The introduction of bare metal stents (BMS) over 30 years ago was a significant milestone in the evolution of percutaneous coronary intervention. Soon after, it was apparent that these stents led to a troubling phenomenon of in-stent restenosis (ISR), which requires repeat revascularization, was associated with increased morbidity and mortality, and posed a therapeutic challenge. The quest for optimal therapy for ISR has begun, but in parallel, continued efforts were devoted to improve the stent technology. These iterations included design and alloy modification, reducing strut thickness, and adding a polymer to elute an antiproliferative drug. Drug-eluting stents (DES) significantly reduced the occurrence of exuberant neointimal proliferation. However, in spite of the wide use and experience gained with novel stent technologies and implantation techniques, the rates of ISR in both BMS and DES are still relatively high. In a contemporary report on a large cohort (n=10,004), routine angiographic surveillance 6 to 8 months after stent implantation has revealed ISR rates of 30.1%, 14.6%, and 12.2% for BMS, first-generation DES, and second-generation DES, respectively.

To optimize the treatment of ISR, it is imperative to identify and understand the major etiologies for ISR that have been traditionally classified and characterized as (1) operator or technique dependent, including stent undersizing, incomplete lesion coverage, stent underexpansion, and malapposition; (2) mechanical and design properties of stents that may lead to recoil because of loss of radial force, stent fractures, and altering increase in shear stress; (3) patient- and biologically related conditions, such as metal allergy, local hypersensitivity reactions with immunologic and inflammatory response to the drug or the polymer, often characterized with inflammatory cells and smooth muscle cells that transformed to rigid scar tissue within the stent. This local inflammation can lead to the development of neatherosclerosis characterized by accumulation of lipid-laden foamy macrophages within the neointima with or without a necrotic core formation and calcification, which can occur years after stent placement.

With the introduction of DES, it was apparent that there are differences with respect to the time course and the phenotypic appearance of ISR across the BMS and DES generations, exhibiting a more diffuse and proliferative pattern for BMS versus more focal and soft lesions for the DES, however, more resistant to treatment. Neoatherosclerosis occurs more frequently and at an earlier time in the first- and second-generation DES when compared with BMS. These mechanistic complexities make the treatment of ISR even more challenging because both mechanical and biological factors can influence treatment outcomes.

Over the years, there were many attempts to find an optimal therapy for ISR; among them there were the high-pressure balloons, scoring balloons, ablative therapy with laser and rotational atherectomy devices, and local drug-delivery strategies. But the most successful approaches were vascular brachytherapy, restenting with same or different DES, and drug-coated balloons (DCB), which are supported by the European guidelines with similar levels of evidence. A recently published network meta-analysis addressed the question of which strategy was preferred for the treatment of ISR, with the primary outcome defined as the percent diameter stenosis at angiographic follow-up. Angiographic follow-up was available for 4975 (84%) of 5923 patients. This analysis suggested that percutaneous coronary intervention with everolimus-eluting stents (EES) was the most effective treatment, whereas percutaneous coronary intervention with DCB was ranked as the second most effective treatment but without significant differences from first-generation DES. Two additional similar design meta-analyses have reported similar findings.

In this issue of Circulation: Cardiovascular Interventions, Alfonso et al present a pooled analysis of the RIBS V (Restenosis Intra-Stent of Bare Metal Stents: Paclitaxel-Eluting Balloon vs Everolimus-Eluting Stent) and RIBS IV (Restenosis Intra-Stent of Drug-Eluting Stents: Paclitaxel-Eluting Balloon vs Everolimus-Eluting Stent) multicenter randomized trials, comparing the efficacy of EES in patients with BMS-ISR and DES-ISR. The study detected clinical and morphological differences of ISR in BMS versus DES, including for the later more focal ISR pattern and delayed onset of presentation. Nevertheless, the outcome of the patients with DES restenosis was less favorable with regard to the angiographic indices, including lumen diameter post procedure and at follow-up. At 1-year clinical follow-up of all patients, the DES-ISR group treated with EES had both increased mortality and need for target vessel revascularization as compared with BMS-ISR group. The authors conclude that EES provides favorable outcomes in patients with ISR and that the results of EES are less satisfactory.
in patients with DES-ISR than in those with BMS-ISR. The analysis has several limitations, primary being a post hoc sub-analysis of data from 2 prior studies with no randomization done. In addition, special caution should also be required when interpreting the study’s clinical outcomes because the current analysis was not powered to address any outcome measures. Nevertheless, several questions remain, including whether all ISR are the same, why is there a different response to the same therapy modality, what should be the optimal treatment strategy for DES-ISR, and can we eradicate ISR or at least mitigate its impact on patient’s outcomes?

