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Review Article

Drug-coated balloon in the treatment of coronary bifurcation lesions: A hope or hype?

Debabrata Dash [b, *], Rohit Mody [a], Naveed Ahmed [b], Sugandhna Reno Malan [b], Bhavya Mody [c]

[a] Department of Cardiology, Max Superspeciality Hospital, Bathinda, India
[b] Department of Cardiology, Aster Hospital, Dubai, United Arab Emirates
[c] Department of Medicine, Kasturba Medical College, Manipal, Karnataka, India

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ABSTRACT

When compared to non-bifurcation lesions, percutaneous coronary intervention in coronary bifurcation lesions is technically demanding and has historically been limited by lower procedural success rates and inferior clinical results. Following the development of drug-eluting stents, dramatically better results have been demonstrated. In most of the bifurcation lesions, the provisional technique of implanting a single stent in the main branch (MB) remains the default approach. However, some cases require more complex two-stent techniques which carry the risk of side branch (SB) restenosis. The concept of leaving no permanent implant behind is appealing because of the complexity of bifurcation anatomy with significant size mismatch between proximal and distal MB which may drive rates of in-stent restenosis and the potential impact of MB stenting affecting SB coronary flow dynamics. With the perspective of leaving lower metallic burden, a drug-coated balloon (DCB) has been utilized to treat bifurcations in both the MB and SB. The author gives an overview of the existing state of knowledge and prospects for the future for using DCB to treat bifurcation lesions.

1. Introduction

A bifurcation lesion is designated as a lesion occurring at or adjacent to a significant side branch (SB) that an operator does not want to lose during percutaneous coronary intervention (PCI).[1] This lesion subset is frequent in routine practice and represent 15–20% of all lesions undergoing PCI.[2] Bifurcation PCIs are limited by a higher incidence of procedural complications, a higher rate of restenosis and inferior clinical outcomes compared with non-bifurcation PCI.[3] More complications, higher rates of restenosis, and inferior clinical outcomes have been seen in bifurcation PCIs than in non-bifurcation PCIs.[3] With the development of drug-eluting stents (DES), the outcome has improved in this complicated lesion group, but certain issues including stent thrombosis (ST) and in-stent restenosis (ISR) are still considerable and need to be tackled. In some cases, complex two-stent techniques are contemplated, even though provisional one-stent technique has been the default strategy. Leaving a lower metallic burden in these lesions is appealing. By delivering antiproliferative drugs to local arterial tissue leaving no implant behind, the drug-coated balloon (DCB) represents an enhancement of the therapeutic repertoire for the interventionists. ISR[4] and small vessel coronary artery disease have already proved this novel technology to be a successful alternative to DES. Bifurcation PCI with DCB has shown promising results in many investigations. However lack of large randomized controlled trials (RCTs) or international consensus documents limit dissemination this approach so far. Accordingly, the current manuscript reviews existing literature on DCB's usage for bifurcation coronary lesions and gives insight into what the future may hold.

2. Classification, anatomy and rheology of bifurcation

Many bifurcation[5–8] classification schemes (Fig. 1) have been proposed, all of which share the same basic principles. However, the majority of them haven't been able to make the leap into actual clinical practice. For its ease of use and reproducibility, the Medina[9] classification system is the most often used. In this categorization,

* Corresponding author. Aster Hospital, Al Mankhool, Kuwait Road, P.O. Box: 119428, Dubai, United Arab Emirates.
E-mail address: dr_dash2003@yahoo.com (D. Dash).

