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STATE-OF-THE-ART PAPER

Paclitaxel Drug-Coated Balloons

CME

A Review of Current Status and Emerging Applications in Native Coronary Artery De Novo Lesions

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JACC: CARDIOVASCULAR INTERVENTIONS CME

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Paclitaxel Drug-Coated Balloons

A Review of Current Status and Emerging Applications in Native Coronary Artery De Novo Lesions

The paclitaxel drug-coated balloon (DCB) is an emerging device in percutaneous coronary intervention, which has shown promising results by means of a high-concentration, rapid local release of an antirestenotic drug without the use of a durable polymer or metal scaffold. DCB have already proven effective in clinical trials for the treatment of in-stent restenosis. Its coronary applications may potentially be widened to a host of complex coronary de novo lesion subsets, such as small-caliber vessels, diabetes, and diffuse lesions, where the use of stents may be hampered by suboptimal results. Recently, this technology has rapidly evolved with newer studies added to assess the value of DCB in coronary applications other than in-stent restenosis. We present a review of the role of DCB in de novo coronary lesions based on this latest clinical evidence. (J Am Coll Cardiol Intv 2012;5:1001–12) © 2012 by the American College of Cardiology Foundation

The paclitaxel drug-coated balloon (DCB) is an emerging device in percutaneous coronary intervention (PCI) developed to circumvent some of the limitations faced by drug-eluting stents (DES). These limitations include late and very late stent thrombosis (ST) (1); bleeding risks associated with prolonged dual antiplatelet therapy (DAPT) (2); and reduced efficacy in complex patient and lesion subsets (3). DCB are semicompliant angioplasty balloons covered with an antirestenotic drug that is rapidly released locally into the vessel wall during balloon contact. Various companies manufacture paclitaxel-coated DCB because of their lipophilicity and tissue retention characteristics (4). Table 1 shows the DCB currently being evaluated in coronary applications. These paclitaxel DCB differ in drug-delivery technology and excipients used, thereby resulting in differences in specific elution kinetics and tissue retention (5). These mechanistic differences are not well understood, however, and their clinical significance is even less clear.

DCB technology has demonstrated safety and efficacy in the treatment of coronary in-stent restenosis (6–8). Currently, bare-metal stent (BMS) in-stent restenosis is the only approved indication for DCB use in the European guidelines. The purpose of this review is to detail the other emerging indications for the utilization of DCB for de novo coronary lesions, to present the available clinical data, and to discuss their potential role in this area.

DCB Use in Small Vessel Disease

Stents have limited utility in small-caliber coronary arteries, hampered by late lumen loss (LLL), which is found to be independent of vessel diameter (9,10). Even with DES use, small vessel size remains a strong predictor of restenosis (11). The potential advantage of DCB is less vessel inflammation in the absence of metallic stents and polymer, while allowing the artery's original anatomy to remain intact, thus reducing abnormal flow patterns (5).

The first study to explore DCB use in small vessels was the PEPCAD (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) I study, a single-arm trial investigating SeQuent Please DCB (B. Braun Melsungen AG, Berlin, Germany) in vessels with a mean diameter of 2.36 mm (12) (Table 2). The DCB-only group achieved impressive angiographic and clinical results at 6 months (binary restenosis: 5.5%; target lesion revascularization [TLR]: 4.9%). In contrast, 28% of patients who had BMS fared much worse, with 8× higher restenosis and 5× higher TLR. Most restenosis (77%) occurred at the stent edges, highlighting the potential pitfall of geographic mismatch where a longer BMS was placed outside of the shorter DCB-treated area. Vessel thrombosis occurred in 6.3% of the DCB + BMS group and in no patient from the DCB-only group, despite a longer duration of DAPT (3 months vs. 1 month).

The PICCOLETTO (Paclitaxel-Coated Balloon Versus Drug-Eluting Stent During Percutaneous Coronary Intervention of Small Coronary Vessels) study was the first randomized trial comparing first-generation Dior-I DCB (Eurocor, Bonn, Germany) with Taxus Libertè DES (Boston Scientific Corporation, Natick, Massachusetts) in vessels <2.75 mm in diameter (13). This study was halted prematurely due to clear superiority of the DES group demonstrating less restenosis and a trend toward lower TLR. The worse-than-expected results, as compared to PEPCAD I, were attributed to lower tissue drug dosage in the Dior-I DCB. In addition, procedural differences, such as lower pre-dilation rates and lower inflation pressures employed in the DCB group, may have adversely affected its

outcome. Contrary to PEPCAD I, binary restenosis was similar between DCB with bailout BMS and DCB-only subgroups, suggesting the possibility of exploring routine BMS implantation after DCB in future studies.

The prospective Spanish DIOR (Results of Paclitaxel Eluting Balloon) registry assessed first- and second-generation Dior DCB in very small vessels (mean diameter: 1.99 mm) and demonstrated encouraging preliminary results (14). Angiographic restenosis occurred in 20% of cases, but only 3% required revascularization; the 1-year major adverse cardiac event (MACE) rate was low at 5.8%. In contrast to the other studies, only 7% required bailout BMS to treat dissections.

