Received: 29 June 2023 | Accepted: 30 September 2023

DOI: 10.1002/ccd.30891

REVIEW

WILEY

The evolution and revolution of drug coated balloons in coronary angioplasty: An up-to-date review of literature data

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Abstract

European Society of Cardiology (ESC) guidelines gave class I A indication for use of DCB in in-stent restenosis. However, no indication exists for the usage of DCB in de novo lesions. Although the current generation DES offer excellent results, as we embark more complex lesions such as calcified lesion and chronic total occlusion, restenosis and stent thrombosis are higher and tend to increase within the years. There is increasing desire to leave nothing behind to abolish the risk of restenosis and stent thrombosis and hence the absorbable scaffolds were introduced, but with disappointing results. In addition, they take several years to be absorbed. Drug coated balloons offer an alternative to stents with no permanent implant of metal or polymer. They are already in use in in Europe and Asia and they have been approved for the first time in the United States for clinical trials specifically for restenotic lesions. There is emerging data in de novo lesions which have shown that DCB are noninferior and in some studies maybe even superior to current generation DES especially in small vessels. In this article, we provide a comprehensive review of the literature on this expanding technology focussing on the evidence in both re-stenotic and de novo lesions.

KEYWORDS

DCB, drug-coated balloons

1 | INTRODUCTION

There is a consistent drive in the interventional community to improvise treatment of coronary artery disease ranging from new innovations in pharmacology and device therapy. This had led us to various innovations since its inception in 1978 where we have seen interventional cardiology evolved from early days of plain old balloon angioplasty (POBA) to current generation drug eluting stents that are excellent with low event rates. However, as we embark more complex patients and lesions subsets such as chronic total occlusions (CTOs) and calcified lesions especially in patients with diabetes and chronic kidney disease, rate of restenosis and stent thrombosis is relatively high. This has led to the idea of leaving nothing behind as stents are only needed in the initial phase of angioplasty to prevent acute recoil and seal flow limiting dissection. Drug coated balloons (DCB) offer an alternative to stents as the antiproliferative drugs are delivered via balloons and hence there is no permanent implant of metal or polymer. Their use is escalating across the globe and some of them have now been approved in US for clinical trials. In this article, we aim to provide a comprehensive review of DCB going through the

Abbreviations: BMS, bare-metal stent; BRS, bioresorbable scaffolds; CTO, chronic total occlusion; DCB, drug-coated balloon; DES, drug-eluting stent; ISR, in-stent restenosis; LLL, late lumen loss; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; TLR, target lesion revascularisation; TVMI, target vessel myocardial infarction; TVR, target vessel revascularisation.

rationale, technology, evidence, guidelines, ongoing trials, and potential future course.

1.1 | Rationale for drug coated balloons over drug eluting stents

The breakthrough success of POBA in the initial phase of coronary intervention was overshadowed by high rates of complications (abrupt vessel closure from recoil and flow-limiting dissections) including restenosis.[1] This necessitated the development of new technologies that resulted in bare-metal stents, which addressed acute complications, but metal scaffolding resulted in high rates of in-stent restenosis (ISR), although the rates of restenosis were still better than POBA alone.[2] To combat restenosis, DES were introduced which delivered antiproliferative drugs locally which significantly reduced the rates of ISR.[3] However, the drug and polymer posed a risk of dreadful complications such as stent thrombosis which had high rates of mortality.[4] Since the first report of stent thrombosis in 2006, there have been significant improvements in the DES technology and current generation devices have very low rates of stent thrombosis and restenosis.[5] This is also complemented by improvement in antiplatelet therapy. Despite all these improvements, the risk of ISR and stent thrombosis remains and can never be eliminated especially when we embark more complex lesions subsets (calcified lesions and chronic total occlusion).[6] The stents are only needed in the initial phase to provide scaffolding to prevent recoil and seal dissections, rather than permanently caging the vessel. Leaving nothing behind post PCI is exciting and hence bioresorbable scaffolds (BRS) were designed to address long-term issues with DES as they dissolved over a time period of up to 5 years.[7,8] However, first generation BRS proved inferior to current generation DES in randomized trials which led many centers across the globe to abandon the idea.[9–12] Although they are making a comeback with improvements in scaffold platforms,[13] this may take number of years before we can see global acceptance. DCB offer excellent alternative to stents as the drug is delivered via the balloon with no need for permanent metal platform or polymer. They were initially designed for the treatment of ISR with an aim to avoid another layer of metal in a previously failed stent.[14] However, their use has also been extended to de novo lesions especially in patients and lesion subsets where stents are not ideal such as small vessels, diffuse disease and in patients with high-bleeding risk who may not be able to take dual antiplatelet therapy for an extended period.[15]

