Advances in Cardiac Research

REVIEW

Coronary Drug-Coated Balloons: Should We Choose a Stentless Approach?

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Abstract

Although drug-eluting stents are still the standard interventional treatment for coronary artery disease, drug-coated balloons (DCBs) represent a novel alternative therapeutic approach in specific anatomic situations. DCBs work by rapidly and uniformly transferring antiproliferative medications into the vessel wall during single balloon inflation using a lipophilic matrix, all without the need for long-term implants. Despite the fact that their usage is well-established for in-stent restenosis of both bare-metal and drug-eluting stents, current randomized trial data show a strong effectiveness and safety profile in de novo small-vessel disease and high bleeding risk. There are also newer signs that are emerging, such as bifurcation lesions, large-vessel disease, diabetes mellitus, and acute coronary syndromes. These expanding indications for DCBs may potentially reduce the reliance on coronary stents or shift towards a stentless perspective.

Keywords: Coronary artery disease, DCBs, drug-coated balloons, indication, perspective

Introduction

Drug-coated balloons (DCBs) are a unique method of treating coronary artery disease that rapidly and uniformly transfers antiproliferative medications into the arterial wall during balloon inflation without needing long-term implants.[1] The idea behind treating coronary stenoses using DCB-only percutaneous coronary intervention (PCI) is to restrict the requirement for permanent or semipermanent implants to those lesions that are more at risk for acute artery closure or adverse long-term outcomes. Every PCI could potentially strive to use the DCB-only technique, which denotes a consistent method for lesion preparation. This calls for the best possible angioplasty outcome, which can be determined by angiography, physiology, or intravascular imaging. A DCB is then used for medication delivery. [1,2]

The absence of permanent metallic implants offers several potential benefits over the medium and long term, including mitigation of stent-related mechanisms leading to restenosis, thrombosis, and accelerated neoatherosclerosis. The antiproliferative effects of the drug delivered on the endothelial tissue reduce exaggerated neointimal hyperplasia after treatment-related vessel wall injury. Although their effectiveness and safety have been demonstrated for both native small-vessel disease and in-stent restenosis (ISR), there are also new indications (such as bifurcation lesions, large-vessel disease, and high bleeding risk) worth mentioning.[3] These expanding indications for DCBs may potentially reduce the reliance on coronary stents or shift towards a stentless perspective.

Drug-Coated Balloon

DCBs are essentially conventional semi-compliant Percutaneous Transluminal Coronary Angioplasty (PTCA) balloon catheters with a drug coating the outer surface of the balloon in contact with the lumen. In contrast to Drug Eluting Stents (DES), which provide long-term and sustained drug release,

DCBs rely on rapid drug uptake and drug persistence on the target tissue. Paclitaxel, with a dose of 2 and 3.5 µg/mm is the drug of choice for coating as it is highly lipophilic and provides adequate drug uptake and tissue persistence. Other than paclitaxel, several sirolimus DCBs are also available commercially (Table 1). [1,4]

Table 1. Commercially available DCBs and their characteristics[1]

Drug and Device	Company	Additive	Substance Class	Dose (µg/mm^2)	Balloon Diameter (mm)
Paclitaxel					
Agent	Boston Scientific	Acetyl tributyl citrate	Plasticizer	2	2.00 – 4.00
Elutax SV	Aachen Resonance	None		2.2	2.00 – 4.00
Danubio	Minvasys	n-Butyryl tri-n-hexyl citrate	Plasticizer	2.5	1.50 – 4.00
SeQuent Please	B. Braun	Iopromide	X-ray contrast medium	3	2.00 – 4.00
Pantera Lux	Biotronik	n-Butyryl tri-n-hexyl citrate	Plasticizer	3	2.00 – 4.00
RESTORE	Cardionovum	Shellac	Varnish	3	2.00 – 4.00
AngioSculptX	Spectranetics	Nordihydroguaiaretic acid	Antioxidant	3	2.00 – 3.50
Chocolate Touch	QT Vascular	Undisclosed		3	2.50 – 3.50
Dior II, BioStream	Eurocor Biosensors	Shellac	Varnish	3	2.00 – 4.00 2.00 – 4.00
Essential	iVascular	Undisclosed		3	1.50 – 4.00
Prevail	Medtronic	Urea	Endogenous metabolite	3.5	2.00 – 4.00
Sirolimus					
Selution	Med Alliance	Biodegradable polymer	Microreservoirs		1.50 – 5.00
Virtue	Caliber Therapeutics	Biodegradable polyester-based polymers	Submicrometer nanoparticles		
Magic Touch	Concept Medical		Phospholipids		1.50 – 4.00
Sequent Please SCB	B. Braun		Crystalline sirolimus	4	2.00 – 4.00