Positive findings were presented from the BELLO (Balloon Elution and Late Loss Optimization) trial, a randomized study comparing the In.Pact Falcon DCB (Medtronic-Invatec, Fraunfeld, Switzerland) to Taxus DES in vessels with a mean diameter of 2.15 mm (15). The DCB demonstrated superiority over the DES in the primary endpoint of LLL at 6 months (0.09 vs. 0.30 mm, $p = 0.001$). However, bailout BMS occurred in 21.1% of DCB patients; in this group, LLL was 0.33 mm, approximating the DES result. MACE rates at follow-up were comparable between DCB and DES groups (10% vs. 16.3%, $p = 0.18$).

From these limited data, it appears that a DCB-only strategy with provisional BMS might be a reasonable and attractive approach in small vessels, avoiding further reduction of lumen diameter with stent struts. The upcoming DCB-only small vessel disease worldwide registry set up by the PEPCAD investigators will add further insight into the utility of the DCB-only strategy in small vessels.

DCB + BMS in De Novo Coronary Lesions

DES use is limited by accrued risks of late ST facilitated by delayed stent endothelial coverage; dependence on prolonged DAPT also accounts for higher costs and increased bleeding risks. Whereas DCB provide homogeneous and rapid antiproliferative drug transfer to the entire vessel, inhibiting neointimal hyperplasia with little impact on long-term healing, they cannot overcome the mechanical limitation of acute recoil post-balloon angioplasty. By combining DCB and BMS, this has the potential for improved long-term safety while requiring a shorter DAPT duration and may be a viable therapeutic alternative to DES use in at-risk patients.

The LOCAL TAX (Local Intracoronary Delivery of Paclitaxel After Stent Implantation for Prevention of Restenosis in Comparison With Implantation of a Bare Metal Stent Alone or With Implantation of a Paclitaxel-Coated Stent) study used a different balloon design (Genie catheter, Acrostak, Geneva, Switzerland) with distal and proximal occlusive segments and a central segment that allowed for local delivery of fluid paclitaxel to the vessel wall (16) (Table 3). The theoretical advantages of such a design are the flexibility of using different drugs and the possibility of treating longer or more complex vessel segments medically without mechanical trauma. Compared with BMS-only patients, patients randomized to receive a BMS plus local paclitaxel demonstrated superior angiographic results and showed noninferiority compared with paclitaxel-eluting stents. Correspondingly, revascularization rates were identical in both the BMS plus local paclitaxel and DES arms, but they were halved when compared with revascularization rates in the BMS-only arm. The encouraging results prompted the investigators to start a registry evaluating the use of this device in in-stent restenosis, chronic total occlusions (CTO), and bifurcation lesions.

The largest randomized trial to date involving DCB in coronary applications is PEPCAD III, which investigated the Coroflex DEBlue system (hybrid of BMS premounted onto a SeQuent Please DCB) (B. Braun Melsungen AG) as a possible alternative to DES, comparing it to the Cypher sirolimus-eluting stent (Cordis Corporation, Miami Lakes, Florida) in patients with a single de novo lesion (17). In this first evaluation of a DCB + BMS hybrid, it failed to meet noninferiority to DES, showing almost 3 times higher in-stent LLL, translating to significantly more revascularizations. However, the result obtained by this combination system was at least comparable to published data on paclitaxel-eluting stents, and in-segment LLL analysis demonstrated possible DCB efficacy at the stent margins, which was comparable to that achieved by sirolimus-eluting stents. Although there was no difference in MACE rates (15% vs. 18%), ST was higher in the Coroflex DEBlue group than in the DES group (2.0% vs. 0.3% $p < 0.05$), though duration of DAPT was the same at 6 months.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CTO = chronic total occlusion(s)
DAPT = dual antiplatelet therapy
DCB = drug-coated balloon(s)
DES = drug-eluting stent(s)
EPC = endothelial progenitor cell
LLL = late lumen loss
MACE = major adverse cardiac event(s)
MB = main branch
PCI = percutaneous coronary intervention
SB = side branch
ST = stent thrombosis
TLR = target lesion revascularization

The SeQuent Please DCB was also used in conjunction with the endothelial progenitor cell (EPC)-capturing stent (OrbusNeich Medical GmbH, Wiesbaden, Germany) in the PERfECT Stent (Prospective, Randomized Trial Evaluating a Paclitaxel-Coated Balloon in Patients Treated With EPC Stents for De Novo Coronary Artery Disease) study (18). Theoretically, this combination reduced neointimal proliferations and ST risks by facilitating rapid endothelialization. Patients randomized to EPC stent implantation followed by DCB post-dilation demonstrated superior LLL and markedly reduced restenosis rates from 23.2% to

