
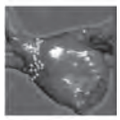


Paclitaxel-eluting balloons or paclitaxel-eluting stents for the treatment of small-vessel coronary artery disease?

"*...drug-eluting balloons appear to be effective in* de novo *lesions and could be an alternative to drug-eluting stents when a stent may not be the ideal device.*"

KEYWORDS: drug-eluting balloon ■ drug-eluting stent ■ small-vessel lesion

Obstructive lesions in small coronary vessels are frequent, but the percutaneous coronary intervention (PCI) of these lesions remains a challenge in contemporary practice. Failure of revascularization after PCI is principally related to restenosis of the treated vessel [1]. After PCI, vessel caliber is inversely proportional to the antirestenotic efficacy of the treatment [2,3]. Consequently, the drawbacks intrinsic to PCI, such as mechanical vessel recoil and constrictive remodeling (after plain old balloon angioplasty), as well as neointimal hyperplasia (after stent implantation), become deleterious in this setting, principally due to the vessel's reduced ability to accommodate a given degree of late lumen loss necessitating repeat revascularization procedures. The introduction of bare-metal stents (BMS) has represented a monumental leap in interventional cardiology; however, their use in small vessels did not provide the benefits demonstrated in other types of lesions. A noteworthy trial, ISAR-SMART, comparing balloon angioplasty with BMS in vessels with a caliber between 2.0 and 2.8 mm, showed no significant differences between the two groups in angiographic or clinical restenosis at follow-up [4]. The limitations of BMS for preventing restenosis are explained by the fact that the absolute magnitude of extra acute gain achievable by stenting over balloon angioplasty in small-vessel disease is relatively small and does not compensate for the reduced capacity of these small-caliber vessels to accommodate for increased neointimal hyperplasia seen after stent implantation. The pathophysiological mechanisms underlying BMS failure in this setting have led to the search for pharmaceutical methods and biological modalities to prevent restenosis. Therefore, by targeting the biological mechanisms that underlie neointimal hyperplasia and by providing an effective delivery system that results in adequate local tissue–drug concentrations, drug-eluting stents (DES) have been able to reduce restenosis in vessels with a reference diameter under 2.8 mm. This has been well established in several randomized trials that demonstrated the greater antirestenotic effect of DES compared with BMS, with consequently better outcomes [5,6], especially in patients with small-vessel disease [7–9]. Despite their undisputed benefit, DES use in small-vessel lesions is still afflicted with a relatively high incidence of restenosis, especially in real-world patients and registries [10,11]. The delayed healing of the stented vessel segment seems to underline a scope of late adverse events comprising stent thrombosis, late luminal creep, defective vascular responsiveness and persistent inflammatory response to nonerodible polymer coatings that seem to play a central role [12–15]. Concerns related to this delayed healing have favored the development of novel technologies that deliver high antirestenotic efficacy with reduced impact on arterial healing.

In the last few years, drug-eluting balloon (DEB) therapy has emerged as a promising therapeutic intervention for the management of obstructive cardiovascular disease [16,17]. The dictum of this novel technology is that effective prevention of restenosis may be achieved by the short-term transfer of antiproliferative drugs to local arterial tissue by means of single balloon dilatation angioplasty, typically lasting 30–60 s. Its main attraction is that there is no foreign body implanted and the vessel is left uncaged. Consequently, the risk of late inflammatory response to device components is precluded and positive remodeling of the vessel is not prevented. This aspect renders the use of this device in treating small-vessel disease attractive, especially when treating longer *de novo* lesions or very small vessels (<2.5 mm). Indeed, there are few doubts regarding the benefits of second-generation DES to treat focal lesions in vessels

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with a diameter between 2.5 and 2.75 mm. However, many physicians feel uncomfortable when implanting longer stents in vessels smaller than 2.5 mm because of the risk of restenosis. It is this particular subset where DEBs may be an efficacious alternative to DES.

Studies of drug-coated balloon therapy in small-vessel disease

Theoretical advantages of DEBs in preventing restenosis compared with DES is still a matter of discussion. Only a few studies have evaluated their role as compared with DES in small-vessel disease.

> *"There are currently no data available comparing drug-eluting balloons with second-generation drug-eluting stents, which are the current standard of care."*