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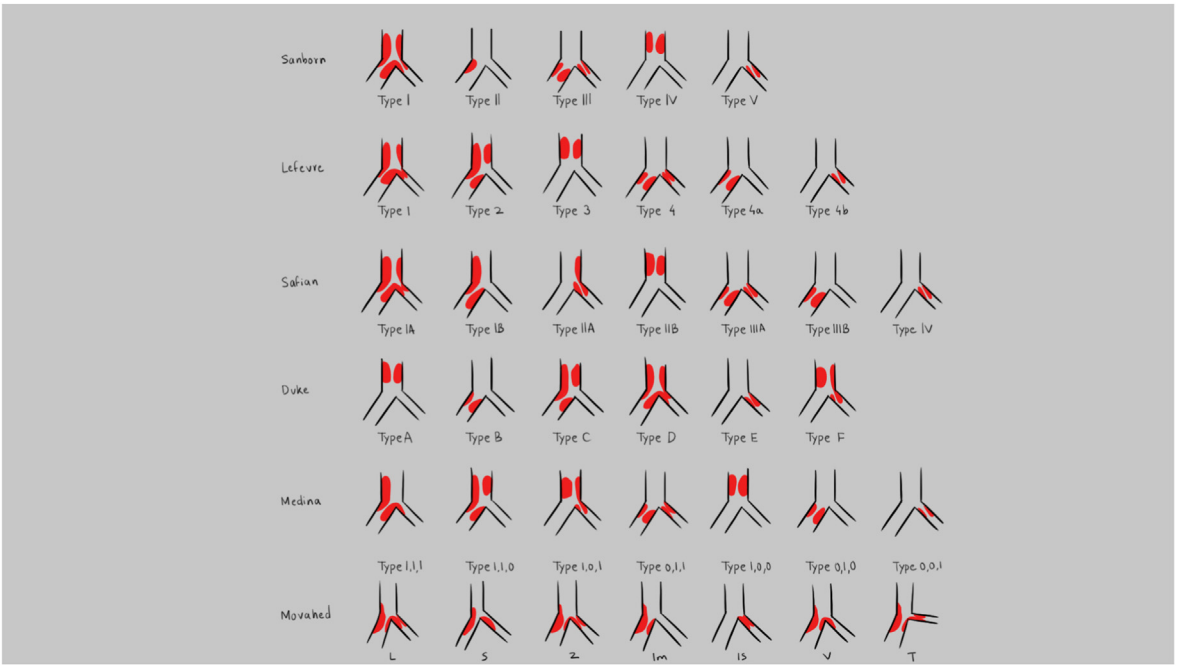

Fig. 1. Classification of coronary artery bifurcation lesion.

three segments are taken account, and each part must have a stenosis of ≥50% to qualify (indicated with 1 or 0 in the presence or absence of the stenosis). This classification has several limitations, since it does not consider the plaque burden, branch diameter, lesion length, bifurcation angles, the presence of ostial disease, or calcification.[3]

A coronary bifurcation is a branching artery formed by a MB and a SB. The segment proximal to the origin of the SB is referred as proximal MB, whereas the one that is distal is to it is designated as referred as distal MB. The MB-SB "transition zone" is referred as "bifurcation carina" which is crucial in bifurcation anatomy. The polygon of confluence (POC) is an independent area between the proximal MB, distal MB and the SB. A bifurcation constitutes a conical shape connecting proximal and distal segments, larger proximal MB reference diameter, the SB ostial negative remodeling, proximal to distal segment tapering and nonuniform geometrical distribution of atherosclerotic plaque that can involve any anatomical segments, sparing the carina.[10] Atherosclerotic plaques are usually located in the lateral walls of MB and SB with low wall shear stress (WSS) and rarely involve the carina which is characterized by high WSS. 3D computational fluid dynamics model demonstrates the development of atherosclerotic plaque at sites of bifurcation where low WSS, oscillating WSS, flow division, and stasis appear. Medina 1.0.0 bifurcation carries the greatest risk of plaque formation. Medina 1.1.0, 1.1.1, and 1.0.1 bifurcation resist atherogenesis better due to high WSS.[11] A larger carinal angle produces lower and more oscillatory WSS in the lateral walls of the MB and SB. A low WSS has also been linked with rupture-prone plaques.

3. Rational of DCB in bifurcation

Despite significant decrease in restenosis, DES restenosis persists in diabetic individuals and those with complex lesions. Furthermore, the efficacy of DES has been questioned by the danger of late stent thrombosis, which is very rare and unexpected. Another drawback of DES is non-uniform distribution of drug on the arterial wall with highest concentration at the stent struts and the lowest between the struts and the margins. Other drawbacks include small vessel disease treatment because of stent thickness, stent layers left in the artery with arterial vasomotricity abnormalities after multiple layers and issues pertaining to the duration of dual antiplatelet therapy (DAPT).[12]

Stent malapposition and fracture, which can lead to thrombosis and restenosis, as well as allergic events to the foreign body, can be prevented using DCB. This novel technique respects the original anatomy of bifurcation, which is especially important in the carina area, and allows for the homogeneous application of a high dose of antiproliferative drug on the entire blood vessel surface. Compared to any of the two-stent techniques, DCB use in the SB eliminates the possibility of an uncontrolled drug release due to lack of proper bifurcation coverage, ostium scaffolding, MB stent deformation, or the crushing of several metal layers and polymers. Technically, re-wiring, re-ballooning the SB and wire jailing and final kissing balloon inflation (KBI) may be avoided with DCB. A DCB is theoretically superior to a regular balloon in terms of vascular remodeling and plaque stabilization as well as better late angiography outcomes, even for a simplest provisional technique.[13]