Table 1. Overview of DCB Used in Clinical Trials of De Novo Coronary Lesions

Drug-Coated Balloon	Manufacturer	Drug-Delivery Technology	Excipient	Dose Density, $\mu g/m^2$
Dior I	Eurocor (Bonn, Germany)	Nanoporous balloon	Dimethyl sulfate	3
Dior II	Eurocor (Bonn, Germany)	Nanoporous balloon	Shellac	3
Elutax	Aachen Resonance (Aachen, Germany)	Coated	None	2
Genie	Acrostak Corp. (Geneva, Switzerland)	Nanoporous double balloon	None Uses a liquid drug delivery catheter	10 μmol/l
In.Pact Falcon	Medtronic-Invatec (Frauenfeld, Switzerland)	Coated	FreePac urea	3
Moxy	Lutonix Inc. (Maple Grove, Minnesota)	Coated	Nonpolymeric	2
Pantera Lux	Biotronik (Bulach, Switzerland)	Coated	Butyryl-tri-hexyl citrate	3
SeQuent Please	B. Braun Melsungen AG (Berlin, Germany)	Coated	Iopromide	3
Coroflex DEBlue (Hybrid system of Coroflex blue cobalt chromium BMS premounted onto SeQuent Please DCB)	B. Braun Melsungen AG (Berlin, Germany)	Coated	Iopromide	3

BMS = bare-metal stent(s); DCB = drug-coated balloon.

5.1% as compared to EPC-capturing stent implantation alone. No ST events occurred in either group. The contrasting efficacy and safety results in this trial as compared to PEPCAD III may be related to different procedural techniques. In PEPCAD III, the premounted BMS on DCB may have affected negatively on paclitaxel dose, distribution, and retention in the vessel wall, whereas the EPC stent and DCB were 2 separate devices in the PERfECT Stent study. Mandatory pre-dilation was performed in the PERfECT Stent study, whereas direct stenting was performed in one-half of the PEPCAD III patients. Furthermore, the use of EPC stents and their purported effects on promoting endothelialization may have eradicated ST risks even though the duration of DAPT was halved.

Other DCB + BMS strategies have also been tested against newer-generation DES with less compelling results. Pre-dilation with the Elutax DCB (Aachen Resonance, Aachen, Germany) followed by BMS was significantly inferior to the everolimus-eluting Xience DES (Abbott Vascular, Abbott Park, Illinois) with excessive revascularization rates at 9 months (19). Post-dilation with SeQuent Please DCB following BMS was inferior to Xience in inhibiting neointimal proliferation as assessed by optical coherence tomography (20).

The differing efficacy of the DCB + BMS combination from the preceding studies may in part be influenced by the sequence of using DCB for either pre- or post-dilation in conjunction with BMS. The following studies were designed to examine this issue.

The INDICOR (Paclitaxel-Eluting PTCA-Balloon Catheter in Combination with a Cobalt-Chromium Stent to Treat Coronary Artery Disease in a Real World Scenario) pilot trial randomized patients using the SeQuent Please DCB + BMS (21); and the De Novo Pilot study used the

Table 2. Clinical Trials of DCB Use in Small Vessel Disease

Study	Design	Patients, N	Primary Endpoint (Follow-Up, Months)	TLR, % (Follow-Up, Months)	Bailout Stent Rate, %	Ref. #
PEPCAD I	SeQuent Please	118	LLL 0.18 mm in DCB-only, 0.73 in DCB + BMS (6)	4.9 in DCB-only, 27.1 in DCB + BMS (12)	28	(12)
PICCOLETTO	Dior I vs. Taxus	57	Diameter stenosis 43.6% vs. 24.3% (6) Noninferiority not met	32.1 vs. 10.3 (9)	36	(13)
Spanish DIOR registry	Dior I/II	103	LLL 0.34 mm (6)	3 (12)	7	(14)
BELLO	In.Pact Falcon vs. Taxus	182	LLL 0.09 vs. 0.30 mm (6) Superiority of DCB	4.4 vs. 7.7 (6)	21	(15)
DCB-Only Small Vessel Disease Worldwide registry	SeQuent Please	Ongoing				

BELLO = Balloon Elution and Late Loss Optimization study; DIOR = Results of Paclitaxel Eluting Balloon registry; LLL = late luminal loss; PEPCAD = Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease trial; PICCOLETTO = Paclitaxel-Coated Balloon Versus Drug-Eluting Stent During Percutaneous Coronary Intervention of Small Coronary Vessels study; TLR = target lesion revascularization; other abbreviations as in Table 1.