DCB = drug-coated balloon

Lesion Preparation and DCB Procedure

Lesion preparation before DCB insertion is crucial for successful revascularization. Pre-dilation using a semi or non-compliant balloon with a balloon-to-vessel ratio of 0.8:1-1:1 and greater than nominal pressure is recommended. Although there are exceptions, such as when there is vessel underfilling or potential undersizing, it is recommended to use a smaller diameter balloon to pre-dilate and to reassess vessel diameter after use of vasodilator. And in ISR, the use of either a cutting or scoring balloon to avoid balloon slippage or a non-compliant high-pressure balloon is recommended to provide adequate expansion and ideal lesion preparation. [1,5]

After lesion preparation, confirming adequate pre-dilation results and identifying any flow-limiting dissection is essential. Generally, type A and B dissections are benign and have no increase in mortality or morbidity compared to those without dissection and it is recommended to proceed to DCB, but presence of type C or greater dissection warrants use of DES. Additionally, there should be <30% residual stenosis after pre-dilation.[1,5]

Delivering the DCB, using the passage of the pre-dilation balloon as a guide, guide the DCB over the pre-dilated area with an additional 2mm proximally and distally and inflate the DCB to nominal pressure for at least 30 seconds (Figure 1.). It is important to be careful when handling a DCB and take note of transit time and minimum inflation time as drug or carrier may shed after contact during preparation or contact with liquid. [1,5]

DCB Indications

In-Stent Restenosis (ISR)

ISR differs histologically from restenosis following angioplasty because neointimal hyperplasia is increased early after stent insertion. Neointimal hyperplasia is a typical feature of bare-metal stent (BMS) ISR, whereas neointimal hyperplasia with late neoatherosclerotic alterations is a characteristic of DES ISR. Patients who present with both BMS ISR and DES ISR may benefit from DCBs in ISR populations. The potential relative efficacy of DCBs versus DES, depending on the underlying tissue substrate (e.g., neointimal hyperplasia vs. neoatherosclerosis) may differ. However, patients with DES ISR represent a chosen high-risk population with primary failure of local drug delivery by the stent.[6]

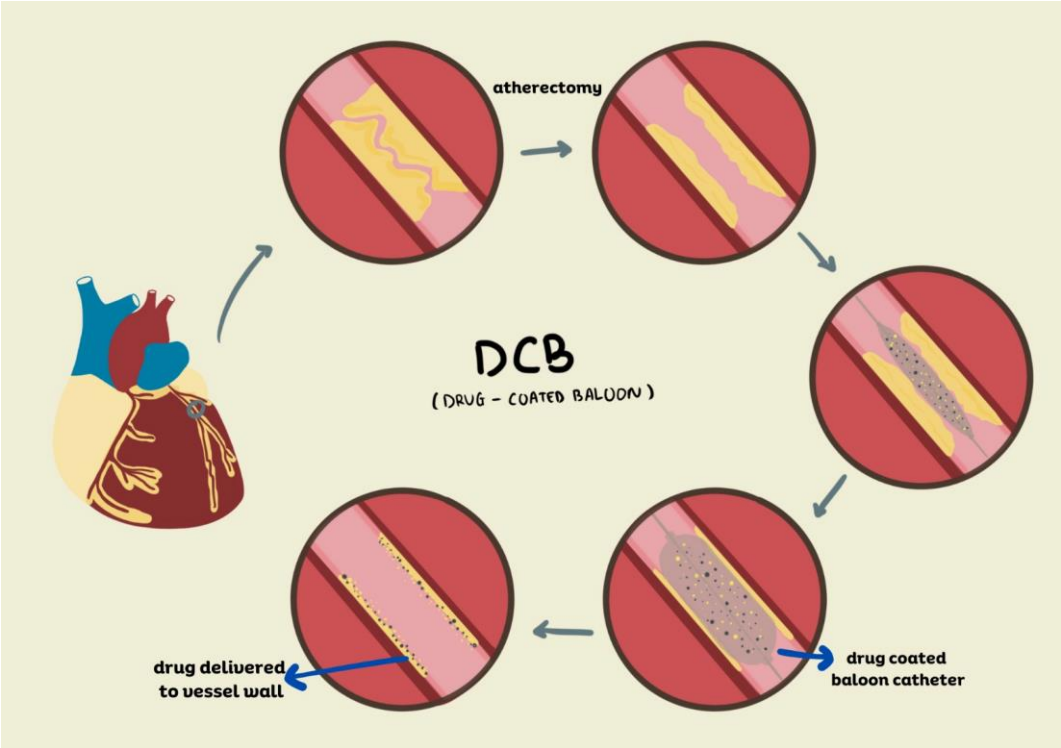

Figure 1. Drug Coated Balloon.