4. Should bifurcation be treated without stents?

The European Society of Cardiology[14] recommends MB stenting with provisional SB stenting as the default strategy because it decreases treatment time, contrast burden, and radiation exposure while reducing the necessity for a two-stent strategy.[14,15] The European Bifurcation Club (EBC) also supports the use of a MB-only stenting in the majority of cases with provisional SB stenting in T, TAP and culottes fashion only if required due to severe SB recoil or flow limitations after stenting the MB.[2] The rational for this recommendation derived from two factors: inadequate SB ostial covering and struts that protrude into the MB. There has been less angiographic re-stenosis of SB using a complex two-stent technique that involves more stents and takes more procedural and fluoroscopy time, contrast volume.[16] After a 5-year follow-up of the

Nordic Bifurcation Study (Nordic bifurcation V), a provisional one-stent method was shown to be just as successful as a complex strategy of stenting both the MB and the SB, with equal clinical studies.[17] According to a meta-analysis, two-stent techniques carry a higher risk of late stent thrombosis and myocardial infarction (MI) compared to one stent.[18] For SBs which are large with the disease that extends beyond the vessel ostium by more than 10 mm, two stents are often required which makes the procedure challenging.[19] About 17%–22% of bifurcation PCI cases still confront with SB closure and target vessel revascularization (TVR), with or without a final KBI.[20] DCB therapy of the SB seems to be superior to ordinary plain balloon angioplasty (POBA) in this scenario. Compared to the traditional DES, DCB may prevent the carina shift, which is thought to be a significant cause of SB narrowing after MB treatment.[21] DCBs appear to be appealing in coronary bifurcation with the evidence supporting the KISSS (keep it swift, simple and safe) principle.[22] The EBC's current meeting has emphasized DCBs as an area of interest for bifurcation PCI and suggests an option to preserve a provisional strategy particularly when the anatomy is suitable as in the Medina 0,0,1 classification[23] with a recent international DCB consensus group highlighting the role of DCBs in this subset of lesion.[24]

5. Lesion preparation

DCB's Achilles' heel in coronary arteries is the recoil, negative remodeling, and dissections. Drug transfer and bioavailability and decrease drug transit time which is subject to adequate lesion preparation and meticulous angioplasty using the reference balloon artery ratio between 0.8 and 1.0 is critical to DCB efficacy. While flushing and preparing the catheter, it's important to avoid manipulating the balloon. Preventing drug loss by bringing the balloon as rapidly as possible to the target and inflating gently is of paramount importance. For 30–60 s, the balloon should be inflated at a pressure of 7–8 atm.[12,25] Minor dissections (Type A or B) and residual stenosis <30 percent are acceptable and may be left unstented. Adjunctive plaque modification devices like non-compliant high pressure balloons, cutting or scoring balloons, rotational atherectomy and intravascular lithotripsy should be utilized liberally (Fig. 2). An optical coherence tomography (OCT), fractional flow reserve (FFR), or intravascular ultrasound may be required if results are ambiguous. Proper lesion preparation can result in improved acute gain, remodeling, and the avoidance of severe flow-limiting dissections. According to Tanaka et al,[26] unsatisfactory angiographic pre-dilatation (TIMI flow <3, >30% DS, and/or substantial dissections) before DCB application is an independent predictor of target lesion revascularization (TLR). DCB leads in non-flow limiting dissections, which are typically benign in the majority of patients. Moreover 40% of non-flow limiting dissections had the same adverse outcomes as the non-dissection cohort, according to Cortese et al.[27] Approximately 5% of patients required bailout stenting because of flow limiting dissection. At follow-up, DCB also showed signs of positive remodelling. A bailout stenting following DCB usage has worse outcmes.[28]

6. Various strategies

When it comes to treating bifurcation, DCB isn't necessarily the best therapeutic approach. Different aspects must be taken into account by the PCI operator such as the type of bifurcation lesions, the presence of others concomitant coronary artery stenosis, comorbidities, feasibility of an adequate DAPT, etc.

6.1. DCB strategy for the MB of bifurcation

The goal of an interventional cardiologist is to leave no metal behind. Based on the few available data, this method looks provocative, but it is viable in non-calcified non-left main (LM) bifurcation lesions.