1.2 | Drug coated balloon technology

Drug coated balloons aim to deliver high concentration of antiproliferative drug to a target lesion with an aim of preventing neointimal hyperplasia.[15–17] The two antiproliferative drugs currently used in DCBs are Paclitaxel and Sirolimus. Paclitaxel is a lipophilic agent, which allows rapid transportation of the drug into the cell membranes of the tunica intima.[16] Paclitaxel achieves its intended outcome by irreversibly binding to the β subunit of tubulin, halting microtubule function and as a result stopping mitotic cellular division.[18] Stabilization of microtubules by paclitaxel inhibits the proliferation and migration of smooth muscle cells, fibroblasts, and white bloods cells.[18,19] It also inhibits the secretion of extracellular matrix. Through this combination of actions, paclitaxel prevents smooth muscle proliferation, migration, and formation of extracellular matrix in the vessel wall.[16] With this established, further studies demonstrated that both perfusion balloons and microporous balloons are effective for delivering Paclitaxel in situ.[20–22] Research into the optimum delivery of Paclitaxel concluded that pairing it with a solvent or excipient achieved higher rates of efficacy.[23,24] Scheller and colleagues first demonstrated that delivering Paclitaxel with iopromide resulted in complete inhibition of proliferation of the smooth muscle. The effect was superior to that achieved by Paclitaxel alone.[24] The importance of the choice of excipient was also highlighted by Radke and colleagues who compared histological and morphological differences in vessels treated with Paclitaxel paired with varying excipients. Radke and colleagues defined a successful drug transfer as delayed endothelial healing, which could be quantified by the degree of fibrin deposition and inflammation, and found iopromide and BTHC to be more effective excipient than Lecithin.[23] There are several Paclitaxel DCB currently available for clinical use with different excipients and we have provided the comprehensive list in Table 1.

Paclitaxel was used in the first-generation DES along with Sirolimus, however the Paclitaxel DES is now obsolete as the Limus drug has a better safety data and hence remain the default drug of choice in current generation DES.[25–27] There is an increasing aspiration toward developing -limus coated balloons as the drug has a wide therapeutic window and it is cytostatic unlike Paclitaxel which is cytotoxic with narrower therapeutic window.[28] Sirolimus binds reversibly to the FKBP 12 receptor and inhibits cell proliferation by forming a complex with rapamycin.[29,30] This complex formation blocks cell cycle progression between the G1 and S phase.[30] Sirolimus leads to localized cytostatic inhibition of proliferation of vascular smooth muscle cells in the arterial wall and also inhibits recruitment of lymphocytes during the initial phases of restenosis.[31] However, the challenges in pharmacokinetics had hindered its development. Unlike Paclitaxel, the Limus is not lipophilic and hence need a carrier to transfer it onto the vessel wall.[27] In Table 2, we have highlighted the differences between the pharmacokinetics and mechanism of action between the two drugs. The intact arterial wall poses a significant barrier to drug penetration. Previous studies have indicated that the intimal and medial layers of elastic arteries are mostly impermeable to drug delivery, both in normal as well as in atherosclerotic vessels.[32,33] As a result, much of the drug load may remain unabsorbed, and strategies to increase local drug availability are critical to improve the efficiency of the system.[33]

There are two major challenges in developing a limus-based balloon technology.

TABLE 1 Drug coated balloons available in the European market in 2023.