Table 3. Clinical Trials of DCB Used in Combination With BMS

Study	Design	Patients, N	Primary Endpoint (Follow-Up, Months)	TLR, % (Follow-Up, Months)	Bailout Stent Rate, %	Ref. #
LOCAL TAX	Genie + BMS vs. BMS vs. Taxus	202	LLL 0.61 vs. 0.99 vs. 0.44 mm (6)	13.4 vs. 22.1 vs. 13.4 (6)		(16)
PEPCAD III	Coroflex DEBlue vs. Cypher	637	LLL 0.41 vs. 0.16 mm (9) Noninferiority not met	10.5 vs. 4.7		(17)
PERfECT	SeQuent Please + EPC-capturing stent vs. EPC-capturing stent	120	LLL 0.34 vs. 0.88 mm (6)	4.8 vs. 17.2 (6)		(18)
Liistro et al.	Elutax + BMS vs. Xience	125	Noninferiority not met	14 vs. 2 (9)		(19)
OCTOPUS	BMS + SeQuent Please vs. Xience	80	OCT neointimal proliferation 15.69 vs. 11.21 mm^3/cm (6) No difference in stent strut coverage	4 vs. 2 (6)		(20)
INDICOR	SeQuent Please followed by BMS vs. BMS followed by SeQuent Please	97	LLL 0.50 vs. 0.49 mm (6) No difference	4.1 vs. 2.1 (12)		(21)
De Novo Pilot study	Moxy followed by BMS vs. BMS followed by Moxy	26	OCT neointimal volume obstruction 25.5% vs. 24.9% (6) No difference	15.4 vs. 15.4 (6)		(22)
IN-PACT CORO	In.Pact Falcon for pre- or post-dilation followed by BMS		OCT neointimal area and strut coverage (6)			NCT01057563
PEPCAD IV	SeQuent Please + BMS vs. Taxus	84	LLL 0.51 vs. 0.53 mm (6) No difference	7.7 vs. 8.3 (9)		(26)
PEPCAD CTO	BMS followed by SeQuent Please vs. Taxus	50	LLL 0.64 vs. 0.43 mm (6) No difference	12.5 vs. 12.5 (6)		(27)
DEBAMI	SeQuent Please + BMS	30	TLR 17% (12)	17 (12)		(31)
DEB-AMI	Dior II + BMS vs. BMS vs. Taxus	149	LLL 0.64 vs. 0.74 vs. 0.21 mm (6) No difference between DCB + BMS and BMS	20 vs. 17.6 vs. 2 (6)		(32)
PAPPA	Pantera Lux	100	MACE 3% (1)	2 (1)	41	(33)

CTO = chronic total occlusions; DEBAMI = Drug-Eluting Balloon in Acute Myocardial Infarction trial; DEB-AMI = Drug Eluting Balloon in Acute ST-Segment Elevation Myocardial Infarction trial; EPC = endothelial progenitor cell; INDICOR = Paclitaxel-Eluting PTCA-Balloon Catheter in Combination With a Cobalt-Chromium Stent to Treat Coronary Artery Disease in a Real World Scenario trial; IN-PACT CORO = Intimal Hyperplasia Evaluated by Optical Coherence Tomography (OCT) in De Novo Coronary Lesions Treated by Drug-Eluting Balloon and Bare-Metal Stent study; LOCAL TAX = Local Intracoronary Delivery of Paclitaxel After Stent Implantation for Prevention of Restenosis in Comparison With Implantation of a Bare-Metal Stent Alone or With Implantation of a Paclitaxel-Coated Stent; MACE = major adverse cardiac events; OCT = optical coherence tomography; OCTOPUS = Optical Coherence Tomography to Evaluate Paclitaxel-Eluting Balloons and Everolimus Eluting Coronary Stents; PAPPA = Paclitaxel-Eluting Balloon in Primary Percutaneous Coronary Intervention in Amsterdam study; PERfECT = Prospective, Randomized Trial Evaluating a Paclitaxel-Coated Balloon in Patients Treated With EPC Stents for De Novo Coronary Artery Disease; other abbreviations as in Tables 1 and 2.

Moxy DCB (Lutonix, Maple Grove, Minnesota) plus BMS (22). Either sequence, DCB first or BMS first, was found to result in similar LLL, MACE, and in-stent neointimal hyperplasia assessed by optical coherence tomography. The In.Pact Falcon DCB (Medtronic-Invatec) is currently being tested for pre- versus post-dilation against BMS as the control (the IN-PACT CORO [Intimal Hyperplasia Evaluated by Optical Coherence Tomography (OCT) in De Novo Coronary Lesions Treated by Drug-Eluting Balloon and Bare-Metal Stent] trial, NCT01057563). These studies suggest that as long as a BMS is not premounted onto a DCB, either sequence of DCB use for pre- or post-dilation results in similar efficacy comparable to that of paclitaxel-eluting stents. The clinical significance is that BMS may be used as a bailout strategy for a suboptimal DCB angioplasty result.

The motivation for combining BMS and DCB in de novo lesions was to reduce the need for prolonged DAPT. However, the results of this combination strategy showed higher late loss, posed a higher ST risk when compared with best-in-class DES, and did not have the proven ability to reduce the DAPT duration. Therefore, the future of this combination strategy is in question because of the inferiority of DCB + BMS to DES, higher costs, and no apparent advantage.

DCB + BMS in Diabetes Mellitus

Diabetic vessels are usually small in caliber, and coupled with high plaque burden and diffuse nature of lesions, the risk of restenosis is extremely high even with DES use (23–25). DCB deliver antiproliferative agents homoge-

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neously along the entire device length and may offer a valuable treatment alternative. PEPCAD IV randomized patients to the SeQuent Please DCB + BMS versus Taxus Liberté DES in diabetic patients (26). Results demonstrated comparable angiographic and clinical outcomes despite the DCB + BMS group undergoing less pre-dilation (31% vs. 97%) and achieving lower post-procedure minimum lumen diameter. However, this result may not be sufficient to demonstrate any added advantage of DCB + BMS when compared with the limus-family of DES in treating diabetic patients.

