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Editorial

Peripheral Drug-Coated Balloon for Coronary Drug-Eluting Stent In-Stent Restenosis: Off-Label, Off-Target

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The reported annual rate of in-stent restenosis (ISR) for drug-eluting stents (DES) in the United States now surpasses 10% of total percutaneous coronary interventions (PCI) despite advances in DES technology.[1] Managing DES-ISR continues to present a significant challenge, and the search for an effective remedy for this phenomenon persists.

Over the past decade, advances in intracoronary imaging have enhanced our understanding of the mechanisms of ISR, which are now categorized into biological, mechanical, or mixed etiologies.[2] Understanding the mechanism of ISR is pivotal to selecting the optimal treatment, such as high-pressure balloon for underexpanded stents or employing an antiproliferative modality, such as vascular brachytherapy (VBT), DES, or drug-coated balloon (DCB) to address tissue proliferation within the stent. Currently, treatment options for DES-ISR include plain old balloon angioplasty (POBA), which is used primarily for underexpanded stents and stent recoil; however, POBA with or without ablative devices, such as mechanical or laser atherectomy, is associated with high rates of recurrence.[1] Repeat DES, involving additional layers of metal, poses a risk of stent thrombosis and neointima recurrence.[3] VBT, although highly effective, is available in only a few centers in the United States and is linked to late ISR recurrence.[4] Coronary DCB, with a class I indication for ISR treatment in Europe,[5] are not yet approved for marketing in the United States.

The data on DCB for DES-ISR yield mixed results compared with repeat DES, leading to a contentious debate, which is reflected in the guidelines. European guidelines classify DCB for ISR as a class I indication, whereas the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography & Interventions guidelines recommend second DES use as a class I recommendation.[5,6] Despite these management options, none provide a definitive cure, with ISR recurrence rates ranging from 10% to 36% at 12 months postsuccessful ISR treatment.[3,4] Finally, coronary artery bypass grafting is generally undesirable for most patients, especially when redo surgery is required.

In the issue of *JSCAI*, Madhavan et al[7] report on the off-label use of peripheral paclitaxel DCB (P-DCB) for coronary ISR treatment in a single center. The authors report their experience on 31 patients treated with P-DCB for coronary ISR: 14 had first-time ISR, whereas 17 had recurrent ISR. The results of this off-label use of P-DCB treatment were disappointing; more than one-third (35%) of patients presented with recurrent ISR.

Several factors could explain the failure of P-DCB in treating coronary DES-ISR. First, it may be attributed to resistance within the target tissue, previously treated with an antiproliferative agent. Second, the ISR mechanism in these cases might have been predominantly mechanical. Third, the bulkiness of the P-DCB could have resulted in drug loss during its transition to the target lesion. Finally, it is plausible that P-DCB may simply not be effective for recurrent coronary DES-ISR.

Moreover, it is crucial to highlight that the 1-year rate of recurrent ISR (35%) observed in the current study utilizing P-DCB is notably higher than the rates of target lesion revascularization (TLR; 12.4%) reported in the pivotal AGENT IDE clinical trial for the AGENT coronary paclitaxel DCB (Boston Scientific).[8] Madhavan et al[7] further note that a substantial majority (68%) of patients in their study exhibited a diffuse pattern of ISR, which is recognized as more challenging to treat and linked to poorer outcomes compared with focal ISR lesions.[9] It is imperative to recognize the distinctions between P-DCB and coronary DCB. P-DCB are bulkier and longer (with the shortest available length being 40 mm and the smallest diameter being 4 mm) than coronary DCB. Additionally, the recommended inflation time for P-DCB is 120 to 180 seconds for adequate drug delivery in contrast to the shorter 30 to 60 seconds recommended for coronary DCB. Given these differences, operators might have been cautious about inflating the bulky P-DCB for an extended duration to treat coronary ISR due to concerns of potential ischemic injury and an increased risk of myocardial damage. Suboptimal inflation time and pressure could result in inadequate drug delivery to the vessel, leading to less favorable outcomes.[10]

Madhavan et al[7] did not provide detailed information about the ISR lesion preparation in most cases or how many subjects underwent intravascular imaging-guided PCI. Lesion preparation for DCB and the use of intracoronary imaging are crucial for optimizing results and ensuring optimal drug delivery to the vessel wall. It is essential to emphasize that DCB are designed primarily for optimal drug delivery

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rather than optimal angioplasty. Predilating the target lesion with an uncoated balloon is a key step, creating traumatic intimal tears that facilitate better drug delivery to the vessel wall.[11] Despite the relatively large size of P-DCB, importantly, the study did not report any safety concerns, including perforations or dissections requiring additional intervention, and there were no postprocedural myocardial infarctions.

Although no studies have reported the off-label use of P-DCB (designed for peripheral arteries) specifically to treat coronary DES-ISR, P-DCB are commonly utilized for ISR treatment in peripheral arteries. In those, P-DCB have demonstrated lower TLR rates with no significant differences in safety, including amputations, when compared with standard POBA[12]; however, concerns arise regarding the durability of DCB efficacy beyond 1 year, as TLR rates reach 43% at the 5-year mark.[13] This finding suggests a potential "late catchup" phenomenon with P-DCB, where the initial suppression of neointimal growth by the antiproliferative drug diminishes over time, resulting in a loss of therapeutic effect. This phenomenon may be attributed to paclitaxel's known dose-dependent effect on inhibiting neointimal proliferation.[14]

In conclusion, the findings reported by Madhavan et al[7] underscore the complexities inherent in treating DES-ISR. The proof-of-concept use of P-DCB failed to demonstrate effectiveness as a promising treatment strategy. It was inferior to VBT and recurrent DES. This outcome also raises questions about the potential efficacy of coronary DCB for treating recurrent DES-ISR. Consequently, the off-label use of P-DCB for coronary DES-ISR treatment appears to be off-target, prompting the need for further investigation with future technologies, including both current DCB and next-generation DCB containing sirolimus, to assess their effectiveness in DES-ISR treatment. Until an ideal therapy is identified, it is prudent to consider steps aimed at reducing ISR, such as minimizing stent use, opting for DCB for de novo lesions, incorporating imaging more extensively during stent placement, and focusing on vessel preparation to optimize stent placement, thereby proactively reducing the incidence of DES-ISR.

Declaration of competing interest

Ron Waksman served on the advisory board of Abbott Vascular, Boston Scientific, Medtronic, Philips IGT, Pi-Cardia Ltd; Consultant: Abbott Vascular, Append Medical, Biotronik, Boston Scientific, JC Medical, MedAlliance/Cordis, Medtronic, Philips IGT, Pi-Cardia Ltd, Swiss Interventional/SIS Medical AG, Transmural Systems Inc; institutional grant support: Biotronik, Medtronic, Philips IGT; investor: Transmural Systems Inc. Waiel Abusnina reported no financial interests.

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