Name of DCB	Manufacturer	Active drug	Dose (μg/mm^2)	Excipient
SeQuent Please	B. Braun	Paclitaxel	3.0	Iopromide
Restore	Cardionovum	Paclitaxel	3.0	Shellac
Agent	Boston Scientific	Paclitaxel	2.0	Acetyl tributyl citrate
Prevail	Meditronic	Paclitaxel	3.0	Urea
Pantera Lux	Biotronik	Paclitaxel	3.0	n-Butyryl citrate
Elutax SV	Aachen Resonance	Paclitaxel	2.2	Ice and Snow layers™
MagicTouch	Concept Medcial	Sirolimus	1.27	Phospholipid nanocarriers
Selution	Med Alliance	Sirollmus	1.0	Mirco-reservoirs
SeQuent SCB	B. Braun	Sirolimus	4.0	Crystalline

TABLE 2 Main characteristics and differences among paclitaxel and sirolimus intended per release from drug coated balloons.

Characteristics	Sirolimus	Paclitaxel
Lipophilicity	Lower	Higher
Mode of action	Cytostatic with antimitotic properties	Cytotoxic, impairing intracellular microtubule function
Binding	Reversible	Irreversible
Anti-inflammatory effect	Yes	No
Margin of safety, approximate	10,000 fold	100 fold
Tissue retention	Longer	Shorter
Tissue absorption	Slow	Fast

1.2.1 | Enhanced tissue absorption

Unlike paclitaxel, the sirolimus has a very poor lipophilicity, which means the tissue absorption of the drug is poor especially from transient balloon inflation (60-s) as it does not rapidly transfer into the vessel wall.[28] Thus, some kind of "instant glue" to transfer the drug efficiently is required.[27]

1.2.2 | Extended tissue retention

The drug must be continuously delivered over time, so some form of time release mechanism must be employed to maintain therapeutic levels.

1.3 | Sirolimus-coated balloon technology

Despite all these challenges, we now have four sirolimus coated balloons that have being marketed in Europe for clinical practice. The first of its kind was from Concept Medical, India (MagicTouch), which obtained the CE mark in 2016. Two other Sirolimus technologies have been developed: SELUTION SLR (MedAlliance) and Sequent sirolimus-coated balloon (B. Braun).

1.3.1 | MagicTouch SCB

MagicTouch SCB is one of the widely used coronary SCB in Europe and Asia with robust clinical data.

The MagicTouch SCB utilizes nanocarriers (in the form of nanoparticles) which offers an additional and different approach for increasing local bioavailability.[34] The cellular uptake of nanoparticles is a rapid process, which also occurs actively, via endocytosis.[35] The endothelial coverage, which is the first and ultimate barrier for drug penetration in the arterial wall, has previously been shown to be responsive to nanoparticle uptake.[36,37] Both within the extracellular and intracellular compartments, nanoparticles provide sustained release and prolonged drug effects, along with a protection against degradation for the encapsulated agent.[37] By encapsulating the drug in a protective packet, nanoparticle-based technology allows for the development of drug-delivery devices that work on Fick's law of

diffusion and the concentration gradient of tissue. The Sirolimus drug is converted into submicron particles which is encapsulated in a phospholipid layer.[34,38] The basic unit for the novel carrier is a phospholipid bilayer nanoparticle which encapsulates the drug in a gently inflated balloon and folded back. When the balloon (semi-compliant) is fully inflated, these nano-particle (encapsulating the drug) come in contact with the endothelium and get transferred onto the vessel wall. Upon entering the intima, the phospholipid carrier acts as a reservoir from which drug is slowly released over 2-week period.[38] Studies on animal model have shown that the blood concentration of the drug falls to negligible level (0.8 ng/mL) within 24-h,[38] however the tissue concentration remains at a treatment level up-to 8-week (Figure 1).