DCB + BMS in CTO

The theoretical advantage of homogeneous nonpolymeric paclitaxel delivery over polymer-based DES was tested in a cohort of patients with native CTO (27). In the PEPCAD-CTO trial, following successful balloon dilation, the entire lesion length was covered with BMS followed by SeQuent Please DCB treatment in the stented segments and beyond the edges. The BMS + DCB group achieved similar angiographic and clinical restenosis rates as compared to historically matched controls of CTO patients treated with a paclitaxel-eluting stent. This trial offers a new and expanding possibility of DCB use in increasingly complex lesion subsets.

DCB + BMS in Acute Myocardial Infarction

DES use in acute myocardial infarction reduces restenosis, but it carries the risks of uncovered stent struts and late malapposition, which could potentially increase the risk of late ST, especially with premature cessation of DAPT (28–30). DCB technology in this highly inflammatory setting provides the opportunity for highly concentrated, rapid local drug release and the avoidance of sustained drug-polymer effects on the vessel wall. If the culprit lesion is only briefly exposed to the antiproliferative drug, theoretically endothelial healing and function should not be affected. However, the recent clinical data have been disappointing.

In the DEB-AMI (Drug-Eluting Balloon in Acute Myocardial Infarction) pilot trial, despite adequate lesion preparation with thrombectomy and pre-dilation followed by SeQuent Please DCB + BMS, restenosis was unacceptably high, leading to a target vessel revascularization rate of 17% at 1 year (31). Angiography at 9 months demonstrated in-stent LLL of 0.48 mm. It may be of concern that 2 cases (6%) of ST occurred, 1 while still on DAPT at 2 months and another at 6 months on single-agent therapy.

Perhaps the clearest signal that the DCB + BMS approach has no role in acute myocardial infarction comes from the recently published DEB-AMI trial (32). In primary PCI, the Dior-II DCB + BMS combination conferred no advantage over BMS alone, with similar 6-month LLL, binary restenosis, and MACE on follow-up. In contrast, those receiving DES showed significantly superior angiographic and clinical outcomes. Optical coherence tomography subanalysis on DCB + BMS patients demonstrated significantly more uncovered and malapposed struts compared with BMS patients, but less compared with DES patients, suggesting that although no apparent angiographic and clinical benefit on restenosis was demonstrated, there is a drug effect induced by the DCB on the vessel wall. These disappointing results were attributed to insufficient paclitaxel bioavailability at the treatment site, less pre-dilation (60% in DCB + BMS, 100% in others), and absence of DCB treatment in segments receiving additional BMS implantation (up to 20% of patients in the DCB subgroup).

Much is still unknown, however, about drug uptake in ruptured plaques with high thrombus burden, which warrants further pharmacokinetic studies. Perhaps the efficacy of a DCB is hampered by the presence of a BMS, and the same investigators are enrolling patients for a DCB-only strategy. This approach, however, is limited by a dependence on bailout stenting, as demonstrated in the PAPP-A (Paclitaxel-Eluting Balloon in Primary Percutaneous Coronary Intervention in Amsterdam) pilot study that recorded a bailout rate of 41% (33), which may limit long-term efficacy.

DCB-Only Approach in De Novo Coronary Lesions

The emerging evidence thus far suggests that a DCB-only strategy achieves superior LLL than does DCB + BMS, with a bailout rate of up to 25% (Table 4). Increased late loss in the DCB + BMS group could be reasoned by inflammation induced by deeper penetration of stent struts into the vessel wall and the antiproliferative drug transfer from DCB, which lacks sufficient depth.

To evaluate this DCB-only strategy, the Valentines II registry (Table 5) was set up using DCB as an adjunct to balloon angioplasty in treating de novo coronary stenoses (34). In a cohort of 103 patients, the primary endpoint of MACE at 8 months was 8.7%; target vessel revascularization was 6.9%, demonstrating efficacy; and cardiac death and myocardial infarction were 2%, demonstrating safety. The results were even more impressive in the nondiabetic subgroup as compared to the diabetics (MACE 6.8% vs. 13.8%, respectively). This trial achieved high pre-dilation rates at 85%; bailout stenting occurred in 11.3%. A snapshot angiographic follow-up demonstrated LLL of 0.30 mm and a 10.7% binary restenosis rate. The results of this study were similar to the Spanish DIOR Registry for small vessels. A similar all-comer SeQuent Please WorldWide Registry demonstrated a much higher rate of bailout stenting (35). Patients with an additional BMS, however, had similarly low rates of TLR and MACE at 10 months when compared with patients receiving a DCB only. These trials offer

Table 4. Comparison of DCB-Only vs. DCB + BMS Angiographic LLL and Bailout Stenting Rates

