VIA MEDICA

EDITORIAL

Cardiology Journal
2024, Vol. 31, No. 4, 507–511
DOI: 10.5603/cj.98927

ISSN 1897–5593
eISSN 1898–018X

Are we at dawn of the drug-coated balloons era? Current evidence, future directions, and tasks of the newly established working group of the Association of Cardiovascular Interventions

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Optimal treatment method of coronary lesions remains a subject of debate. The current-generation drug-eluting stents (DES) have become the gold standard of interventional treatment of coronary lesions thanks to a lower risk of in-stent restenosis (ISR) and stent thrombosis compared to bare-metal stents and first-generation DES [1]. However, in the past decade, a concept of "leaving nothing behind" has emerged to address late stent-related issues (including recurrent ISR, multiple layers of stents or impaired vasomotor function) and avoid stenting of potential sites of coronary bypass anastomoses [2, 3]. Bioresorbable scaffolds were developed in line with this concept, but their first generation failed to demonstrate at least non-inferiority compared with the currently available DES [3].

Consequently, in recent years, drug-coated balloons (DCBs) have gained particular interest

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Received: 15.01.2024 Accepted: 05.06.2024

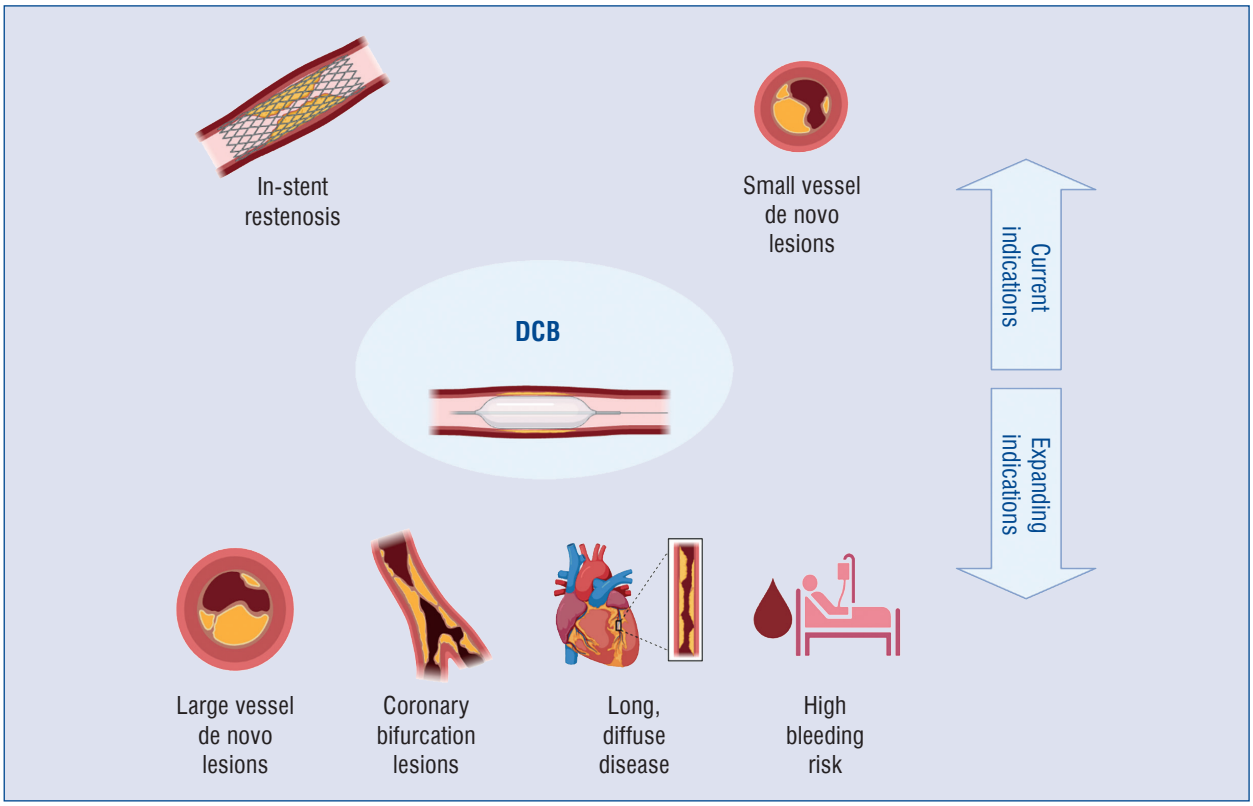

Figure 1. The current and expanding applications of drug-coated balloons

as yet another technology fitting into the "leaving nothing behind" concept. Although the idea of delivering antiproliferative agents such as paclitaxel or sirolimus directly into the coronary lesion to prevent restenosis is not entirely new, the recent developments in balloons and excipients allowed conquering the initial problems with tissue absorption and retention of the drug [2]. Since then, multiple DCBs have become available on the European market, and different indications for their use have started to be evaluated in registries and randomized controlled trials (RCTs) (Fig. 1) [2, 4].

The most extensive available evidence exists on the DCB utilization for ISR treatment. To date, the results of several RCTs have been published, confirming the safety and efficacy of DCBs in this indication [5]. Based on their findings, DCB use for ISR is currently supported by the European Society of Cardiology recommendations (class IA) and, to date, represents the sole indication for DCBs [6]. Of note, the largest individual patient data meta-analysis of 10 RCTs showed a moderately higher incidence of the primary efficacy endpoint of target-lesion revascularization (TLR) at three years in patients treated with paclitaxel-coated balloons compared to DES (16.0% vs. 12.0%; p = 