Based on data from randomized trials that were included in a significant meta-analysis, DCBs are about as effective as DES in reducing revascularization for BMS ISR. However, they are slightly less effective in DES ISR. Repeat DES implantation is less alluring than using a DCB because a fresh permanent metal layer is required. As a result, many operators favor DCBs over DES in patients who present with their initial ISR, saving the use of a new DES layer for patients who experience recurrences after receiving DCB treatment. With several previous stent layers, important side branches emerging from the stent with ISR, and patients who may benefit clinically from a shorter dual-antiplatelet regimen, DCB rather than repeat DES implantation is particularly appealing. A recommendation (Class I, Level of Evidence: A) has been added to the most recent cardiac revascularization guidelines to address the management of ISR.[1,6]

Coronary Small Vessel Disease

Coronary small-vessel disease, typically characterized as lesions in arteries less than 2.75 or 3.0 mm, is challenging to treat with intervention. Although DES is equally effective in small and big vessels, the late lumen loss that results takes up a larger portion of the diameter of the corresponding vessel, which results in increased rates of ISR and clinical events.[7] Small vessel size is the best predictor of restenosis, and coronary operations are conducted in 30% to 50% of all coronary artery interventions worldwide each year. Numerous studies have shown that DCB is effective in treating coronary small vessel disease.[4]

The effectiveness of a DCB in small vessels was initially evaluated in the PEPCAD I (The Paclitaxel-Eluting PTCA-Balloon Catheter to Treat Small Vessel) study. In-segment late lumen loss (LLL) at six months was 0.28 0.53 mm in 114 patients with lesions smaller than 2.8 mm, with an 18% binary restenosis incidence. LLL was 0.62 to 0.73 mm when bailout stenting with a BMS was required. LLL, on the other hand, was 0.16 0.38 mm in patients who only had DCB treatment. Target lesion revascularization (TLR) was necessary, so the Major Adverse Cardiac Event (MACE) rate at 12 months was 15%. The PEPCAD I result after a 36-month follow-up showed that the DCB-only group had an outstanding clinical outcome.[8]

In the BELLO (Balloon Elution and Late Loss Optimization) trial, 182 patients with lesions smaller than 2.8 mm were randomly assigned to one of two arms for treatment with the TAXUS DES and an In.Pact Falcon balloon; 97% of patients in the DCB-arm and 81% in the DES-arm completed lesion preparation. LLL was substantially lower in the DCB-arm than in the DES arm at the end of 6 months (0.08 0.38 mm vs. 0.29 0.44 mm; P = 0.001).[9] Regarding angiographic endpoints, this was the first randomized experiment to show the superiority of the DCB versus DES. The most exciting results were that, after three years, the angiographic superiority had finally transferred into clinical superiority; MACE rates in the DCB group were considerably lower than in the DES group (14.4% vs. 30.4%; P = 0.015).[10]

Coronary Bifurcation

Due to disappointing clinical results, mainly in the side branch (SB), coronary bifurcation lesions continue to be difficult for PCI. Even after DES treatment, unacceptably high restenosis rates persist, especially when more advanced procedures are applied. Recent trial findings have led to the preferred method being the placement of a permanent stent in the major branch (MB) and a temporary stent in the small branch. When compared to Percutaneous Balloon Angioplasty (POBA), DCB therapy in the SB may be superior.[11] Some investigators believe the DCB-only approach is the best coronary application for bifurcation lesions. The DCB-only method was compared with POBA in 64 patients with coronary bifurcation lesions as part of the multicenter, randomized, controlled PEPCAD BIF trial. Restenosis occurred at a rate of 6% in the DCB-only group after nine months of follow-up compared to 26% in the POBA group (P = 0.045). The outcomes showed that, following meticulous lesion preparation, the DCB-only approach would be sensible for bifurcation lesions with satisfactory angiographic results.[12]