In a single-arm, prospective observational trial, Schulz et al (Table 1)[29] examined whether a DCB-only treatment was beneficial in 39 consecutive patients of coronary bifurcation lesion with SB $\geq$ 2 mm. With the second generation DCB (SeQuent Please and In. Pact Falcon), the frequency of restenosis was found to be low for the SB and MB (3.3 percent and 6.7 percent, respectively). Moreover, a lower rate of major adverse cardiac events (MACE [7.7%]) was also observed. 33.3% of these lesions were attributed to LM bifurcations, which are shown to be an independent predictor of TLR. This study concluded that PCI with DCB only strategy in de novo bifurcation lesions is a safe therapy with low rates of concluded that restenosis and TLR. LM bifurcation treatment with DCB only is a feasible treatment option in patients not eligible for coronary artery bypass graft and with the need of shorter DAPT.

PEPCAD-BIF (Table 1) is the first DCB only RCT randomizing patients ($n = 64$) to either DCB or POBA only approach for bifurcation lesions that did not incorporate proximal MB disease (i.e. Medina 0,1,0, 0,0,1 or 0,1,1). It incorporated mainly small vessels (mean vessel diameter 2.4 mm). In the DCB arm, late lumen loss (LLL) was dramatically improved.[30] This trial demonstrated the promising results for the use of DCB only bifurcation.

Bruch et al (Table 1).[31] recruited 127 patients with coronary bifurcation lesions including a SB > 2 mm in diameter of any Medina class compared a DCB-only method with a DCB strategy that also included stenting. At 9 months, patients treated exclusively with DCB showed no signs of thrombotic events, while TLR and MACE were reported to be 4.5% and 6.1%, respectively. A DCB-only therapy for bifurcation lesions was shown to be both safe and effective by the study team.

A DCB-only PCI to the MB is often supported by the fact that ostial SB lesions may exhibit positive remodeling. Her et al[32] performed a single center, prospective observational study in bifurcation lesions (with a SB $\geq$ 1.5 mm) that incorporated a DCB only approach for the MB with a primary outcome of OCT lumen area of both MB and SB at angiographic follow-up at 9 months. The SB ostial area with similar increase in mean lumen area was observed. DCB only approach to MB, therefore, may be an excellent option to avoid compromise of the SB ostium (Table 1).

6.2. DCB strategy for the SB of bifurcation

The first-in-man observational study, PEPCAD-V (Table 1) which enrolled 28 patients demonstrated 100% success rate after 9 months with DCB application to bifurcations, predominantly when used as stand-alone procedures if SB stenting could be avoided. The MB LLL was 0.38 ± 0.46 mm, while the SB LLL was 0.21 ± 0.48 mm, both of which were very encouraging outcomes for the research.[33] when the DCB was used in combination with a BMS (MB), the possibility of late stent thrombosis cannot be ruled out however.

DEBIUT,[34] Herrador et al[35] and BABILON (Table 1)[36] investigated the comparative performance DCB use in the SB of a bifurcation lesion with POBA or DES, all using LLL at angiographic follow-up as primary outcomes.

DEBIUT compared DCB in both the MB and SB and BMS in the MB or with a BMS in the MB and POBA in the SB or paclitaxel DES in the MB and POBA in the SB. This study demonstrated similar angiographic outcome in the group with DCB + BMS compared