Study	DCB Used	LLL, mm		Bailout Stenting, %
		DCB Only	DCB + BMS	
PEPCAD I	SeQuent Please	0.18	0.73	28
Spanish DIOR registry	Dior I	0.34 (overall)		7
BELLO	In.Pact Falcon	0.03	0.33	21
LOCAL TAX	Genie		0.61	
PEPCAD III	SeQuent Please	0.12 (In-segment)	0.41 (In-stent)	
PERfECT	SeQuent Please		0.34	
INDICOR	SeQuent Please		0.5	
De Novo Pilot study	Moxy		0.49	
PEPCAD IV	SeQuent Please	0.37 (In-segment)	0.51 (In-stent)	
PEPCAD CTO	SeQuent Please		0.64	
DEBAMI	SeQuent Please	0.42 (In-segment)	0.48 (In-stent)	
DEB-AMI	Dior II		0.64	
Valentines II	Dior II	0.30 (overall)		11
Pilot Long Lesion study	Unknown	0.48 (overall)		
DEBIUT trial	Dior I	0.11 (SB)	0.42 (MB)	7.5 (SB stenting)
PEPCAD V	SeQuent Please	0.12 (SB)	0.66 (SB)	14 (SB stenting)

DEBIUT = Drug Eluting Balloon in Bifurcations Trial; MB = main branch; SB = side branch; other abbreviations as in Tables 1 to 3.

DCB-only as a viable alternative to stenting in patients who may be unsuitable for DES implantation.

DCB-Only Approach In Diffuse Disease

Stent length independently predicts restenosis and stent thrombosis (36,37). The attractiveness of a DCB-only approach with spot-stenting is that it reduces the amount of metal in the vessels while retaining the possibility of future coronary artery bypass grafting. The Pilot Long Lesion Study enrolled 12 patients (mean lesion length of 74 mm) and employed optimal balloon angioplasty followed by DCB, and if required, spot-stenting with BMS for flow-limiting dissections and/or significant residual stenoses (38). Intravascular ultrasound was used to guide and optimize PCI results. Six-month follow-up demonstrated LLL of 0.48 mm, with 16% binary restenosis leading to TLR. With encouraging results from this preliminary analysis, the STARDUST (Spot Bare-Metal Stenting Provisional Implantation plus Drug-Eluting Balloon Against Drug-Eluting Stenting) trial is currently being conducted to test this approach against DES.

DCB in Bifurcation Lesions

Tackling the side branch (SB) remains a significant challenge in coronary bifurcation PCI. Even with DES use, SB treatment often results in unacceptably high restenosis rates. Based on recent trial results, the approach of main branch (MB) stenting with provisional SB stenting has become the preferred method (39,40). In this regard, DCB treatment of the SB may prove advantageous as compared to regular balloon angioplasty. With these hypotheses, several studies have evaluated DCB in bifurcation lesions (Table 6).

The DEBIUT (Drug Eluting Balloon in Bifurcation Utrecht) registry used the Dior-I DCB to treat both the MB and SB following adequate pre-dilation with regular balloons (41). This was followed by the provisional T-stenting technique with BMS in the MB and final kissing post-dilation with normal balloons. No patients required

Table 5. Clinical Trials Using a DCB-Only Strategy

Study	Design	Patients, N	Primary Endpoint (Follow-Up, Months)	TLR, % (Follow-Up, Months)	Bailout Stent Rate, %	Ref. #
Valentines II	Dior II	103	MACE 8.7% (8)	2.9 (8)	11.9	(34)
SeQuent Please Worldwide registry	SeQuent Please	572	MACE 2.6% in DCB-only, 2.4% in DCB + BMS (10)	1% in DCB-only, 2.4% in DCB + BMS (10)	29	(35)
Pilot Long Lesion study	DCB + BMS spot stent	12	LLL 0.48 mm (6)	16 (6)		(38)
STARDUST	DCB + BMS spot stent vs. DES	Ongoing				

DES = drug-eluting stent(s); STARDUST = Spot Bare-Metal Stenting Provisional Implantation Plus Drug-Eluting Balloon Against Drug-Eluting Stenting; other abbreviations as in Tables 1 to 3.

Table 6. Clinical Trials of DCB Use in Bifurcation Lesions

Study	Design	Patients, N	Primary Endpoint (Follow-Up, Months)	TLR, % (Follow-Up, Months)	Bailout Stent Rate, %	Ref. #
DEBIUT registry	Dior I (MB + SB) followed by BMS MB	20	MACE none (4)	0 (4)		(41)
DEBIUT trial	Dior I (MB + SB) followed by BMS MB vs. BMS MB vs. DES MB	117	LLL distal MB 0.41 vs. 0.49 vs. 0.19 mm LLL SB 0.19 vs. 0.21 vs. −0.11 mm (6) Superiority of DCB over BMS not met	20 vs. 27 vs. 15 (18)	7.5 (SB stenting)	(42)
PEPCAD V	SeQuent Please (MB + SB) followed by BMS MB	28	LLL MB 0.38 mm LLL SB 0.21 mm (9)	3.8 (9)	14	(43)
Sgueglia et al.	BMS MB followed by kissing DCB (SeQuent Please, In.Pact Falcon, Dior II, Pantera Lux)	12	Procedural success 100% No MACE (8)	0 (8)		(44)
KISSING DEBBIE	BMS MB followed by kissing DCB	Ongoing				NCT01009996
BABILON	SeQuent Please SB + Taxus MB vs. Taxus MB	Ongoing				NCT01278186

BABILON = Study of the Paclitaxel-Coated Balloon Catheter in Bifurcated Coronary Lesions; KISSING DEBBIE = Efficacy Study of Kissing Drug-Eluting Balloons in Coronary Bifurcation Lesions study; other abbreviations as in Tables 1 to 5.

additional BMS in SB treatment. There was no MACE reported at the 4-month clinical follow-up.

