Editorial

Is the Sirolimus encapsulated balloon a reliable tool for treating the in-stent restenosis?—insights from the SABRE trial

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The introduction of drug-eluting stents (DES), has positively changed of the outcomes of percutaneous coronary interventions (PCI), due to the dramatically decreased incidence of in-stent restenosis (ISR) (1). The overall improvement in safety profile of drug-eluting and newer generation DES, due to advancement in technology, platform, polymer and type of drug have pushed the interventionalist to treat more complex patients and coronary stenoses (2,3). Accordingly, the latest European Guidelines on Myocardial Revascularization (4) state that DES should be considered as first line choice in all patients and coronary lesion subsets.

As a consequence ISR has not been fully eradicated and still angiographically encountered in around 12% of cases (5). Treatment of coronary ISR has been addressed with different strategies, including plain old balloon angioplasty (POBA), brachytherapy, cutting balloons, atherectomy, repeat stenting with bare metal stents (BMS) and DES, and most recently with paclitaxel-coated balloons (PCBs). DES became the current standard of care insofar as the metal scaffold helped to maintain lumen diameter while controlling repeat neointimal hyperplasia with paclitaxel or a limus drug, with improved outcomes compared with prior therapies. A limitation of this approach is the addition of concentric layers of the metal stent strut that progressively reduces vessel flexibility and lumen diameter, whereas stimulating neointimal hyperplasia and requiring long-term use of dual antiplatelet therapy.

PCBs extensive application for treatment of BMS ISR resulted in a positive result when compared to POBA (6-9) or first generation DES (10). The PCBs concept was based on local drug delivery without additional stent layers implantation.

The early studies showed superiority of PCBs over POBA in terms of acute and long-term angiographic and clinical results. More recently several studies evaluated the effects of PCBs in DES-ISR treatment compared to POBA (11,12), paclitaxel-eluting stent (13) or both approaches (14). ISR treatment with PCB obtained a significantly lower late lumen loss, in-stent residual diameter stenosis (%) and lower clinical event rates in comparison with balloon angioplasty alone (11,12). Additionally, drug-coated balloon-PCI reached the angio results obtainable with DES stent-in-stent technique (13,14) for ISR treatment. Finally, PCB use for treatment of both BMS and DES-ISR has been added to class IA recommendation by the European Society of Cardiology (4).

Previous studies investigating the efficacy and safety of PCB angioplasty to treat DES-ISR reported TLR rates between 2.9% (9) and 22.1%, at 6- and 12-month (14), respectively and concomitant cardiac adverse events rate between 6.6% (9) and 23.5% (14).

It is well known that lipophilic drugs, such as paclitaxel, may be delivered to the vessel wall even with short balloon

inflation times. Therefore, these premises allowed for DCB development and clinical use. DCB technology has reached the goal to release drugs inhibiting neointimal proliferation without the implantation of an additional stent, thus avoiding multiple stent strut layers inside the vessel wall in ISR treatment.

Indeed, so far, non-inferiority of PCB angioplasty versus first-generation DES (10,13,14) has been reported in several studies and meta-analyses while few data are available regarding the comparison of PCB effectiveness over newer generation DES when ISR after DES implantation occurs. Almalla *et al.* (15) compared PCB angioplasty to EES implantation in a DES-ISR patient using a historic control arm, showing definitely lower TLR and MACE rates in the PCB arm. Somehow different appears to be the ISR after bare-metal stent implantation; indeed, the RIBS V (Restenosis Intra-stent: Drug-eluting Balloon *vs.* Everolimus eluting Stent) trial (16), describing the first randomized evaluation of PCB angioplasty with everolimus-eluting stent in 189 patients, showed superior late lumen loss and diameter stenosis after EES implantation. However, despite restenosis rate was low and similar in both groups (4.7% *vs.* 9.5%, P=0.22), the study did not demonstrate clinical benefits associated with better angiographic results.

A tight correlation between MACE rate and timing between DES implantation and ISR occurrence at 12 months has been shown by Auffret *et al.* (17) in the French GARO registry, enrolling 206 consecutive patients treated with PCB for ISR. The shorter the time interval between DES implantation and DES-ISR is, the less likely ISR may be caused by neointimal hyperplasia whereas mechanical factors probably play a crucial role. Additionally, early ISR presentation has been associated with diffuse ISR patterns which may explain the worse results observed in the sub-group of patients with a short delay between DES implantation and ISR. Moreover, the morphological pattern of DES-ISR is an additional important predictor of clinical outcomes, especially TLR (18).