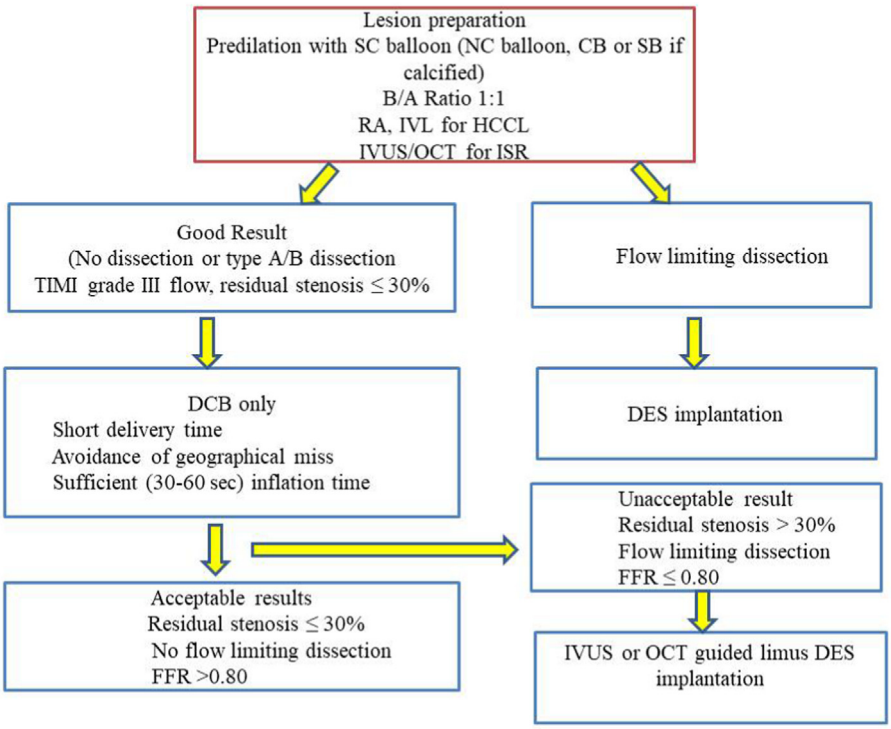

Fig. 2. Tips and tricks of drug-coated balloon use B/A, balloon/artery; CB, cutting balloon; DCB, drug-coated balloon; DES, drug-eluting stent; FFR; fractional flow reserve, HCCL, heavy calcific coronary lesion; IVUS, intravascular ultrasound; ISR. In-stent restenosis; IVI, Intravascular lithotripsy; NC, noncompliant; OCT, optical coherence tomography; RA, Rotational atherectomy; SB, scoring balloon; SC, semicomlaint.

with BMS only, but inferior to the group with DES in the MB, suggesting that pretreatment with DCB was not advantageous over DES. The inferior result could be attributed to matrix-free DCB. It has been found that matrix-free DCBs are less effective than those DCB with matrix consisting of an excipient in addition to the drug, allowing rapid absorption of paclitaxel into the vascular wall.[37]

The DEBSIDE trial investigated the role of a DCB (Danubio) in the SB, after implantation of a DES in the MB in 52 patients with bifurcation lesions suitable for stenting. The results were encouraging, with TLR occurring in the MB or SB at a rate of 10% and 2% respectively.[38] DCB is safe and effective and results in very low LLL and a low restenosis rate at the SB ostium. The BIOLUX-I[39] is prospective, multi-center study conducted in 35 patients with coronary bifurcation lesions. Angiographic and intravascular ultrasound assessments were conducted at 9 months; clinical follow-up was conducted until 12 months. It evaluated the feasibility of provisional stenting with DES in the MB and DCB in the SB and found decreased MACE and TLR after a 9-month follow-up period, recommending the combined use of DES and DCB in bifurcation lesions (Table 1). The efficacy of DCB at the SB ostium after DES implantation in the MB was demonstrated in the single-arm prospective registry (SARPEDON study) with good angiographic outcome and low restenosis rate, although an increased MACE at 1 year.[40]

Analysing the safety and efficacy of kissing second-generation DCB (SeQuent Please, In. Pact Falcon, DIOR II and Pantera Lux), Sgueglia et al[41] demonstrated no MACE after 8 months. At the advent of dedicated bifurcation stents, kissing DCB appears to be safe and effective bifurcation techniques. Herrador et al[35] compared treatment of the SB either with the DCB or with POBA when the MB was treated with a DES. MACE at 12 months in POBA and DCB were 24% and 11% ($P = 0.11$) respectively, with greater TLR in the POBA group (22% vs.12%, $P = 0.16$). Angiographic follow-up demonstrated a reduced percentage of SB restenosis in the DCB group, with lower LLL.

Megaly et al[42] performed a systematic review of 4 studies with 349 patients of coronary bifurcation. The SB stenting was performed in 7.5% vs 8.6% in the DCB and BA groups, respectively. Angiographic follow-up performed after a mean follow-up of 9 months demonstrated that DCB was associated with lower SB LLL compared with BA (mean difference, −0.19 mm; 95% confidence interval [CI], −0.37 to −0.01; $P = 0.04$). There was no difference in the risk of SB binary restenosis (odds ratio [OR], 0.52; 95% CI, 0.18−1.47; $P = 22$). During a mean follow-up of 15.1 ± 5.8 months, DCB and BA had similar risk of MACE (OR, 0.76; 95% CI, 0.4−1.4; $P = 40$), and TLR (OR, 0.85; 95% CI, 0.3−2.4; $P = 76$).

Corballis et al[43] observed that DCB outperformed POBA in the SB treatment for bifurcation in a focused meta-analysis. DCBs appear to be safe in the MB with improved SB LLL. when compared with DES or POBA. Ikuta et al[44] observed an acute SB gain of 0.65 ± 0.55 mm and an LLL of −0.13 ± 0.422 mm in a study of 159 bifurcation lesions (158 patients) treated with DCB in the SB and DES in the MB. Within a year, all-cause mortality and TLR rates were 1.4% and 3.5% respectively.

