

## Drug-coated balloons on the “big stage”: is this technology ready for an all-comer population with *de novo* lesions?

### *El balón liberador de fármaco en la palestra, ¿está la tecnología preparada para la población general con lesiones de novo?*

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Percutaneous coronary interventions with drug-eluting stent (DES) implantation have become a well-established treatment for obstructive coronary artery disease, improving long-term outcomes.<sup>1</sup> However, despite recent improvements including thinner strut platforms and more biocompatible polymers, the Achilles' heel of DES strategy remains the risk of DES-related adverse events such as in-stent restenosis or stent thrombosis in the short term,<sup>2</sup> along with an increase in hard clinical events at a rate of 2.0 to 3.5% yearly after the first year.<sup>3,4</sup>

Drug-coated balloons (DCB) have been developed as an alternative to percutaneous coronary intervention with DES implantation in selected populations for the treatment of coronary artery disease. The main advantage of this technology is its ability to deliver an antiproliferative drug to the treated lesion without leaving any layer of metal, which might cause late adverse events. Another advantage is the potential reduction in the duration or discontinuation of dual antiplatelet therapy, especially in patients at high risk of bleeding.

Several studies have investigated the role of DCB in real-world patients, who are those mainly affected by in-stent restenosis or *de novo* small vessel disease.<sup>5-9</sup> The only randomized study of DCB in *de novo* small vessels with a clinical primary endpoint was BASKET-SMALL-2. This study demonstrated the noninferiority of DCB vs DES (vessel size 2-3 mm), which was maintained up to 3 years follow-up in terms of all clinical endpoints.<sup>5</sup>

The initial fear of leaving behind a residual coronary dissection, especially in *de novo* lesions, could limit the widespread use of DCB. However, it has been shown that a nonflow-limiting dissection after DCB treatment tends to heal during the first few months, with both the paclitaxel and sirolimus technologies, without leading to acute or subacute vessel closure.<sup>10,11</sup>

The main message regarding DCB is that they should be used as the final step of percutaneous coronary intervention and only when a proper lesion preparation has been performed with a fully expanded balloon of the correct size for the vessel, with accurate management of calcifications and no residual stenosis greater than 30% that could impair drug delivery to the vessel and limit the potential of this technology.

Recently, a new generation of DCB eluting sirolimus (SCB, Magic Touch, Concept Medical, United States) has been introduced that uses nanoparticles composed of a dual layer of phospholipids encapsulating the antiproliferative agent. Histopathologic studies have demonstrated therapeutic concentrations of the drug within the vessel wall for up to 60 days after percutaneous coronary intervention.<sup>12</sup>

Notably, the angiographic performance of this class of drug seems to be inferior to that provided by paclitaxel. The recently published TRANSFORM I trial showed that SeQuent Please DCB (B. Braun, Germany) outperformed SCB in terms of angiographic parameters at 6 months of follow-up, but without showing any difference in clinical endpoints. This lower performance of SCB seems to occur particularly in cases of complex lesions, emphasizing the importance of adequate lesion preparation, especially with the less lipophilic drug sirolimus (figure 1).<sup>13</sup> Somewhat reassuringly, the performance of SCB in terms of clinical endpoints has been demonstrated in all-comer populations, especially in the prospective EASTBOURNE study, which showed a good safety and efficacy profile up to 2 years of follow-up in 2123 patients/2440 lesions.<sup>14</sup>

The next step to ensure wider use of this new generation DCB will be direct comparison with DES, as in the TRANSFORM II (NCT04893291) trial. This is an international, multicenter, prospective, investigator-driven, open-label, randomized (1:1) clinical trial designed to test the efficacy of SCB vs DES in native coronary artery vessels with diameters between 2.0 and 3.5 mm. Inclusion and randomization are being performed after adequate lesion preparation in the absence of flow-limiting dissection and acute vessel recoil. The study population has been calculated expecting the noninferiority of SCB in terms of target lesion failure at 12 months, and its sequential superiority in terms of net-adverse clinical events, including BARC 3-5 bleeding events. Interestingly, patients will be followed up clinically for 5 years to observe the potential superiority of DCB in the long-term. This trial, which includes 7 Spanish centers, is including patients at 40 centers allocated in 11 countries in Europe, Asia, and South America.<sup>15</sup> By November 20<sup>th</sup>, 2023, 600 patients out of the planned 1820 had been enrolled.