1.3.2 | SELUTION SLR drug eluting balloon

SELUTION SCB has obtained its CE mark only recently (2021) with no published data on coronary interventions yet, with an ongoing large clinical trial, which is in the initial phase of recruitment. The technology involves the formation of spherical micro-reservoirs made from biodegradable polymer intermixed with the drug. These micro-reservoirs provide controlled and sustained release of the drug. The continuous manufacturing process for micro-reservoir formation provides millions of precisely formed, miniature drug delivery systems, each one the same in size with the same drug elution properties. The micro-reservoirs bind to the surface of the balloon, using proprietary Cell Adherent Technology. This mixes the micro-reservoirs with amphiphatic lipids (those that contain both positive and negative ions). The lipids envelop the micro-reservoirs, ensuring that they remain on the balloon during its insertion into the artery and delivery to the lesion. As the balloon is expanded at the lesion site, the amphiphatic lipid carrier is attracted to negatively charged membranes in the endothelial cells, resulting in enhanced adhesion of the micro- reservoir coating. Once the micro-reservoirs are deposited in the endothelium of the artery at the lesion site, they begin drug delivery and are able to maintain clinically effective levels of sirolimus in the vessel for over 60 days. SELUTION SLR™ is the only DEB using drug delivery micro-reservoirs, which provide a long and effective PK release profile. During the drug release phase, the micro-reservoirs biodegrade, while continuously releasing their sirolimus payload. After 3 months, the micro-reservoirs are fully biodegraded, and the vessel is returned to its natural state with nothing left behind.

1.3.3 | Sequent sirolimus coated balloon

B. Braun has been the pioneer in developing the DCB technology and their Sequent Neo Paclitaxel balloon is widely used in the globe. The company now has designed Sirolimus DCB, which utilizes crystalline coatings of Sirolimus for persistent transfer of the drug into the vessel wall with Butyl-hydroxy-toluene (BHT) as excipient. The drug dose of Sirolimus is higher than the other 2 SCB, 4 μg/mm^2. There are currently three small sized clinical trials already published.

Although head-to-head comparisons between paclitaxel and sirolimus are limited, there are initial signals that positive remodeling of the vessel occurs easily after paclitaxel applications, but is much less frequent after sirolimus. Whether this effect has any clinical impact has to be studied in head-to-head clinical trials.[39–41]

1.4 | Evidence for DCB in ISR

The largest and most exhaustive bodies of evidence for the use of DCB exists in the context of ISR. The 2014 and 2018 ESC guidelines have provided class IA indication for the use of DCB in ISR.

The first study on ISR by Scheller (PACCOCATH ISR 1 trial) randomized 52-patients with POBA versus DCB.[42] The primary

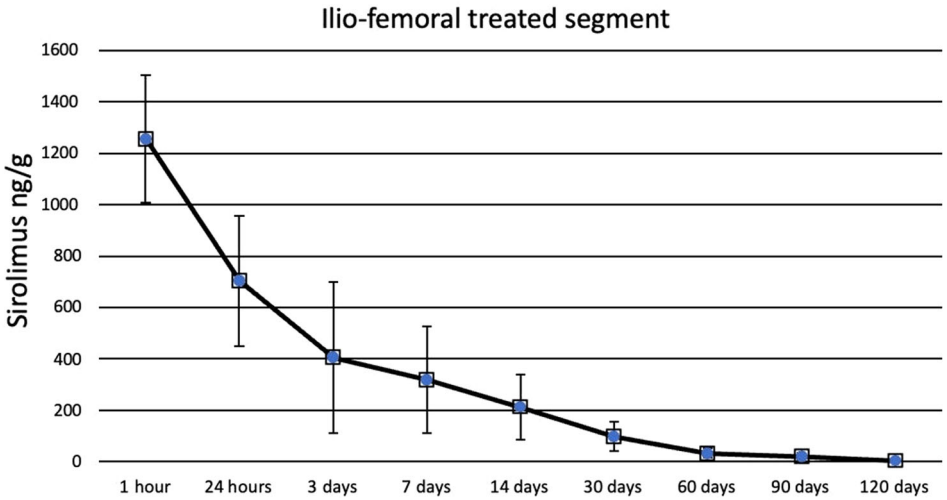

FIGURE 1 Sirolimus retention after MagicTouch angioplasty in the ilio-femoral segment in a porcine animal model (data unpublished, from concept medical). [Color figure can be viewed at wileyonlinelibrary.com]

endpoint late lumen loss was 0.74 mm in POBA versus 0.03 mm ($p = 0.002$) in DCB group at 6-month angiographic follow-up. In addition, binary restenosis was seen in 43% of patients treated with POBA as compared to 5% in the DCB group. During the long-term follow-up of 5-year; MACE rate was 59% (POBA) versus 28% (DCB) which was mainly driven by high rates of TLR in the POBA group (39%).[42]