The BEYOND (A drug-eluting Balloon for the trEatment of coronarY bifurcation lesions in the side branch: a prospective multicenter randomized) trial demonstrated that at the 9-month follow-up SB dilation with the DCB group generated better angiographic results in terms of lower target lesion stenosis than therapy with the POBA group in de novo non LM bifurcations treated with provisional T stenting (Table 1).[45]

Independent of the approved indications, it may be advisable to implant a DES in the MB and use a DCB in a case of hemodynamically relevant SB stenosis. This procedure, theoretically, offers the benefit of possibly increasing the SB's long-term patency while ensuring a reduced metallic burden at the carina location. The

Table 1
Trials and registries of DCB use in coronary bifurcation lesions.

Study	No of patients	Design	DCB type	Primary Endpoint	Secondary Endpoint	TLR/TVR	MACE	LLL (mm)	Conclusion
Schulz et al[29]	39	DCB in both MB and SB (single arm observational study)	SeQuent Please or In.Pact Falcon®, (Medtronic, USA)	Binary restenosis at 4 months (10%)					DCB only PCI is safe
PEPCAD-BIF[30]	64	DCB (32) vs POBA (32) [RCT]	SeQuent® Please (B-Braun Germany	LLL		3.1% vs 9.4%		0.13 in DCB vs 0.51 in POBA $P = 0.013$	Better outcome of DCB after MB stenting than with POBA
Bruch et al.[31]	127	DCB only (70) vs DCB + BMS (57) [single arm observational study]	SeQuent® Please (B-Braun Germany)	Clinically driven TLR at 9 months	MACE	4.5% vs 3.6% $P = 0.80$	6.1% vs 7.3% $P = 0.789$		DCB-only strategy is safe & effective
Her et al[32]	16	DCB to MB with OCT to assess SB		SB ostial lumen area at 9 months (OCT) Mean gain: 0.6 ± 0.93 mm^2					DCB in MB results in ostial SB area
PEPCAD-V[33]	28	DCB in MB & SB followed by BMS in MB (4 received bailout stenting of SB)	SeQuent® Please (B-Braun Germany)	Cardiac Death, non fatal MI, TVR up to 1 year	BARC type 3 to 5 Bleeding. long-term outcome up to 3 years			LLL in MB: 0.38 ± 0.46 LLL in SB: 0.21 ± 0.458	DCB is feasible without increased early & late complications
DEBIUT[34]	120	DCB of MB & SB followed by BMS in the MB and DES in MB (RCT)	Dior I Eurocor® (Germany)	6 month LLL	6-month binary restenosis and 12-month MACE: death, MI, TVR		Similar rate of MACE (20%, 29.7% & 17.5%) for DCB, BMS & DES	(0.49 for DCB vs. 0.41 for BMS (p = NS) DES: superior outcome (LLL 0.19 mm)	Lack of angiographic superiority of DCB as compared to BMS,
Herrador et al.[35]	100	DCB in SB ($n = 50$) Vs POBA in bifurcations treated with T-stenting	SeQuent® Please (B-Braun Germany)			22% in POBA vs 12% in DCB($p = 0.16$)	24% in POBA vs 11% in DCB($p = 0.1$)	20% SB restenosis in DCB vs 7% in POBA ($p = 0.08$) LLL 0.40 mm vs 0.09 mm ($p = 0.01$)	
BABILON[3]	108	DCB in MB and SB + BMS in MB DES in MB	SeQuent® Please (B-Braun Germany)	In-segment LLL in the MB and SB at 9 months	MACE and TLR at 24-month		MACE (7.1 vs. 17.3%; $p = 0.105$).	0.31 ± 0.48 mm vs. 0.16 ± 0.38; $P = 0.150$	DCB + BMS has worse angiographic & clinical outcome comparde to DES
DEBSIDE[38]	50	DES in MB and DCB in SB	Danubio balloon	LLL at 6 months at ostium of SB	MB LLL, binary restenosis of the SB and MB.and clinically driven revascularisation rates for both	10% in MB. 2% in SB		SB LLL = 0.04 ± 0.34 mm MB LLL = 0.54 ± 0.60 mm	Good angiographic & clinical outcomes in SB
BIOLUX-I[39]	35	DCB in SB + DES in MB	Pantera Lux® (Biotronik AG)	LLL at 9 months	MACE and TVR	2.9%	5.9%	SB LLL of 0.10 ± 0.43 mm	DES in MB & DCB in SB is safe & effective
SARPEDON[40]	58	DES in MB + DCB in SB	Pantera Lux® (Biotronik AG)	Restenosis at 6 months	1-year TVR and MACE	3.0%	19%	0.21 ± 0.35 mm in MB 0.09 ± 0.21 mm in SB	Good result with DCB after DES in MB
Sgueglia et al.[41]	14	Provisional stenting with BMS and final KBI with Second generation DCB	SeQuent® Please (B-Braun Germany) In.Pact Falcon (Medtronic Invatec, Italy)	MACE: Cardiac Death, Nonfatal MI, & TVR.			Nil		Kissing DCB is safe & effective
Megaly et al.[42]	349	Metaanalysis. Outcomes of DCB vs POBA in the treatment of the SB		SB LLL, SB binary restenosis, TLR, and MACE rate		Similar TLR	Similar risk of MACE	Lower in DCB group	DCB rsults in lower SB LLL but no improvement in clinical outcome
BEYOND[45]	222	DES in the MB DCB vs POBA in the SB (RCT)	Bingo® (Yinyi Biotech, Dalian, China)	SB LLL @ 9 months	TLR, TVR, MACE	Similar TLR	Similar MACE	LLL lower in the DCB group than in the POBA (-0.06 ± 0.32 vs. 0.18 ± 0.34 mm, $P < 0.0001$)	In non-left main bifurcations treated with provisional T stenting, DCB in SB group demonstrated better angiographic results than treatment with regular BA