Using this provisional T-stenting technique, the DEBIUT (Drug Eluting Balloon in Bifurcations Trial), which randomized patients in 3 arms: Dior-I DCB pre-treatment + BMS; BMS with uncoated balloon; and paclitaxel DES with uncoated balloon (42). Despite achieving good results with DCB + BMS (MB LLL: 0.41 mm; SB LLL: 0.19 mm), it failed to demonstrate superiority over BMS mostly due to unexpectedly good results in the normal balloon angioplasty-treated SB of both BMS and DES arms, and it may also be related to the inferior drug delivery attributes of the Dior-I DCB.

The single-arm PEPCAD V trial evaluated pre-treatment of both SB and MB using the SeQuent Please DCB followed by provisional T-stenting of the MB with BMS similar to DEBIUT, except there was no obligatory pre-dilation of SB using a normal balloon (43). The procedure was successful in all patients, meeting the study's primary endpoint. SB stenting occurred in 14.3% of patients. Angiographic follow-up at 9 months demonstrated comparable results to historical control subjects with BMS-only in the MB and a DES-like effect in the SB. Consistent with prior observations, DCB-only SB treatment results in superior LLL as compared to DCB + BMS (0.12 vs. 0.66 mm, respectively). MACE occurred in 10.7% of patients, and 2 patients (7.1%) had late ST beyond the prescribed 3 months of DAPT that was attributed to incomplete stent apposition.

Separately, another group of investigators evaluated bifurcation treatment with 4 different new-generation DCB (SeQuent Please, In.Pact Falcon, Dior-II, and Pantera Lux [Biotronick, Bulach, Switzerland]) (44). The rationale in this study was to avert primary SB pre-dilation, which may increase the risk of dissection and SB stenting. Instead, provisional bare-metal stenting with final kissing balloon using DCB was employed with 100% procedural success; no MACE was reported at a mean follow-up of 8 months. A prospective registry of the kissing DCB technique is ongoing (KISSING DEBBIE [Efficacy Study of Kissing Drug-Eluting Balloons in Coronary Bifurcation Lesions] study, NCT01009996).

The preceding trials used BMS in the MB, as there was no significant safety data for DES + DCB. The BABILON (Study of the Paclitaxel-Coated Balloon Catheter in Bifurcated Coronary Lesions [NCT01278186]) is currently being conducted evaluating the SeQuent Please DCB in SB treatment with paclitaxel DES in the MB. The possibility of using a DCB alone in bifurcations should also be considered in future studies. More data are needed comparing DCB strategies in bifurcation treatment against the use of newer-generation DES, which have improved safety and efficacy. As of now, DCB treatment of the SB appears promising in a provisional SB stenting approach.

DCB + DES

Patients with high-risk lesions for restenosis, such as insulin-dependent diabetes and very diffuse lesions, may benefit from added doses of antiproliferative agents in the vessel wall. At present, though, there are no clinical or pre-clinical data on the efficacy and safety of DCB + DES. The closest available evidence comes from studies evaluating

overlapping DES. Initial safety concerns arose from the animal studies, where overlapped segments using homogeneous DES have higher drug and polymer concentrations, resulting in delayed healing and increased inflammation (45). Moreover, overlapping heterogeneous paclitaxel and sirolimus DES had better histological outcomes compared with homogeneous drug use (46). However, clinical data suggested no difference between overlapping homogeneous and heterogeneous DES use (47,48). Overlapped DES result in higher restenosis rates and adverse clinical outcomes compared with nonoverlapped DES (49). Herein lies the attractiveness of using a single layer of DES (with added antiproliferative effects) over DCB and should be the focus of future studies.

DAPT Requirements With DCB

Using a protocol of 1-month DAPT, earlier trials demonstrated no thrombotic complications even beyond 2 years (6,7). Whereas a DCB-only approach confers little risk of vessel thrombosis, this risk increases when coupled with a BMS. Most studies prescribed 3 months of DAPT following clopidogrel-loading with reasonable safety; however, there were still reports of thrombosis occurring beyond 6 months (Table 7). Perhaps the DCB + BMS combination should be treated like DES implantation with 6 to 12 months of DAPT. This is even more relevant in lesion subsets at high thrombotic risk, such as bifurcations; here, DAPT should be considered for a full 12 months. The hypothesis of reducing DAPT duration with various DCB treatments is not supported by current data. Future recommendations will depend on more clinical evidence, particularly if the DCB technique can be optimized to avoid stenting.

Conclusions and Future Perspectives

The limitations of the currently available evidence are that the studies are mainly based on small registries and few small randomized trials. Moreover, the results offered by these studies do not comprehensively answer specifically to the DCB indications. Most of these studies use LLL as a surrogate endpoint to restenosis instead of clinical outcomes. Longer-term follow-up data are also desired; however, these emerging data hold promise mainly in lesion subsets in which implanting a stent is not desirable or is technically challenging.

