

EDITORIAL COMMENT

Exploring New Avenues for De Novo Coronary Artery Disease

Next Steps Forward With Drug-Coated Balloons



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The introduction of drug-eluting stents (DESs) has significantly advanced contemporary percutaneous coronary intervention (PCI), yet concerns about their long-term efficacy and safety persist. Despite advancements in newer-generation DESs, including improved biocompatibility and reduced strut thickness, the annual stent failure rate remains approximately 2%, according to a pooled analysis of prospective randomized controlled trials (RCTs).¹ This issue has particular significance in complex PCI settings, where the risk of adverse clinical events is heightened because of greater metallic footprints and the need for prolonged dual antiplatelet therapy (DAPT).^{2,3} To address these concerns, drug-coated balloon (DCB)-based revascularization has emerged as a potential strategy to reduce the overall stent burden and long-term stent-related complications.^{4,5} This approach can be used flexibly, either as a stand-alone treatment or in combination with a DES. Given its proven efficacy and safety in treating in-stent restenosis and small vessel coronary artery disease (CAD),^{6,7} DCB-based treatment is currently being investigated for its applicability across various subsets of CAD lesions. This may be particularly relevant in complex CAD lesions, where multiple stent implantations and prolonged use of DAPT strategy are often necessary.

In this issue of *JACC: Asia*, Joh et al⁸ present the results from a single-center experience that evaluated the therapeutic efficacy of DCB-based treatment compared to a DES-only strategy for complex de novo CAD. Complex CAD was mostly defined according to commonly used criteria:⁹ bifurcation involvement, chronic total occlusion, unprotected left main disease, diffuse long lesions (≥ 38 mm), multivessel disease, lesions requiring 3 or more devices, or lesions with severe calcification. To adjust the differences of baseline characteristics, the investigators matched 126 patients treated with DCB-based PCI to 234 patients who underwent DES-only PCI in a 1:2 ratio. The key findings suggested that the 2-year risk of target vessel failure (a composite of cardiac death, target vessel-related myocardial infarction, and ischemia-driven target vessel revascularization) was comparable between DCB-based and DES-only PCIs (7.6% vs 8.1%; HR: 0.81; 95% CI: 0.33-1.99). Moreover, the 2-year target vessel failure rates were similar across different subsets of complex CAD between the groups, suggesting that clinical outcomes were consistent regardless of specific lesion characteristics.

Although recent studies on DCB-based PCI in complex de novo CAD have shown promising results regarding its efficacy and safety, much of the currently available evidence comes from non-randomized observational studies with varying definitions of lesion complexity.¹⁰⁻¹² Despite these limitations, the present study makes a significant contribution to the existing literature by demonstrating the feasibility of DCB-based PCI for treating complex de novo CAD using a stringent definition of lesion complexity.⁹ The key findings were validated through robust adjustment measures, including propensity score matching and inverse probability treatment weighting. However, the present study showed that the DCB-based approach was more

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TABLE 1 Ongoing Randomized Controlled Trials Comparing DCB With DES in Various Scenarios of De Novo CAD

Study Name	Study Design	Patient or Lesion Characteristics and Number of Patients	Treatment Arms	Primary Endpoint
SELUTION DeNovo ¹⁵	Prospective, multicenter, open-label, randomized, controlled, noninferiority trial	Large-vessel de novo CAD (RVD: 2.0-5.0 mm) (N = 3,326; multination)	Sirolimus-DCB vs DES	12-mo TVF
REVERSE (NCT05846893)	Prospective, multicenter, open-label, randomized, controlled, noninferiority trial	Large-vessel de novo CAD (RVD: ≥ 3.0 mm) (N = 1,436; multination)	Paclitaxel-DCB vs DES	12-mo NACE
DCB-HBR (NCT05221931)	Prospective, multicenter, open-label, randomized, controlled, noninferiority trial	De novo CAD with high bleeding risk (N = 1,350; Korea)	Paclitaxel-DCB vs sirolimus-DES	2-y TLF
TRANSFORM II ¹⁶	Prospective, multicenter, open-label, randomized, controlled, noninferiority trial	Small and medium-sized vessel de novo CAD (RVD: 2.0-3.0 mm) (N = 1,325; Italy)	Sirolimus-DCB vs everolimus-DES	12-mo TLF and NACE
PRO-DAVID (NCT04403048)	Prospective, randomized, controlled, noninferiority trial	De novo true bifurcation lesions including left main disease (N = 800; Croatia)	Provisional DCB vs standard provisional approach for side branch treatment	12-mo MACE
CAGE-FREE III (NCT05209412)	Prospective, multicenter, open-label, randomized, controlled, noninferiority trial	Large-vessel de novo CAD (RVD: 2.5-5.0 mm) (N = 370; China)	Paclitaxel-DCB vs zotarolimus-DES	12-mo FFR value
Drug-Coated Balloon Versus Drug-Eluting Stent for De Novo Lesions in Large Coronary Arteries Guided by Optical Coherence Tomography (NCT04664283)	Prospective, multicenter, open-label, randomized, controlled, noninferiority trial	Large-vessel de novo CAD (RVD: 3.0-4.5 mm) (N = 254; China)	Paclitaxel-DCB vs DES (both OCT guidance)	12-mo angiographic LLL
DCB-LVD (NCT05550233)	Prospective, multicenter, open-label, randomized, controlled, noninferiority trial	Large-vessel de novo CAD (RVD: ≥ 3.0 mm) (N = 240; China)	DCB vs DES	12-mo angiographic LLL
Safety and Efficacy of Drug-Coated Balloon Angioplasty for the Treatment of Chronic Total Occlusions (NCT04744571)	Prospective, randomized, controlled, noninferiority trial	De novo chronic total occlusion lesion (N = 200; China)	DCB vs DES	12-mo OCT or IVUS-measured LLL