BARC, bleeding academic research consortium; BMS, bare metal stent; DCB, drug coated balloon, DES, drug-eluting stent; KBI, kissing balloon inflation; LLL, late lumen loss; MB, main branch; MACE, major adverse cardiac events; MI, myocardial infarction; OCT, optical coherence tomography; POBA, plain old balloon angioplasty; RCT, randomized controlled trial; TLR, target lesion revascularization, TVR, target vessel revascularization.

sequence of therapy with DCB for the SB is unclear at this time. In many cases, predilating the SB prior to applying DCB leads to dissection of the SB, which increases the risk of implanting another stent. On the other hand, DCB application after MB stenting would result in difficultly in its recrossing due to rigid profile and poor flexibility. Furthermore, crossing the stent strut may result in disruption of the coating with subsequent high drug wash-out.[13]

7. DCB in bifurcation ISR

Restenosis leading to TVR after provisional and two-stent strategies for bifurcation is still a significant issue, with rates from 5% to 15%. Earlier studies have shown that with a single stent strategy there is a trend towards increased TVR. Binary restenosis rates were considerably greater at 8 months when using a provisional method in DK Crush II trial.[46] Harada et al[47] studied the outcome with DCB PCI following ISR in a bifurcation treated with two stents (66% SB, 26% MB distal and 8% MB proximal). They evaluated two types of paclitaxel-coated balloon, with either an iopromide (iopromide-PCB) or a butyryl tri-n-hexyl citrate (BTHC-PCB) excipient and reported binary restenosis and MACE of 24% at 12 months follow up and there was no stent thrombosis. At 12 months, they reported binary restenosis and MACE of 24%, and there was no stent thrombosis in the research using two separate paclitaxel-coated balloons. Lesions treated with iopromide-PCB or BTHC-PCB showed no significant differences clinically or angiographically. The response was similar in those treated with final KBI versus without.

Lee et al,[48] have documented the outcomes of LM ISR with DCB and DES. One year since PCI with DCB in unprotected LM ISR, all-cause mortality and MACE were lower. Most patients had acute coronary syndrome with high prevalence of comorbidities such as diabetes, hypertension, and renal disease. Multi-vessel coronary artery disease was common in both groups of patients. DCB's efficacy in coronary ISR has been reported in several studies, with MACE rates ranging from 4.0 to 23.5%.[49–53] DCB might be utilized to treat ISR after bifurcation stenting with good outcomes across a spectrum of settings including acute coronary syndromes, LM bifurcation lesions, true bifurcation lesions and small SBs.