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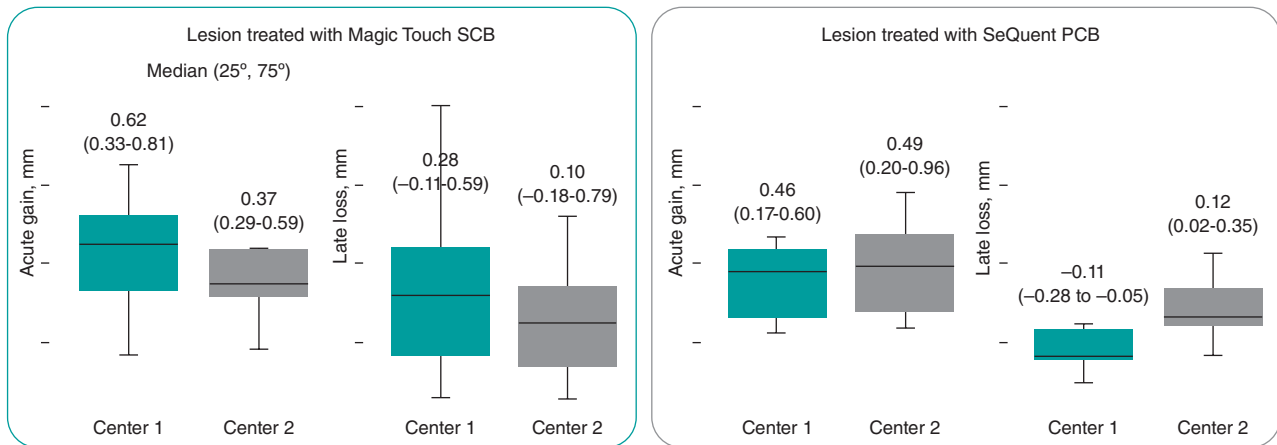
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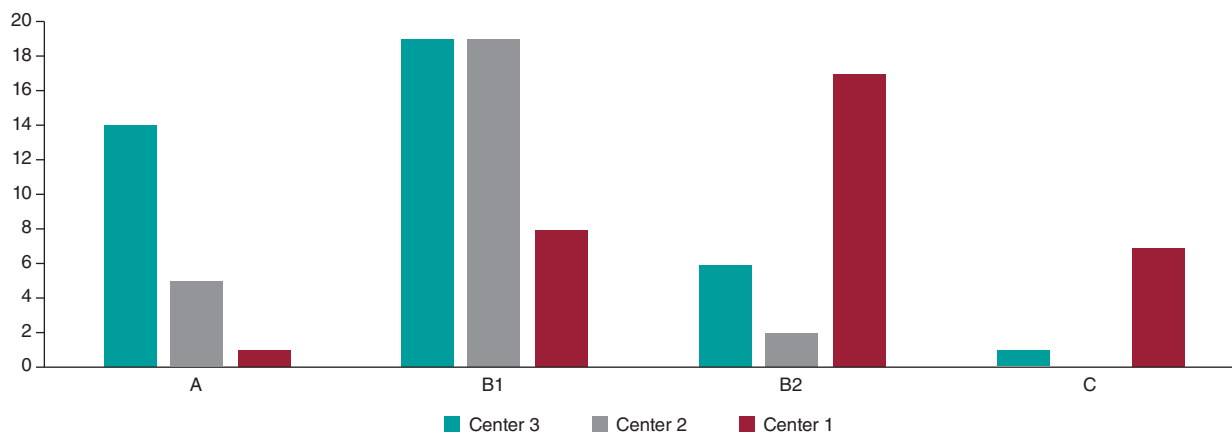
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## A. Different angiographic outcomes between sites in the TRANSFORM I trial



## B. Distribution of lesion complexity among sites



**Figure 1.** Differences in terms of types of lesion and outcomes among 2 top enroller centers for the TRANSFORM II trial. PCB, paclitaxel-coated balloon; SCB, sirolimus-coated balloon.

The TRANSFORM II trial will be an essential test of the maturity of DCB in such an established, prognostically significant arena, challenging DES as the gold standard for the treatment of patients with native coronary artery disease.

## FUNDING

None.

## CONFLICTS OF INTEREST

B. Cortese serves on the advisory board or as a consultant for several companies producing or marketing DCB: Cordis, Medalliance, BBraun, Concept Medical, Medtronic, Innova HTS, and ANT.

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