The PEPCAD II trial on the other hand sought to compare iopromide-based DCB directly with Paclitaxel DES.[43] At 6 months follow-up, the restenosis rates were higher in the DES group as compared to the DCB group (20% vs. 7%, $p = 0.06$). Meanwhile, the in segment late lumen loss was significantly lower in the DES group as compared to the DCB. At 12-month follow-up, the MACE rates were 22% versus 9% ($p = 0.08$) between the DES and DCB groups, respectively.[43]

The ISAR-DESIRE 3 trial was a similar randomized controlled trial where patients with ISR following a limus coated DES were randomized to receive either the same Paclitaxel DCB, Paclitaxel DES, or POBA.[44] Follow-up angiography demonstrated no significant differences in percent stenosis diameter between DES and DCB (37.4% vs. 38.0%, noninferiority $p = 0.007$). Both DES and DCB however proved to have a higher efficacy than POBA. Authors have recently reported the 10-year clinical outcomes and interestingly have discovered no significant differences between the Palcitaxel DCB and DES in the primary (composite of cardiac death, target vessel MI or target lesion thrombosis) or secondary endpoint of TLR (44% vs. 39%, $p = 0.45$), but patients treated with POBA had worse outcomes compared to the other two treatment arms.[44]

On the other hand, the noninferiority of DCB versus everolimus-DES was not observed in the RIBS IV trial.[45] Alfonso and colleagues randomized patients with DES-driven ISR to receive either everolimus eluting stent or a DCB (Sequent Please). Ninety percent of the cohort then received late angiography after 9 months. The DES cohort had a larger minimal lumen diameter (2.03 ± 0.7 mm) as compared to the DCB group (1.80 ± 0.6 mm, $p < 0.01$). The DES group also had a higher net lumen gain as compared to DCB (1.28 mm vs. 1.01 mm, $p < 0.01$) and a lower percent diameter stenosis (23% vs. 30%, $p < 0.01$).[45] The main clinical outcomes were measured as composite of cardiac death, TLR and myocardial infarction at 1 year and were lower in the DES group (10% vs. 18%, $p = 0.04$).[45] The latest follow-up at 3-year showed consistent benefits of the DES with reduced TLR (7.1% vs. 15.6%, $p = 0.015$) and TVR (11% vs. 20.8%, $p = 0.017$).[46] The combined clinical endpoint as before was also significantly reduced in the DES group (12.3% vs. 20.1%, $p = 0.04$). The authors concluded however that despite the relative superiority of DES, both treatments had encouraging long-term outcomes.[46]

The largest meta-analysis on the topic is DAEDALUS, where Giacoppo et al pooled the results from 10 randomized controlled trials that compared the outcomes for paclitaxel-coated balloon vs DES for ISR. The 3-year risk of TLR was higher in the DCB group as compared to the DES group with a hazard ratio on 1.32 (95% CI: 1.02–1.70, $p = 0.035$). However, owing to the heterogeneity between the trials used in the analysis, and the relatively small difference in results, there was no statisitcal difference in the two-stage analysis. The composite endpoint of all cause death, myocardial infarction and target lesion thrombosis was similar (HR 0.80, 95% CI: 0.58–1.09, $p = 0.152$).[47]

1.5 | Evidence for DCB in de novo lesions

Use of DCB in de novo lesion is escalating, but the evidence is relatively lower as compared to restenotic lesions, mainly existing for small vessels in the form of three randomized trials. As of now there is no recommendations in the ESC guidelines for the use of DCB in de novo lesions. However, this may change in the future guidelines as we now have some supporting evidence in this setting, and two of these trials have been published since the last published guidelines in 2018.