The first study to explore DEBs in small vessels was the PEPCAD-I study, a single-arm trial investigating the SeQuent Please DEB (B Braun Melsungen AG, Berlin, Germany), coated with a mixture of the active drug paclitaxel and the contrast agent iopromide (an excipient to enhance lipophilicity and increase local tissue–drug transfer) in vessels with a mean diameter of 2.36 mm [18]. Out of 118 study patients, 70% underwent angioplasty with DEBs alone; the remaining 30% had suboptimal postangioplasty results and proceeded to additional BMS implantation. The primary end point of mean in-segment late lumen loss was 0.28 ± 0.53 mm with binary restenosis occurring in 18% of patients. Overall clinical outcomes at 12 months were also encouraging; the composite of death, myocardial infarction, stent thrombosis and target-lesion revascularization occurred in 14.4% patients; almost all of them were driven by revascularization procedures. Interestingly, the PEPCAD-I investigators also compared outcomes according to treatment received. They observed that patients treated with DEB plus additional BMS implantation had significantly poorer outcomes than those treated with DEB alone: late lumen loss was 0.62 ± 0.73 versus 0.16 ± 0.38 mm ($p < 0.001$) and binary restenosis rate was 45 versus 6% ($p < 0.001$), respectively. Indeed, the late loss magnitude observed in the DEB group with bailout BMS implantation was more in keeping with that seen with low-efficacy DES devices. The conclusion from PEPCAD-I was that DEB therapy in small vessels seemed promising, although in patients with suboptimal angioplasty results requiring additional stent placement, the results were rather less impressive. Moreover the single-arm design permits no insight into how this therapy performs compared with standard clinical practice with DES therapy. The PICCOLETTO study was the first randomized trial, comparing the first-generation Dior-I DEB (Eurocor, Bonn, Germany) with Taxus Libertè DES (Boston Scientific Corporation, MA, USA), in vessels <2.75 mm in diameter [19]. The trial was powered to demonstrate noninferiority of the DEB with respect to in-segment percentage diameter stenosis at 6-month follow-up angiography and planned to enroll 80 patients; however, it was stopped prematurely based on the clear superiority in the DES arm. At follow-up, percentage diameter stenosis was 43.6 ± 27.4 with DEB versus 24.3 ± 25.1 with DES ($p = 0.029$), and binary restenosis occurred in nine patients (32.1%) treated with DEB versus three patients (10.3%) treated with DES ($p = 0.043$). The worse-than-expected results compared with PEPCAD-I, were attributed to lower tissue–drug dosage in the Dior-I balloon. Moreover, procedural differences, such as lower predilation rates and lower inflation pressures employed in the DEB group, may have adversely affected its outcome. Positive findings were recently observed in the BELLO trial, a randomized study comparing the IN.PACT Falcon DEB (Medtronic Inc., CA, USA) with Taxus DES in vessels with a mean diameter of 2.15 mm [20]. The primary end point of in-stent (in-balloon) late loss was significantly less with DEBs compared with DES (0.08 ± 0.38 vs 0.29 ± 0.44 mm; $p < 0.001$). At 6 months, DEBs and DES were associated with similar rates of angiographic restenosis (8.9 vs 13.2%), target-lesion revascularization (4.4 vs 7.6%) and major adverse cardiac events (7.8 vs 13.2%). The validity of late loss as a primary end point in a study comparing a balloon with a stent in *de novo* disease may be questioned. In previous studies comparing balloon angioplasty with BMS in *de novo* coronary disease, balloon angioplasty was associated with a smaller minimal lumen diameter, less acute gain and lower late loss at follow-up. However, in the BELLO trial, despite a similar suboptimal acute angiographic result, DEBs were associated with similar angiographic restenosis and repeat revascularization rates as compared with DES. This is probably explained by the fact that the lower acute gain with DEBs was counterbalanced by the very low late loss resulting in a similar net lumen gain. The contradictory results observed in the

PICCOLETTO and BELLO studies can be justified by the different DEBs used. Although the Dior-I and IN.PACT Falcon DEBs are both coated with paclitaxel at 3 μg/mm^2, these technologies are not comparable and differ significantly with regards to the balloon technology, drug-coating process, and the excipient used as a drug carrier and transport facilitator to the vessel wall. As with DES, we cannot assume a class effect for DEBs, but they need to be evaluated specifically for the type of DEB utilized. There are currently no data available comparing DEBs with second-generation DES, which are the current standard of care. It should also be emphasized that the deliverability of most DEBs is inferior to that of regular PCI balloons and is certainly not superior to most new-generation DES.

Conclusion

Small-vessel disease represents a particularly challenging subset to treat with percutaneous interventional therapies, frequently technically difficult and historically complicated by high rates of restenosis. Although DEB therapy has shown promising results in some disease subtypes, limited data exist regarding its use in small-vessel disease. The recently published BELLO study led us to consider DEBs as an additional tool in the hands of the interventional cardiologist, particularly useful when the operator may not be fully confident with deploying a DES. DEB therapy becomes advantageous especially in treating longer lesions in small-vessel disease, thus, avoiding the use of longer and multiple DES. Although there are no data in this regard, in the BELLO study there was an average lesion length of 15 mm in the TAXUS arm requiring an average stent length of 18.5 ± 5.6 mm. Furthermore, the contrasting results obtained with different types of DEB underline the necessity for further data pertaining to outcomes of DEBs in small vessels, aiming to better identify the best performing device. Finally, it cannot be excluded that better-performing balloon catheters combined with newer antiproliferative drugs, as well as the adoption of new excipients that enhance drug transfer and retention in the vessel wall may deliver improved outcomes with this technology. In conclusion, DEBs appear to be effective in *de novo* lesions and could be an alternative to DES when a stent may not be the ideal device.

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