The studies are presented in order of the highest expected number of enrolled participants.

CAD = coronary artery disease; CAGE-FREE III = Paclitaxel-Coated Balloon Versus Zotarolimus-Eluting Stent for Treatment of De Novo Coronary Artery Lesions; DCB = drug-coated balloon; DCB-HBR = Drug-Coated Balloon in Patients With High Bleeding Risk; DES = drug-eluting stent(s); FFR = fractional flow reserve; IVUS = intravascular ultrasound; LLL = late lumen loss; MACE = major adverse cardiovascular event(s); NACE = net adverse clinical event(s); OCT = optical coherence tomography; PRO-DAVID = Drug-Coated Balloon for Side Branch Treatment vs Conventional Approach in True Bifurcation Coronary Disease; REVERSE = Drug-Coated Balloon vs Drug-Eluting Stent for Clinical Outcomes in Patients With Large Coronary Artery Disease; RVD = reference vessel diameter; TLF = target lesion failure; TRANSFORM II = Sirolimus-Coated Balloon Versus Drug-Eluting Stent in Native Coronary Vessels; TVF = target vessel failure.

preferably used to treat multivessel disease, chronic total occlusion, and multiple device deployments compared with the DES-only approach. The DCB-based strategy demonstrated a numerically lower risk of target vessel myocardial infarction and higher revascularization rates compared to the DES-only strategy. In addition, the present analysis did not present any clinical data regarding temporal changes in DAPT regimen and consequent safety benefit following the DCB-based strategy. Taken together, these findings suggest that the DCB-based approach might serve as a reasonable alternative to the DES-only strategy for treating complex de novo CAD. However, it may have limitations in its general application for various complex CAD scenarios and may pose an increased risk of ischemia-driven revascularization.

Despite the optimistic outcomes of DCB-based PCI in the treatment of complex de novo CAD in this study, it is essential to acknowledge that the devil is in the details. In this study, DCB-based PCI was predominantly used as a complement to DES implantation, as evidenced by the average number of stents implanted per patient being more than 1 even in the DCB-based group (DCB-based vs DES-only approach: 1.5 ± 1.3 vs 1.9 ± 0.9 ; $P = 0.003$). The limited use of DCB-only PCI makes it challenging to apply the current findings to the emerging concept of primary DCB application for most cases of CAD. Moreover, the lack of detailed information on the specific procedural steps necessary for optimal lesion preparation and the absence of angiographic data (eg, dissection severity) further restrict its generalizability to routine clinical practice. This information is critical because

the individual interventional cardiologist's approach to DCB-based PCI—whether focusing on primary DCB treatment or using DCB as an adjunctive strategy to DES—can significantly affect procedural decisions and potentially affect clinical outcomes. Optimal lesion preparation is paramount for primary DCB-based procedures; inadequate preparation can result in suboptimal outcomes or the need for additional stents.^{4,13,14} Without a clear understanding of the specific procedural steps involved in lesion preparation before DCB treatment, replicating these outcomes into other clinical settings becomes challenging.

Given these complexities, more comprehensive studies are needed to gain a deeper understanding of the procedural techniques and to validate the efficacy and safety of primary DCB-based approaches for complex de novo CAD. Nevertheless, the present study paves the way for future RCTs to explore the clinical benefits of primary DCB-based treatment across a broader spectrum of CAD. Future research should assess whether DCB treatment can serve as a viable alternative to DES-only strategies, with the potential to reduce stent burden and improve patient outcomes.

Ongoing RCTs are currently exploring the role of DCB treatment in various subsets of complex de novo CAD, addressing both lesion-specific and patient-specific factors (Table 1).^{15,16} These trials are anticipated to provide valuable insights into the feasibility and effectiveness of primary DCB-based treatments

across various CAD subsets, including complex lesions, large-vessel lesions, and patients with high thrombotic risk or high bleeding risk. By addressing current knowledge gaps, these studies can offer practical evidence on how DCB-based approaches compare to conventional DES-only PCI. Additionally, these findings could help identify specific patient groups or lesion types that would benefit most from DCB-based PCI, thereby guiding personalized treatment strategies. With more comprehensive data, clinicians will be better equipped to make informed decisions regarding the optimal DCB use in the daily practice.

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