The BELLO trial was the first RCT that compared In.Pact DCB (Medtronic, USA, $n = 90$) versus Paclitaxel DES ($n = 92$) in small vessel de novo lesions.[48] Ninety percent of lesions had diameter of 2.5 mm or less indicating it was a genuine small vessel study. During the 6-month angiographic follow-up patients treated with DCB were not only noninferior to DES, but in-fact were superior. The DCB arm has a late-lumen loss of 0.08+/-0.38 mm versus 0.29 ± 0.44 mm in the DES arm.[48] There were no differences in the clinical outcomes at 6-month, but during the long-term follow-up (3-year) MACE rates were significantly higher in the DES group (30.4% vs. 14.4% in the DCB arm, $p = 0.015$).[49] However, this trial has a little impact on the current daily practice as the comparator stent used in this trial was the first-generation Paclitaxel DES which is not being used since a decade.

BASKET-SMALL 2 trial was a RCT which compared Sequent Please DCB versus DES (75% EES, 25% PES) in small and mid-sized coronary vessel disease.[50] This was a noninferiority trial powered for cumulative clinical endpoints at 12-month. A total of 758 patients were randomized to either DCB or DES and at 12-month primary endpoint MACE in the DCB arm was noninferior to DES (7.5% vs. 7.3%, $p = 0.84$) and this was maintained during the long-term follow-up of 3-year (15% in both groups, HR 0.99, CI 0.68;1.45).[50] This result has been perceived by the scientific community with mixed enthusiasm: for DCB believers it was a positive sign that DCB could be considered an option in the de novo small vessels. However, a DCB critic may argue that DCB offers no additional benefit over stents even in small vessel and continue to endorse DES in all de novo lesions.

PICCOLETO II trial randomized 232 patients to either DCB ($n = 118$) or second-generation EES ($n = 114$) and during the angiographic follow-up at 6-month, DCB arm had an impressive late loss of 0.04 ± 0.28 mm as compared to 0.17 ± 0.39 mm in the DES arm, thus achieving not only non-inferiority, but also superiority ($p = 0.03$). At the 12-month clinical follow-up, the MACE rates were comparable among the two groups (7.5% in DES group vs. 5.6% in the DCB group, $p = 0.55$).[51] However, the 3-year follow-up for this cohort recently concluded that MACE rates (20.8% DES vs. 10.8% DCB, $p = 0.046$) and acute vessel occlusion (4% DES and 0% DCB,

$p = 0.042$) were both higher in the DES as compared to the DCB group.[52] This is the only study so far that has shown superiority of DCB over DES in both clinical and angiographic endpoints. Interestingly, also in this study like in other previously published a late lumen enlargement was discovered in the DCB arm.[39,40,52]

1.6 | Clinical data on sirolimus coated balloons

Most of the data in the literature exists for paclitaxel coated balloons as they were designed early in the phase of coronary intervention and the first data came out as year 2007. In fact, the first SCB to be clinically used in Europe was in 2016 and hence the data available is relatively less. However, there are several publications and ongoing studies, with a growing evidence for SCB in both de novo lesions and in-stent restenosis. In the following section, we discuss the data that exists so far in the literature and the upcoming important trials.

1.7 | Registry data

There are several studies performed and published with SCB, mainly the MagicTouch one: FASICO, NATIVES, and Nanolutè registries. All these studies showed the good safety profile of this device, with good clinical outcome until 2 years, along a good angiographic performance as described in the NATIVES study, where LLL was 0.09 ± 0.034 mm in a consecutive series of patients with small coronary vessel disease at 6-month follow-up.[41,53,54]

EASTBOURNE is an investigator-driven, multicenter study on the performance of MagicTouch SCB, the largest prospective study on DCB so far. It enrolled 2123 patients (2440 lesions) from 38 centers distributed between Europe and Asia. All events were assessed by an independent CEC. Diabetic patients were 41.5%, de novo lesions 56% and bailout stenting occurred in 7.7% of the patients. Primary endpoint, TLR at 12 months, occurred in 5.9% of the lesions, more frequently in the ISR cohort of patients (10.5% vs. 2.0%, RR: 1.90; 95% CI 1.13–3.19). MACE occurred in 9.9% of the patients and spontaneous MI in 2.4%. The safety of the device was attested by a cardiac death rate of 1.5%. The main determinant for the occurrence of TLR was ISR (OR 5.5).[55,56] The 2-year outcome has been recently presented during EuroPCR 2023.

