Editorial

Novel treatments for in-stent restenosis: sirolimus-eluting balloons enter the arena

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In-stent restenosis (ISR), defined as a ≥50% reduction in coronary lumen diameter within the stent or within 5 mm of the stent edges, remains a relevant issue in the field percutaneous coronary intervention (PCI) (1). As first iteration in PCI, balloon angioplasty presented several drawbacks, including intimal and media dissection, abrupt vessel occlusion, late structural remodeling and, importantly, diffuse proliferative neointimal response due to traumatic vessel injury, resulting in a rate of restenosis greater than 40% (2). The introduction of coronary stents substantially improved procedural success and clinical outcomes after PCI by significantly reducing the risk of restenosis and nearly eliminating the risk of acute vessel closure with the consequent need for surgical standby (2). However, the lack of antiproliferative drug release from bare metallic platforms remained associated with higher rates of ISR and target vessel revascularization. Contemporary new-generation drug-eluting stents (DES), with improved effective local cytostatic drugs and more predictable release, substantially reduced but not eliminated ISR, which is still found in approximately 12% of patients at 6–8 months angiographic follow-up (3). These data should not be overlooked because there is evidence showing a higher risk of mortality among patients developing ISR (4).

A large number of factors may contribute to ISR such as mechanical factors (stent underexpansion, stent fracture, nonuniform stent strut distribution), technical factors (stent gap, barotrauma outside stented segment, residual uncovered atherosclerotic plaques) and biological factors (hypersensitivity reactions to stent components, such as stent platform, antirestenotic drug, polymer carrier, or drug resistance). Moreover, specific patient (for example, chronic kidney disease or diabetic patients) and lesion subsets [bifurcation lesions, diffuse coronary artery disease (CAD), small vessels] are associated with a higher risk of ISR.

Over the past years, several techniques have been proposed for the treatment of ISR, including conventional balloon angioplasty, cutting or scoring balloons, vascular brachytherapy, additional stenting, drug-eluting balloons (DEB), and bioresorbable vascular scaffolds (5-7). DEB have the potential advantage to ensure local drug release and therefore avoiding an additional metal layer in previously stented coronary segment. As such, DEB may be considered as a less invasive option and part of a streamlined PCI approach together with the preferential use of radial over femoral access (8). Moreover, DEB as alternative to stent-based approaches may be particularly useful in case of the need for an abbreviated course of dual antiplatelet therapy (patients deemed at high bleeding risk or those requiring non-cardiac surgery) (9,10). Among new-generation DES, everolimus- and zotarolimus-eluting stents have been more frequently tested in randomized trials of ISR, while data from head-to-head comparisons in all-comers patients suggest equipoise between the two types of DES in terms of both safety and efficacy (11). Data from randomized clinical trials and meta-analyses show that DEB

are a safe alternative to new-generation DES, even though associated with a slightly larger diameter stenosis at follow-up angiography (6,12). DEB approved for clinical practice elute paclitaxel, which has been used for DES platforms and considered for many years the drug of choice for DEB technology in view of its intrinsic lipophilicity. However, it is well known that agents of the "limus" family are more effective than paclitaxel and, indeed, sirolimus was already highly effective already at the time of early-generation DES (13-15). Nevertheless, initial attempts to deliver therapeutic doses of sirolimus from balloons were unsuccessful because of molecular instability, slow uptake by the vessel wall, and insufficient drug retention.

Recently, the results of a pilot study, the SABRE trial, have been reported (1,16). This was a single arm study designed with an objective performance goal to test the superiority of a sirolimus-eluting balloon, SEB (the Virtue balloon, Caliber Therapeutics, New Hope, Pennsylvania), over a hypothetical arm of plain balloon angioplasty. A total of 50 patients presenting with bare-metal stents or DES ISR were recruited across nine European centers. Patients were evaluated clinically at 30 days, 6 months, and 1 year, and invasive angiographic follow-up was planned at 6 months after the index PCI. At angiographic follow-up, available in 94% of patients, late lumen loss (LLL), the primary endpoint of the study, attested to 0.31±0.52 mm, fulfilling the criteria for superiority against an historical plain balloon angioplasty arm, whose LLL was assumed at 0.86 mm (P<0.0001). Along the same vein, mean diameter stenosis and the rate of binary restenosis were 30.3% and 19.1%, respectively—somewhat lower than that reported with standard balloon angioplasty. At 12 months follow-up, major adverse cardiac events, a composite of death, target-vessel myocardial infarction, coronary artery bypass surgery, or target-lesion revascularization, were 14.3%. Noteworthy, ischemic events were mainly driven by the need for repeat revascularization at target lesions (12.2%).

How should we interpret the results of the SABRE trial?

First, the study proved the effectiveness of a sirolimus-eluting balloon among patients with ISR. However, it is important to underscore that at variation with other technologies the Virtue balloon does not present a polymer coating. Sirolimus, indeed, is encapsulated with biodegradable polyester-based polymers in submicron particles that are delivered through specific micropores at the time of balloon inflation. In a preclinical study, levels of sirolimus at tissue level were greater than the therapeutic dose of 1 ng/mg after 4 weeks from the index procedure (17). Second, while the observed LLL in the SABRE trial seems higher than that reported with new-generation DES, a total of 14 patients had protocol violations according to study protocol (i.e., close proximity to ostium or major side branch, excessive lesion length or number, geographic miss of lesion or stent). When the analysis was performed after exclusion of these patients, the LLL was very low (0.12 mm) and compatible with data from new-generation DES. This observation raises the question of whether SEB are more effective and comparable to new-generation DES in restenotic lesions at lower complexity, such as those not involving the coronary ostia, bifurcations, long or tortuous segments. Third, although it is well known that ISR is more challenging to manage in case of DES instead of bare-metal stents, LLL in the per protocol population remained as low as 0.20 mm among patients who presented with DES-ISR at the index procedure. Despite speculative, it may be argued that some anti-inflammatory properties of sirolimus, not seen with paclitaxel, become important in case of DES-ISR, which can feature a greater inflammation component and neoatherosclerosis.

The SABRE has renewed the interest in sirolimus as antiproliferative agent for DEB technology. The proof of superiority of SEB compared with balloon angioplasty is an important prerequisite, but before implementing it in clinical practice it is important to know whether this new technology is at least non-inferior (or even superior) to the current standard of care, i.e., paclitaxel-eluting balloons and new-generation DES.

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Footnote

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

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