0.02) [5]. On the other hand, there was no significant difference in terms of the primary safety endpoint (composite of all-cause death, myocardial infarction, or target lesion thrombosis), with a numerically lower rate of this outcome in the DCB arm (9.0% vs. 10.9%; p = 0.18) [5]. This underlines the need for further adequately powered RCTs to evaluate the potential net benefits of the stentless approach for ISR. Moreover, considering differences in the mode of action and pharmacokinetics between sirolimus and paclitaxel, the presence of the class effect is unlikely, and head-to-head comparisons of different DCBs are desired [2, 6].

The lower performance of DES in small vessel (< 3 mm) de novo lesions has intuitively led to the use of DCBs in this setting [2, 7]. Although the body of evidence is less robust compared with ISR, the initial findings of first RCTs are encouraging [2, 7]. Noteworthy, the 3-year outcomes of the PICCOLETO II trial (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment), for the first time, showed the superiority of DCB compared to modern DES in terms of clinical outcomes (major adverse cardiac events and acute vessel occlusion) [7]. This may be attributed to late lumen enlargement observed in patients treated with paclitaxel-coated balloons (and to a lesser extent with limus-based DCBs) and shorter dual

antiplatelet therapy (DAPT) [2, 7]. On the other hand, the DCB use may be challenging for less experienced operators, who may struggle with the elastic recoil and dissections, both of which are relatively frequent reasons for bailout stenting and may limit the external validity of DCB trials conducted in high-volume centers [7].

Recently, the investigational use of DCBs has been extended to de novo large vessel coronary artery disease (CAD). Although data from randomized trials that directly evaluate the DCB-based approach in large vessels have not been published, the results of observational studies are promising. Rosenberg et al. [8] reported the outcomes of 234 patients with de novo CAD treated with SeQuent Please® DCB stratified by the vessel diameter smaller or larger than 2.75 mm. At nine months, the authors observed a comparable major adverse cardiovascular event (MACE) rate of 5.7% in small and 6.1% in large vessel CAD ($p = 0.903$). The incidence of TLR was also acceptable and did not differ between groups (3.8% and 1.0%, $p = 0.20$). Uskela et al. [9] retrospectively analyzed 487 DCB procedures in 562 de-novo complex lesions, including 60% localized in vessels ≥ 3.0 mm in diameter and 79% over 2.75 mm. At 12 months, the MACE rate of 7.1% for stable CAD and 12% for ACS were reported. The incidence of TLR was also low and amounted 1.4% for stable CAD and 2.8% for ACS.