The UK registry from two high-volume centers (Heartlands Hospital, Birmingham and Harefield Hospital, London) reported clinical outcomes from the use of MagicTouch SCB in CAD patients between March-2018 and February-2019, with a follow-up period of 12 months.[57] During the study period, 288 patients (373 lesions) with a mean age of 65.8 were treated with MagicTouch-SCB. Of the population enrolled, 54% had an acute coronary syndrome, 38% had diabetes and, interesting, the device was used in de novo lesions in 62% of the cases. The mean diameter and length of SCB were 2.64 ± 0.56 mm and 24 ± 8.9 mm, respectively. During a median follow-up of 363 days (IQR: 278–435), cardiac death and target vessel myocardial infarction (TVMI) occurred in 5-patients (1.7%) and 10 patients (3.4%), respectively, TLR per-lesion was 12%. Overall MACE rate was 10%. There were no documented cases of acute vessel closure.[57] The results from midterm follow-up with this relatively new technology was encouraging with a low-rates of hard endpoints and acceptable MACE rates despite complex group of patients and lesion subsets.

1.8 | Randomized controlled trials

In a multicenter trial comparing sirolimus with paclitaxel DCB, 70 patients with coronary de novo lesions were enrolled.[58] SeQuent SCB (B. Braun) was compared with the well-known SeQuent Please. The primary endpoint was angiographic LLL at 6 months. Secondary endpoints included MACE and individual clinical endpoints. Quantitative coronary angiography revealed a 6-month in-segment LLL of 0.01 ± 0.33 mm in the PCB group versus 0.10 ± 0.32 mm in the SCB group. The mean difference between SCB and PCB was 0.08 (95% CI: −0.07–0.24) and noninferiority at a predefined margin of 0.35 was encountered. However, as expected negative LLL was more frequent in the PCB group (60% of lesions vs. 32% in the SCB group; $p = 0.019$) due to late lumen enlargement. Major adverse cardiovascular events up to 12 months also did not differ between the groups.[58]

TRANSFORM I is an RCT, which is aimed to compare Sequent Please versus MagicTouch in de novo lesions in vessel <2.75 mm. Patients were recruited following quantitative coronary angiography (QCA) based assessment. Following adequate pre-dilatation, optical coherence tomography (OCT) was performed to confirm the vessel size. Patients were then randomized to either therapy with DCB. Primary study endpoint was net lumen gain during 6-month angiographic follow up, and noninferiority between the two treatment was hypothesized, with a noninferiority margin of 0.35 mm.[59] Study enrollment is finished and outcome is being analyzed.

TRANSFORM II is an ongoing RCT that has started enrollment in Europe and Asia. This study aims to compare MagicTouch SCB to EES in native coronary vessels with size comprised between 2.0 and 3.5 mm. Patients are randomized following adequate predilatation provided that there is no flow-limiting dissection or significant recoil and primary endpoint is target lesion failure, with noninferiority hypothesized at 12 months. Study investigators will also analyze the co-primary endpoint of net-adverse clinical events, where superiority of DCB is hypothesized. Patients will receive a follow-up until 5 years.[60]

1.9 | Evidence for DCB in large vessel de novo lesions

As of now, there are is no published data from RCT to support use of DCB in large vessels (3.0 mm or more). Rosenberg et al stratified 234 patients with de novo CAD treated with SeQuent Please DCB into small and large vessel CAD with a cut off of 2.75 mm.[61] The study demonstrated that even in larger vessels, with a cohort average of 3.16 ± 0.27 mm, the 9-month MACE was 6.1% and similar to the

RCT with DCB in large coronary vessels				
STUDY	**type**	**device**	**planned sample size**	**setting**
SELUTIONS all comer	RCT	SCB	3000	all-comers, native coronary artery disease
PICCOLETO III	RCT	SCB, PCB	600	chronic total occlusions, very long lesions
PICCOLETO IV	RCT	PCB	420	high bleeding risk: single anti-platelet vs dual anti-platelet drugs
TRANSFORM II	RCT	SCB	1820	all-comers, native coronary artery disease
HYPER II	RCT	SCB	500	long lesions
DEBATE	RCT	SCB	540	high bleeding risk
SIROOP	RCT	SCB	1000	all-comers
DCB-BIF	RCT	SCB	780	bifurcations
PICCOLETO V	RCT	SCB, PCB	240	bifurcations
PRO DAVID	RCT	PCB	650	bifurcations