The SABRE (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis) trial published recently by Verheye *et al.* in the JACC Cardiovasc Interventions issue, reports the results of the first in-human, single-arm study evaluating the feasibility, performance and clinical outcomes of a porous balloon designed to locally deliver a nano-encapsulated formulation of sirolimus. Fifty patients with ISR were enrolled at 9 clinical sites in Europe. The study was designed and powered to test the superiority of the sirolimus-eluting balloon (SEB) compared to the POBA for the primary end-point of in-segment late lumen loss, assumed to be 0.86 for POBA according to the historical data. At 6-month angiographic follow-up, in-segment late lumen loss after SEB was 0.31 mm, allowing the rejection of the null hypothesis of no difference and establishing the superiority of SEB with respect to a hypothetical control arm undergoing POBA. Accordingly to these results, the mean diameter stenosis was 30.3%, the change in diameter stenosis 12.7% and the rate of binary restenosis 19.1%, lower than that reported with balloon angioplasty.

Target lesion revascularization was the major adverse cardiac event and was required in 4 (8.2%) patients at 6-month follow-up while in 6 (12.2%) patients at 12-month follow-up.

Which are the take-home messages from this first-in-man trial?

(I) The use of a balloon instead to DES to deliver a drug to the arterial wall allows for uniform delivery, with nearly complete and homogeneous coating of the surface of the lesion. Further limitation of DES includes the need for long lengths to cover the entire surface of a diseased vessel. The superiority of limus-eluting over paclitaxel-eluting stents suggests that a stent-free sirolimus angioplasty balloon could have efficacy advantages over current PCBs. However, initial attempts to deliver therapeutic doses of the drug with balloon angioplasty were unsuccessful due to molecular instability, slow uptake by the vessel wall, and insufficient drug retention (19). The efficacy of a nanoparticle-based SEB is novel and supports the concept of loading semicompliant balloons laser drilled with holes of uniform pattern and density loaded with submicron particles stable in aqueous suspension and encapsulated with sirolimus. Thus, a precise volume of formulation may be delivered to the vessel wall at standard angioplasty pressure (10 to 14 atm) for 30 to 60 s.

(II) Angioplasty balloons coated with a polymer that elutes an antiproliferative agent are designed to compress and disrupt plaque as well as simultaneously deliver a drug to prevent restenosis. Interestingly, almost all trials on drug eluting balloons (DEBs) have used paclitaxel, a drug that inhibits microtubule assembly and selectively inhibits smooth muscle proliferation, migration, and extracellular matrix deposition. Paclitaxel is well suited for delivery by a

DEB because it is highly lipophilic, allowing rapid intracellular uptake after a brief administration. The Sirolimus-based strategy using this potent cytostatic agent with immunosuppressive action and a wide therapeutic range compared to paclitaxel may take a net advantage over the current technology for treating ISR.

(III) Inside the SABRE trial, baseline angiographic analysis by the core lab revealed a number of potential protocol inclusion violations (e.g., close proximity to ostium or major side branch, excessive lesion length or number, geographic miss of lesion or stent, re-restenosis). Thus, 36 patients in the per protocol population were analyzed separately from the ITT group. The results of the study were significantly improved in patients without protocol violations whose mean late lumen loss amounted to 0.12 mm. This interesting observation raises the question of whether SEB may provide a DES-like result in restenotic lesions with lower complexity, such as those not involving the coronary ostium, bifurcations, long or tortuous segments, or recalcitrant ISR. Furthermore, late loss in the per protocol population remained as low as 0.20 mm among patients who presented with DES-ISR at the index procedure. It is tempting to speculate that the anti-inflammatory properties of sirolimus, not present in the case of paclitaxel, may be more beneficial in treating patients with DES-ISR.

In conclusion, despite the small sample size and the single-arm design that would limit applying conclusions to broad patient populations and the significant portion (28%) of patients excluded from the per protocol subset, the SABRE trial provides the first clinical evidence of efficacy of a novel technique for solving ISR. Further larger and randomized studies are needed to confirm SEB superiority over POBA and to assess its non-inferiority to what current guidelines recommend for ISR treatment.

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Footnote

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

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