For now, a DCB-only approach appears feasible in small-vessel coronary artery disease. Similarly, DCB use

Table 7. Vessel Thrombosis Rate in DCB Use and Duration of DAPT

Study	Device	Vessel Thrombosis Rate, % (n/N)	Duration of DAPT, Month(s)	Clinical Follow Up, Months
PEPCAD I	SeQuent Please	0 (0/82) in DCB only 6.3 (2/32) in DCB + BMS	1 3	6
PICCOLETTO	Dior I	0 (0/18) in DCB only 0 (0/10) in DCB + BMS	1 3	9
Spanish DIOR registry	Dior I/II	1 (1/103)	Not available	12
BELLO	In.Pact Falcon	0 (0/94)	Not available	6
LOCAL TAX	Genie + BMS	0 (0/67)	6	6
PEPCAD III	Coroflex DEBlue	2 (6/310)	6	9
PERfECT	SeQuent Please + EPC-capturing stent	0 (0/62)	3	6
INDICOR	SeQuent Please + BMS	6.1 (3/49) in DCB 1st 3.1 (1/48) in BMS 1st	3	12
De Novo Pilot study	Moxy + BMS	0 (0/26)	3	6
PEPCAD IV	SeQuent Please + BMS	0 (0/45)	3	6
PEPCAD CTO	SeQuent Please + BMS	0 (0/48)	3	6
DEBAMI	SeQuent Please + BMS	6.7 (2/30) (1 patient at 2 months, 1 patient at 6 months)	3	12
DEB-AMI	Dior II + BMS	4 (2/50) (1 patient at day 4, 1 patient at day 5)	Not available	6
Valentines II	Dior II	0 (0/103)	3	7.5
Pilot Long Lesion study	DCB (+ provisional BMS)	0 (0/12)	Not available	6
DEBIUT registry	Dior I + BMS	0 (0/20)	3	4
DEBIUT trial	Dior I + BMS	0 (0/40)	3	12
PEPCAD V	SeQuent Please + BMS	7 (2/28) (1 patient at 6 months, 1 patient at 8 months)	3	9
Sgueglia et al.	4 different DCB + BMS	0 (0/12)	3	8

DAPT = dual antiplatelet therapy; other abbreviations as in Tables 1, 2, 3, 5, and 6.

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shows promise in SB treatment in bifurcation lesions, although the technical aspects of this complex procedure are still being evaluated. More data are needed, especially in novel indications such as CTO, diabetes, and diffuse disease. The all-comer registries show DCB to be safe and effective in routine clinical use, with acceptable crossover rates to bailout stenting. Future trials evaluating the DCB-only strategy with bailout or spot-stenting may be required to demonstrate noninferiority to newer-generation DES.

Not all DCB are created equal. Although most of the currently available DCB for coronary applications are based on similar principles using similar paclitaxel doses, specific elution kinetics may differ because of the coating and may result in differing tissue retention characteristics. Unless we have randomized trials with head-to-head data on the different DCB, it is difficult to assume a "class effect." Moreover, these drug-elution profiles have not yet been defined in certain pathologies, such as acute myocardial infarction with high thrombus burden.

Development of paclitaxel DCB originated when the Taxus stent was successfully tested and expectations were high. Moreover, coating methods have evolved such that manufacturers are now familiar with the principles of using paclitaxel. However, we now know that Taxus is inferior to the limus-based drugs in treating restenosis and ST (50,51). These are serious issues to perhaps redirect the industry's focus in designing the next generation of DCB with limus-based drugs. The challenge is in developing more advanced carrier technology (possibly with polymeric nanoparticles) for the limus-based drugs to achieve more stable tissue drug levels for optimal biologic effect (52–54). At present, zotarolimus appears to have the best profile with encouraging pre-clinical data (55).

Operator experience and technical expertise in DCB use are paramount in obtaining good results. Ideally, the stenosis should first be adequately dilated with normal balloon angioplasty to achieve a "stentlike" angiographic result, followed by DCB use for drug delivery at nominal pressure inflation. The DCB should be sized longer than the angioplasty balloon to avoid geographic miss to prevent restenosis in the untreated areas. Pre-dilation is thought to create important "microdissections," which facilitate drug transfer through the intima and media. Based on current evidence, a DCB-only strategy is preferred. However, in cases of significant dissections, residual stenoses or acute closure post-balloon angioplasty, treatment options include DES-only and DCB + BMS. Particular attention should be paid to avoid a geographic miss when a DCB is used in combination with a stent. Bailout stenting outcomes with BMS are inferior to a DCB-only strategy, and this limitation must be considered when using a DCB especially in SB treatment of bifurcation lesions.

The DCB is still trying to find its role in coronary artery disease treatment. Current evidence suggests DCB efficacy and safety in coronary de novo lesions but does not support superiority or even equivalence to the best-in-class DES. We therefore believe that DCB should not be disruptive to DES; when used carefully and with the right technique, DCB may have a niche role in the treatment of coronary lesions not suitable or ideal for DES implantation. Larger randomized clinical trials, and perhaps a push for developing limus-based DCB, are required to further elucidate the role of this technology.

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