Coronary Large Vessels

The effectiveness of the DCB-only approach for the treatment of de novo lesions in large (>3.0-mm) coronary arteries is also supported by mounting data. Based on these observations, treating de novo lesions in large coronary

segments is safe and effective, with low rates of clinical events and acute artery closure.[13,14] The concept of DCB-alone strategy, when used to treat de novo lesions, typically accepts a lower angiographic acute gain than stenting, with follow-up benefits primarily coming from reduced late lumen loss and, occasionally, positive remodeling.[14] As a treatment for de novo coronary lesions, DCB is a good alternative to DES. This may be because no foreign material is present, and the treatment is naturally thrombogenic.[15]

Diabetes Mellitus

Diabetes Mellitus affects more than 25% of patients referred for coronary revascularization treatments. These patients typically have poor outcomes after PCI due to higher rates of ISR, stent thrombosis, myocardial infarction, and death brought on by more complex, diffuse, and long lesions in smaller caliber vessels with lower coronary vasodilator reserves.[16,17] Such patients are typically regarded as having a high risk for cardiovascular events. As DCBs are not susceptible to cracks and inhomogeneous coating distribution, which are seen in DES and may cause platelet aggregation stent thrombosis, inflammation, and ISR, they may be an excellent alternative to DES in these lesions.[18–20]

High Bleeding Risk

Both the number of PCIs performed on older patients and those taking oral anticoagulants for atrial fibrillation are expected to rise, and in both of these categories, the rate of bleeding problems within the first year after PCI is 25% to 40%.[21,22] In individuals with a high risk of bleeding, DCBs are preferable to stent placement. Antithrombotic medications may be stopped in the event of severe life-threatening bleeding sooner after DCB than after DES, although that Dual Anti-Platelet Therapy (DAPT) time after PCI with DES has been reduced. According to expert opinion and positive outcomes in recent clinical studies for patients in stable condition, the suggested time frame for DAPT is four weeks following a DCB-only treatment in de novo arteries. [14,23]

Acute Coronary Syndromes

Only a small number of primary PCI data are currently available. Due to specific issues (such as issues with proper vascular size), this patient population warrants special consideration of DCB.[24,25] While the approach is similar, special care is used to avoid DCBs in cases of apparent angiographic thrombus because they may prevent drug delivery to the vessel wall.[26] Another option that might be particularly appealing for a DCB strategy is restoring Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 before staging interventions.[27] In non-ST-segment elevation myocardial infarction (NSTEMI), the PEPCAD NSTEMI trial demonstrated that a DCB-only approach was non-inferior to stent treatment. In contrast, similar outcomes were discovered in the REVELATION (Revascularization with Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stenting in Acute Myocardial Infarction) trial for ST-segment elevation myocardial infarction.[28]

Critical Perspectives

Currently, DCBs are solely indicated for treating ISR according to the cardiac revascularization recommendations from the European Society of Cardiology.[29] Due to a lack of clinical trial data at the time of guideline publication, there is a difference between these guidelines and the current clinical use of DCBs in Europe. The information available on DCBs for de novo illness has dramatically increased during the last few years. Randomized controlled trials do not yet accurately represent the indications of big coronary arteries and bifurcation lesions.[30–32]

The use of DCB to treat de novo lesions enables the avoidance of a permanent implant, which has been linked to a device-associated risk of long-term effects.[1] It has been established over time that DCB's potential advantages can only be realized when the lesion preparation component of the technique is given priority. As a result, DCB angioplasty can be used with DES to shorten and minimize the number of stents in diffuse coronary artery disease. While DES implantation can only be used on segments that need mechanical support, segments that exhibit satisfactory results after lesion preparation can be treated with DCB angioplasty.[1,33]

Conclusion

Recent randomized controlled trial data demonstrate that the DCB technique with ideal lesion preparation, functional testing, antiproliferative drugs to inhibit intimal hyperplasia, and short-term DAPT has evolved into a viable option for treating coronary artery disease in many clinical circumstances. In de novo lesions of coronary small-vessel disease, a DCB-only approach is now a valid treatment alternative to DES if current recommendations regarding optimal balloon angioplasty and subsequent DCB-delivery are adequately followed, even though DCBs are an established therapeutic option for the treatment of ISR supported by guideline recommendations. There is also mounting proof that other clinical scenarios, like bifurcation lesions, PCI in large coronary arteries, or even complex coronary procedures, may benefit from a DCB-only strategy or stentless.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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