FIGURE 2 Large or mid-zed randomized clinical trials currently ongoing on drug-coated balloons for native coronary artery treatment. [Color figure can be viewed at wileyonlinelibrary.com]

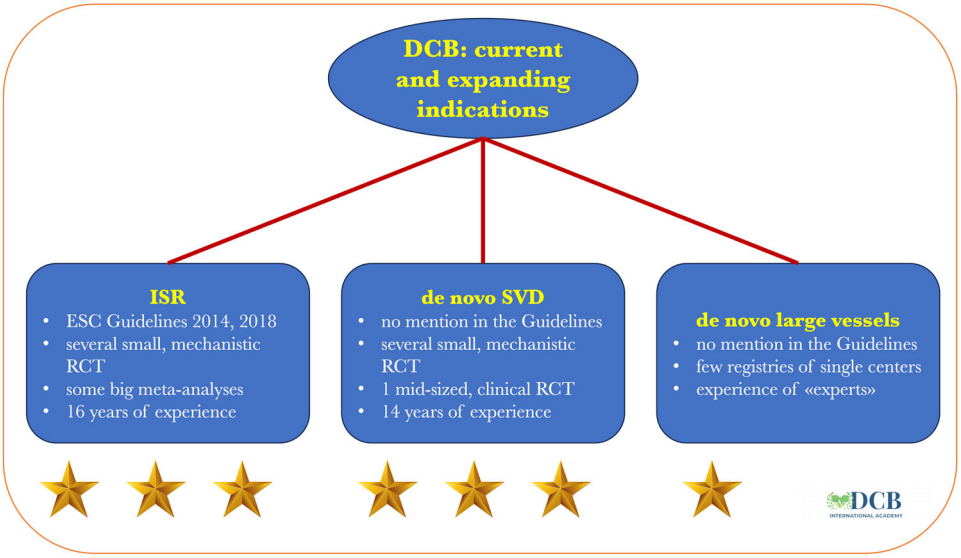

FIGURE 3 DCB: current and expanding indications. DCB, drug-coated balloon. [Color figure can be viewed at wileyonlinelibrary.com]

MACE rate of 5.7% in the small vessel group ($p = 0.903$). TLR occurred in 3.8% in the small vessel group and 1.05% in the large vessel group ($p = 0.20$).[61] This lesion setting represents the last and most interesting frontier for scientific research as regards DCB. Figure 2 describes the ongoing RCT that are testing novel generation DCB in large coronary vessels. Figure 3 describes the current role of DCB in coronary revascularization.

1.10 | Future of DCB

The use of DCB is consistently escalating globally as there is increasing desire to leave nothing behind after angioplasty. Some brands of this class of devices have now been approved in the US for clinical trials, also demonstrating a growing interest in the field. There are several ongoing trials in this field specifically aimed at de novo lesions and hence the future appears bright, especially in the complex lesions setting (chronic total occlusions, bifurcation, and long lesions), aiming at reducing total stent length (Figure 2).

2 | CONCLUSIONS

Drug eluting stents, although currently the gold standard for coronary revascularization, have a number of inherent flaws that predispose them to late complications such as ISR and ST. By using

DCB only, and leaving nothing behind, we may be able to reduce to those aforementioned complications. Literature evidence already supports the use of DCB alone in ISR and suggest noninferiority and promising early results in the use of DCBs for de novo lesions. However, further work is required to settle on the antiproliferative drug of choice, the optimum excipient and the optimum lesion for the DCBs.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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How to cite this article: Cortese B, Kalkat H, Bathia G, Basavarajaiah S. The evolution and revolution of drug coated balloons in coronary angioplasty: an up-to-date review of literature data *Catheter Cardiovasc Interv*. 2023;102:1069-1077. doi:10.1002/ccd.30891