and downstream of the stent implanted (DES or BMS), the atherosclerosis in SVGs remains an unfavorable prognostic factor, with an ultimate impact on TVR and long terms SVG patency rate. Indeed, the main driver of repeat revascularizations in DIVA trial was the ACS.

Still no solid data up to date are available in order to draw solid conclusions on the type of stent to use for SVGs lesions. However, if the results of DIVA trial will be confirmed in a long-term follow-up (5 years), BMS implantation could be consider a viable option for SVGs PCI in countries with high DES prices, without compromising either safety or efficacy.

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Footnote

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

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