8. Proposed DCB strategies in bifurcation

Interventional cardiologists are still uncertain of the best way to treat coronary bifurcations. As there is now growing evidence supporting the use of DCBs in small vessel coronary disease,[28] it follows that DCBs would be an excellent treatment option for the SB lesions in coronary bifurcations. This has been demonstrated in the recent meta-analysis.[43] It is indeed fascinating to see the scarce data for a DCB-only bifurcation strategy. DCB was found to be superior than POBA in the PEPCAD-BIF[30] trial whether used in either the SB or distal MB, however it included both small and large vessels. Bruch et al,[31] added further strength to the data for a DCB-only strategy, with promising low MACE. When a DCB was utilized to treat MB, Her et al[32] observed an increase in the ostial SB area. This might attenuate the high rates of SB-ISR currently associated with bifurcation lesions.[54]

Based on this review, and the experience with the use of DCBs in bifurcation lesions, the author would suggest the following strategies to address a bifurcation lesion with a DCB strategy. If the operator's preference is a DES approach to the MB, a DCB for the SB can be utilized upfront (prior to stenting) if there is significant SB disease. DCB has been shown to be superior to POBA in a meta-analysis.[43] Another approach is proximal optimization technique (POT)-sideDCB-POT[55] method for true bifurcation lesions which adopts the recommendation of EBC[56] consisting of sequential approach to bifurcation stenting using the provisional strategy. The POT-sideDCB-POT is easy to perform and the geometry of all the three bifurcation segments is catered for by using this technique. It includes the following steps: the MB stenting based on distal reference vessel diameter, initial POT (balloon sized according to the MB dimension [mother vessel]), the SB rewiring through distal stent cell, the SB dilatation, the SB PCI with DCB in case of acceptable angiographic result after balloon inflation (of step 2) and no flow limiting dissections, and the rePOT to correct any carina shift and any malapposition because of stent strut attraction after the SB inflation.

A provisional MB approach with a DCB is a reasonable initial option if the operator's preference is a DCB only strategy, either due to anatomical or patient factors. From Her et al's OCT study,[32] if there is pinching of the SB ostium after application of DCB to the MB, there is no need to pursue this as the SB ostial lumen will increase due to positive remodeling. However, a sequential DCB to SB followed by the MB would be a reasonable approach, in case there is an indication to treat the SB too (e.g. long lesion, large vessel, significant territory supplied).[14] The DCB consensus guidelines[24] state that there are usually no need for KBI. However, this could be indicated is if there is loss of flow down either vessel after ballooning in order to restore carinal bifurcation geometry and integrity.

9. Limitations of DCB in bifurcation and future perspectives

Uncertainties persist so far as the best stenting strategy despite the increasing number of RCTs that have been conducted on DES strategies in bifurcation. However, the existing literature on DCB for bifurcation lesions is scarce. Bifurcation studies are difficult to interpret given the lesion variability which will influence outcomes and is neither easily describable nor accountable for. These factors include the bifurcation angle, significance of the SB, the extent of MB disease and the MB-SB size mismatch, none of which has been incorporated in Medina classification. The immediate recoil after balloon angioplasty cannot be overcome by DCB, which inhibits neointimal hyperplasia but not mechanical limitations.[57] Another issue is the lack of a good cost-effectiveness research. It is not clear regarding the most effective bifurcation technique: MB stenting first and final KBI with DCB; DCB use prior or after KBI; DCB use prior to MB stenting; DCB with rePOT; DCB with rePOT with distal optimization. Moreover, there are no clear data about the SB vessel size, considering that those with a diameter >2.75 mm have not yet been investigated.[58] At present, there is no direct comparison between the DCBs with different technologies with different device deliverability and drug uptake. Nevertheless, the concept of 'leaving nothing behind' is appealing like that of bioresorbable vascular scaffolds. Future studies hopefully will solve such unresolved conundrums.

10. Conclusion

Bifurcation lesions remain technically challenging for interventional cardiologists due to sub-optimal results, mainly at the SB. DCB represents a new revolution as an important tool in the field of PCI. Despite the lack of clinical data, the application of DCB in the treatment of bifurcation lesions in addition to provisional MB stenting could be an ideal strategy when SB stenting is not mandated. It avoids additional procedural risk related to complex two-stent techniques and reduces the risk of progression of the SB. DCB inhibits excessive neointimal hyperplasia following POBA, thus allowing for favourable vascular remodeling, eliminating the risk of stent thrombosis and reducing DAPT duration. This novel stentless technology is here to stay that might improve the short and long-

term outcome of bifurcation lesions, allowing a limited use of permanent prosthesis, especially at the SB. Based on limited data, the author recommends DCB for the treatment of the SB after provisional stenting of the MB with a new-generation DES. KBI is usually not necessary. It could be performed in case of loss of blood flow down the either vessel after ballooning in order to restore carinal geometry and integrity. POT-sideDCB-POT may be enough to cater the geometry of all the three bifurcation segments.

DCB application in the SB is feasible and safe, and warrants good angiographic and clinical outcome. However, larger adequately powered RCTs are warranted to further validate the role of DCB in such lesions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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