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EDITORIAL COMMENT

Drug-Coated Balloons for In-Stent Restenosis

A Fierce Fight for a "Me-Too" Space*

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The clinical efficacy of paclitaxel-coated balloons (PCB) for the treatment of coronary in-stent restenosis (ISR) was reported for the first time more than 10 years ago (1). Although embraced with enthusiasm, this nascent field encountered fierce opposition in the already growing drug-eluting stent (DES) era. Several randomized controlled studies confirmed the clinical efficacy of PCB in ISR and small-vessel disease applications; however, the field continues to be challenged by questions regarding long-term clinical benefit and comparative efficacy against DES (2).

The first PCB technology used iopromide as a hydrophilic carrier, resulting in a highly crystalline coating. This formulation demonstrated prolonged paclitaxel tissue retention times and proved to be clinically effective in the prevention of restenosis in multiple clinical settings. Experimental studies have now confirmed the importance of crystallinity coating in drug transfer, tissue retention, and particulate formation at the time of balloon delivery (3). New-generation PCB technologies aim to improve clinical device performance by either modifying crystallinity coating or reducing the total paclitaxel dose. In particular, decreasing the number of paclitaxel particles that are washed off during balloon inflation has become an important technological goal. As PCB technologies continue to evolve, an important question still remains: will new-generation PCB coatings match the clinical performance of first-generation PCB technologies?

In this issue of the *JACC: Cardiovascular Interventions*, Chen et al. (4) published the clinical results of the RESTORE ISR China (Compare the Efficacy and Safety of RESTORE DEB and SeQuent® Please in Chinese Patients With Coronary In-stent Restenosis) trial. This randomized controlled trial performed in China aimed to compare the clinical performance of a new-generation drug-coated balloon in ISR patients. This trial randomized patients with ISR either to a new PCB (Restore, Cardionovum, Germany) or to a clinically available PCB technology (SeQuent Please, B. Braun, Melsungen, Germany). The study PCB contains a new-generation coating (shellac-ammonium salt excipient) promising improved coating integrity. The control device was the well-characterized iopromide-based PCB. Both technologies tested in this study used a similar dose of 3-μg paclitaxel per square millimeter of balloon surface.

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The RESTORE ISR trial is unique because it is the first head-to-head randomized controlled study using contemporary interventional techniques in the treatment of ISR. The study was conducted at 12 interventional centers in China and enrolled 240 patients with a first occurrence of DES-ISR exhibiting similar demographic and lesion profiles compared with other PCB trials. Almost all the lesions included in this trial were single, simple (~60% type I Mehran ISR), and relatively short (~16 mm). All angiographic variables at 9 months (primary endpoint) were comparable between both study groups. At 1 year, although target lesion revascularization rates were similar, a numerically higher number of target vessel revascularization rates was seen in the new PCB study group. Although at first glance a market entry study,

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the RESTORE ISR China trial has important features that deserve to be highlighted.

First, at the beginning of the PCB era, drug loss occurring during device transit was thought to be a determining factor of clinical efficacy. Early studies estimated that at least one-third of the total coating could be potentially lost during balloon transit, especially through the interaction with small-profile catheters. In this study, transradial access was used in ~90% of the cases, and, for the first time, the use of PCB through this vascular access was validated in a randomized controlled study. Second, it has been hypothesized that scoring/cutting pre-dilatation techniques may lead to bigger lumen gain and improve drug uptake during PCB use. In the present study, although dedicated pre-dilatation techniques were used in more than 50% of the cases, no significant differences were seen in post-procedural acute gain or late angiographic outcomes compared with other PCB trials. Third, the potential for distal particle embolization caused by distal coating wash-off occurring at the time of balloon inflation remains an important safety concern, especially in the coronary territory. In this study, the incidence of periprocedural MI was very low (0.8%) in both groups, supporting the safety of the technology for this particular application. Finally, the low 1-year stent thrombosis rates continue to support the long-term safety of PCB in this particular clinical setting.

Re-intervention for DES-ISR is associated with a worse prognosis and its ideal treatment continues to be a matter of debate (5). Some studies suggest that the use of a second DES results in better long-term angiographic and clinical outcomes compared with PCB treatment (6). However, the definitive presence of multiple stent layers and its potential thrombogenic effect is a matter of clinical concern. On the other hand, the use of PCB appears to result in slightly inferior angiographic and clinical results but low stent thrombotic rates at 1 year. Randomized controlled studies in the PCB field are limited by the fact that they have included small sample populations, mixed/simple ISR lesions (bare-metal stents plus DES), or short clinical follow-up. Although studies have tested the clinical performance of these technologies, large randomized studies are critically needed to evaluate their potential in real-world case scenarios. Meanwhile, the interventional world will continue to debate the benefits of adding a second DES layer versus the benefits of balloon-based drug delivery leaving nothing behind.

The RESTORE ISR China study is important because it continues to add clinical evidence in the PCB field. However, although evidence of clinical equivalence was provided for this new PCB, the new technological changes did not seem to have an impact on clinical efficacy. Periprocedural myocardial infarction, the most feared complication of PCB use related to coating particle wash-off, was not only very low but comparable between both groups. It thus seems to be clear that new-generation PCB technologies have rapidly reached a technological class effect and entered a fierce fight in an already crowded space.

The field continues to evolve including the use of new drugs, the development of dedicated delivery systems, and drug encapsulation technologies. The clinical indications of PCB have already been established, especially for the treatment of ISR and small vessel disease. However, in order to expand its clinical indication, emerging technologies will have to match the clinical performance not only of their predecessors but also of metallic DES. Otherwise, the use of balloon-based delivery technologies will continue to be limited to specific clinical settings and considered a second line of therapy in mainstream coronary intervention. The dream of performing coronary interventions leaving nothing behind continues to advance; however, the standards for device performance are very high, and disruption in this market will only occur once the outcomes of metallic DES are at least matched.

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