Gitto et al. [10] compared 147 consecutive patients undergoing a DCB-based treatment on the left anterior descending artery to 701 patients who received conventional PCI with DES. Large vessels (> 3 mm) accounted for most treated lesions in both groups with higher representation in the DES cohort (76.2% vs. 83.5%, $p = 0.036$). In turn, in the DCB group, significantly longer lesions were treated (65 [40–82] vs. 56 [46–66] mm, $p = 0.002$). A propensity score matching analysis composed of 139 matched pairs revealed a lower risk for target lesion failure at two years for DCB-based treatment compared with DES-only PCI (HR 0.2 [95% CI, 0.07–0.58], $p = 0.003$), mainly driven by less TLR.

Other patient populations with de novo lesions who could potentially benefit from DCBs are those with long and diffuse CAD, bifurcation lesions, and patients at high risk of bleeding for whom prolonged DAPT is not recommended [10–14].

Long and diffuse de novo CAD is a growing problem among patients undergoing PCI, and the total stent length independently predicts ISR and stent thrombosis [11]. Recent data suggest approaching long and diffuse lesions using either a DCB-only or a hybrid strategy (including DCB and spot stenting). Preliminary retrospective data suggest such strategies may be comparable or even better when compared to the DES-only approach [10, 12].

Approximately 20% of bifurcation PCI is associated with side-branch (SB) occlusion and the need for reintervention [13]. DCB has been proposed as an alternative to a plain balloon angioplasty for a SB intervention in the stepwise provisional stenting approach of true coronary bifurcation lesions [15]. Compared to the two-stent techniques, DCB use in the SB eliminates the possibility of inadequate bifurcation coverage by stents, ostium scaffolding, main branch stent deformation, or crushing several metal layers and polymers [13, 14]. Moreover, DCB is theoretically superior to a regular balloon in terms of vascular remodeling, plaque stabilization, and late angiography outcomes.

Stent implantation may require potent and prolonged DAPT, which increases the bleeding risk and, consequently, the risk of premature DAPT discontinuation [16, 17]. Delivery of an antiproliferative drug to the coronary artery wall without implanting a metal stent significantly reduces the risk of vessel thrombosis [18]. Thus, shortening of the DAPT regimen following DCB therapy appears to be justified, reducing both the risk of bleeding and, indirectly, ischemic complications.

Acute coronary syndromes are yet another promising indication for DCB use [19, 20]. Especially in the setting of ST-elevation myocardial infarction, the lesion morphology (mostly short, noncalcified), patients' clinical profiles (younger age), and prothrombotic milieu are the factors that might favor the stent-less approach [19]. Despite the theoretical advantages of DCBs in acute coronary syndromes that may be even greater than in the case of stable de novo lesions, the current evidence is limited to a few small RCTs and observational studies that warrant further trials to assess the efficacy of DCB in this setting [19, 20].

Considering the fast-developing field of the stentless approach to CAD, the working group Modern Technologies of Stents and Drug-Coated Balloons has been recently established by the Association of Cardiovascular Interventions of the Polish Cardiac Society. The main aim of this initiative is to provide evidence on DCB use, which is currently limited in most of its potential applications. To achieve this goal, the working group intends to conduct high-quality clinical research, including multicenter registries, RCTs, and

meta-analyses. This will be possible thanks to building the collaboration with national and international experts. Another intention of the working group is to promote the debate on DCB by active participation in scientific meetings. What is more, the working group aims to share knowledge and expertise by organizing webinars and educational sessions dedicated to DCB during cardiology conferences. Finally, the working group's objective is to participate in writing scientific documents (i.e., position and consensus papers) on DCB use in clinical practice.

In conclusion, DCB is an alternative to DES for treating in-stent restenosis and de novo small vessel disease. Moreover, further expansion of indications for DCB is inevitable. The most promising new field is the application of DCB in de novo large coronary vessels, bifurcation lesions and diffuse CAD. Patients at high risk of bleeding are also potential beneficiaries of DCB, especially considering increasing age of PCI recipients.

Funding: Not applicable.

Acknowledgments: None.

Conflict of interest: None declared.

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