Most of the studies indicate directly and indirectly that there are differences between BMS-ISR and DES-ISR. As alluded to before, these differences included a higher overall rate of restenosis, earlier time of presentation, and a more diffuse pattern with BMS. As per the mechanism of the stent failure, there could be similarities with respect to the mechanical issues such as stent undersizing and stent fracture or issues related to inadequate deployment of the DES by the operator. However, with respect to the biological failure, there are differences between BMS-ISR and DES-ISR because DES failure could be a result of hypersensitivity to the drug or the polymer, which does not exist in the BMS. The literature showed inferior results for the treatment of DES versus BMS for ISR, regardless of the therapeutic modality used, including vascular brachytherapy and DCB, and as demonstrated by the present study of Alfonso et al, it is the same for EES. Although BMS-ISR can be treated successfully with DES or DCB, in the case of DES-ISR, the responsiveness to additional drug or radiation is less successful, perhaps, because of the initial failure of the original drug or ongoing inflammation from the polymer of the failed DES. This underscores the importance of understanding the mechanism that led to the failure of the DES. Once identified, this could guide for optimal treatment strategy. Ideally, the treatment of ISR should not include an additional layer of metal, which places DCB and vascular brachytherapy in a better position when compared with DES. DCB is currently not available for use in the United States. In addition, their use has been associated with issues that may limit their use mostly related to the use of paclitaxel and potential of particulates showering to the distal vessel bed, as well as the high profile of the device. Vascular brachytherapy is available in few centers in the United States and is used primarily for recurrence of DES-ISR, but logistic issues and lack of radiation oncology support impede its uses. Therefore, restenting with second-generation DES became the default therapy for DES-ISR. Recently, there were few reports with the use of bioresorbable scaffold for the treatment of DES-ISR. The use of bioresorbable scaffold for this indication potentially eliminates permanent double layers of metallic stent. However, the thickness of the scaffold struts of the current bioresorbable scaffold technology makes it less attractive at this stage.

Like in oncology, a combination therapy may be helpful; thus, radiation and pharmacology or polypharmacology that works on different aspects of the cell cycle may be able to increase the efficacy of the therapy for the patients with recurrence of DES-ISR. However, these strategies may carry a risk of inhibited healing and potentially can lead to unwarranted outcomes, such as stent thrombosis.

In perspective, the clinical burden of ISR in the future may be significantly reduced with the decline in the use of BMS because the cost of DES is gradually reduced worldwide and because the superior efficacy and safety profile of second-generation DES over first-generation DES and BMS have been illustrated in repeated trials and are strongly recommended for various clinical settings. The use of BMS will become nearly obsolete. With regard to DES-ISR, perhaps rather than focusing on how to improve the treatment of DES-ISR, our efforts should continue to be directed to prevention of DES-ISR. This can be accomplished by optimal stent deployment, including imaging-guided implantation by intravascular ultrasound or optical coherence tomography and vessel preparation and adequate coverage of the lesion and verifying stent expansion and apposition to the vessel wall. Reducing the strut thickness and eliminating the polymer could further reduce the restenosis rates of DES.

Finally, in the most recent leap in stent technology, the bioresorbable vascular scaffolds, which are expected to enter the US market, may prove to be a game changer for ISR. The bioresorbable vascular scaffolds have been developed to provide mechanical support and drug-delivery functions similar to those of DES, followed by complete bioresorption over several years. Preclinical studies have demonstrated coverage of struts with endothelialized neointima, low inflammation, and complete integration of struts into the arterial wall. This promising technology has been shown to be noninferior to second-generation EES in the ABSORB III (A Clinical Evaluation of Absorb BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) trial. Although the current bioresorbable vascular scaffolds that have been studied have not been shown to fully prevent ISR, there is promise that future generations of bioresorbable vascular scaffold technologies, incorporating thinner struts and enhanced deliverability along with the elimination of a permanent metal in the vessel wall, may reduce even further the rates of ISR after percutaneous coronary intervention. If indeed this is the case in the years to come, the interventional cardiologists will be able to declare success in finding the remedy for DES-ISR by elimination of the stent and its late complications.

Disclosures
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References
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Ron Waksman and Arie Steinvil

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