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EDITORIAL COMMENT

The Debut of Sirolimus-Eluting Balloons

The Final Nail in the Coffin for In-Stent Restenosis?*

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During its 40-year journey, percutaneous coronary intervention (PCI) has witnessed enormous progress in procedural results and patient outcomes. The efficacy profile of the procedure has greatly improved from initial rates of restenosis of more than 40% with balloon angioplasty to approximatively 10% in the current era of new-generation drug-eluting stents (DES) (1,2). Notwithstanding this, in-stent restenosis (ISR) is not eradicated from any catheter-based percutaneous treatment, and its occurrence continues to negatively impact long-term prognosis (3). Observational studies presented some evidence that ISR following DES implantation is more challenging to treat than bare-metal stent restenosis and may have a far higher long-term disease burden (4). In view of the preferential use of PCI instead of bypass surgery for myocardial revascularization, and the ubiquitous implantation of new-generation DES in clinical practice, ISR remains a clinically relevant issue—particularly in absolute terms—and poses new questions to its treatment.

In the past 15 years, at least 10 strategies for the percutaneous treatment of ISR have been evaluated in randomized clinical trials (5,6). However, the all-round effective option is far from being achieved and unmet need continues. In fact, the greater effectiveness of new-generation DES compared with paclitaxel-coated balloons, resulting in about 10% difference in diameter stenosis at angiographic follow-up (6), presents the unavoidable corollary of a newer metallic layer indwelling in the coronary vessel. Most of us would agree that despite being more effective, a stent-based strategy appears counterintuitive in the modern age of restoration of vascular physiology and anatomy.

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In this issue of *JACC: Cardiovascular Interventions*, Verheye et al. (7) report the results of a first-in-human, single-arm study evaluating the feasibility, angiographic performance, and initial clinical outcomes of a porous balloon equipped to locally deliver a nano-encapsulated formulation of sirolimus. The investigators enrolled a total of 50 patients presenting with ISR at 9 European centers. The study was designed with an objective performance goal to test the superiority of the sirolimus-eluting balloon (SEB) compared with balloon angioplasty for the primary endpoint of in-segment late lumen loss, which was assumed at 0.86 mm for balloon angioplasty on the basis of historical data. At angiographic follow-up, which was performed in 94% of patients at 6 months, in-segment late lumen loss after SEB amounted to 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 balloon angioplasty. In the same vein, the mean diameter stenosis and the rate of binary restenosis were 30.3% and 19.1%, respectively—somewhat lower than that reported with plain balloon angioplasty. Revascularization at the target lesion site accounted for most of adverse cardiac events and was required in 6 patients (12.2%) at 12-month follow-up.

So, how should we interpret the results from this first-in-man trial?

First, although sirolimus proved highly effective already at the time of early-generation DES (8,9), 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 (10). Consequently, the efficacy of a nanoparticle-based SEB,

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initially observed in animal models (11) and now confirmed in a clinical setting, is novel and supports the concept of loading balloons with limus compounds. Once proved feasible, this technology may take advantage of other potential benefits related to using sirolimus in lieu of taxane agents: a cytostatic instead of cytotoxic mechanism of action, larger safety margin, and wider therapeutic range.

Second, although SEB clearly outperformed balloon angioplasty, its optimal positioning in a more contemporary armamentarium for treating ISR, comprising at least paclitaxel-coated balloons and new-generation DES, is not addressed by the study. Indeed, even though SEB seems to confer similar angiographic outcomes to paclitaxel-coated balloons, there is an unquestionable need for further studies with a dedicated randomized trial designed to test the hypothesis of noninferiority between SEB and the current standard of treatment.

Third, 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. Indeed, it is increasingly recognized that neoatherosclerosis, which is characterized by a relevant inflammatory component, is more likely to occur in case of DES-ISR. Nevertheless, the findings of the per protocol analysis should be taken with a grain of salt because of its post hoc nature and the exclusion of about 30% of the overall population, resulting in reduced statistical power. Moreover, it is important to acknowledge that not all protocol violations included in this study represented exclusion criteria in trials of paclitaxel-coated balloons, and this aspect reduces the generalizability of the per protocol analysis to a broader population of ISR patients.

As a final consideration, it is important to keep in mind that the field of PCI has lain fallow for several years while trying to combine limus agents with balloons for the treatment of ISR. This study provides the first evidence for a novel and effective strategy for ISR, and therefore it has the merit of having overcome the gridlock in this research area. However, the proof of superiority over balloon angioplasty is not enough. Before using SEB in clinical practice, it will be important to know whether this technology is at least noninferior to what is currently recommended by guidelines, that is, paclitaxel-coated balloons or new-generation DES (12).

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