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EXPERT REVIEW

Drug-coated balloons for coronary bifurcation lesions

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ABSTRACT

Coronary bifurcation lesions (CBLs) represent a common and challenging subset of coronary artery disease requiring percutaneous coronary intervention (PCI). While drug-eluting stents (DES) remain the cornerstone of treatment, their use is associated with risks such as restenosis, thrombosis, side branch (SB) jailing and the need for prolonged dual antiplatelet therapy. Drug-coated balloons (DCBs) have emerged as a promising alternative, delivering antiproliferative drugs without permanent implants, thereby reducing the risk of late complications and preserving native vessel geometry. This review explores the role of DCBs in CBL management, particularly for SB treatment within the provisional stenting strategy. Evidence from clinical studies indicates that DCBs significantly reduce late lumen loss and restenosis in the SB compared to plain balloon angioplasty, while simplifying PCI procedures and avoiding extensive stenting. Furthermore, hybrid/blended strategies combining DCBs with DES have shown superior clinical and angiographic outcomes in true CBLs compared to DES-only approaches. Despite their potential, the adoption of DCBs faces challenges, including the need for optimal lesion preparation and a lack of standardised procedural techniques. Existing randomised controlled trials are limited by small sample sizes, design heterogeneity, inclusion of bare metal stents either as comparators or as part of the treatment strategy, and inconsistent use of key procedural steps such as proximal optimisation technique and kissing balloon inflation. This manuscript aims to provide interventional cardiologists with practical guidance for managing CBLs, focusing on the effective integration of DCBs into standalone and hybrid strategies. By emphasising procedural optimisation and complication reduction, this review seeks to promote more standardised and reproducible approaches in clinical practice.

Coronary bifurcation lesions (CBLs) are frequently encountered in routine clinical practice, accounting for approximately 20% of percutaneous coronary interventions (PCI)[1]. Bifurcation PCI are associated with lower procedural success rates and worse clinical outcomes compared to PCI in lesions without a bifurcation. Despite advancements in new-generation drug-eluting stents (DES), the use of permanent metallic implants comes with some potential drawbacks. On one hand, the requirement for prolonged dual antiplatelet therapy (DAPT) can pose risks, particularly in elderly patients and those deemed at high bleeding risk (HBR)[2]. On the other hand, a constant risk of long-term stent-related complications (i.e., in-stent restenosis, stent thrombosis, and neoatherosclerosis) with an incidence rate of approximately 2-3% per stent per year has been described with current-era devices[3].

Drug-coated balloons (DCBs) offer theoretical advantages in the setting of bifurcations when integrated into a single-stent provisional approach or as a standalone treatment. These include targeted antiproliferative drug delivery to the side branch (SB), reduced risk of neocarina and stent thrombosis due to the absence of stent struts, and avoidance of issues like stent malapposition and polymer deformation, which may impair the antiproliferative drug delivery[2].

KEYWORDS: coronary bifurcation lesions; drug-coated balloon; drug-eluting stent; high bleeding risk; percutaneous coronary intervention

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However, evidence supporting the use of DCBs in the context of CBLs remains limited and primarily focuses on their application for SB treatment. Furthermore, the use of DCBs for *de novo* lesions, including bifurcations, is not yet endorsed in current European and American guidelines[4]. This review aims to provide a practical overview of the DCB-based PCI techniques for CBLs.

DCB technologies and armamentarium

DCBs mainly differ in the type of antiproliferative drug eluted (i.e., paclitaxel [PTX] vs -limus) and in the coating (excipient) used to facilitate optimal drug release into the vessel wall. A detailed description of the technologies available for DCBs is beyond the scope of the present review, but some information is available in **Supplementary Appendix 1**.

Pivotal clinical trials have demonstrated angiographic non-inferiority of certain -limus technologies compared to PTX-eluting counterparts, while others have shown inferiority, in both cases of in-stent restenosis (ISR) and *de novo* lesions[5]. A recent meta-analysis including 1,861 patients showed angiographic superiority of PTX-coated balloons (PCBs; late lumen loss [LLL] –0.11 mm, 95% confidence interval [CI]: –0.23 to 0.02), while there was no significant difference in target lesion failure (TLF; odds ratio [OR] 1.01, 95% CI: 0.75-1.35)[6].

Old-generation PCBs faced limitations in navigability. New-generation and -limus-based devices are designed to provide enhanced navigability and performance. This is of particular importance in the setting of CBLs, where SB recrossing through main vessel (MV) struts can be challenging with bulky, old-generation devices.

By avoiding vessel caging, DCBs have been linked to the possibility of positive vessel remodelling. Paclitaxel, especially, has been seen to lead to an increased diameter in about 60% of the cases in *de novo* lesions, while the same phenomenon occurs to a lesser degree (about 30% of the cases) with sirolimus. In CBLs, the positive remodelling effect may be attenuated when a DCB is applied to the SB in the setting of provisional MV stenting. This is likely due to the presence of a jailed SB, where the mechanical constraint and altered vessel substrate resulting from stent struts across the SB ostium may limit the extent of positive vessel remodelling typically induced by the antiproliferative drug.

Rationale and advantages of DCB use in coronary bifurcations

The major advantages of DCBs are (1) homogeneous drug transfer to the vessel wall, with a rapid release of high concentrations of the drug that are sustained in the vessel wall for weeks; (2) the absence of inflammatory polymers and permanent implants, which reduces potential triggers for neoatherosclerosis and late thrombosis occurrence (e.g., metallic neocarina); (3) the absence of permanent implants, which spares the side branch from permanent jailing, preserves the native arterial geometry, and maintains physiological vasomotion; and (4) the possibility of DAPT de-escalation, both in terms of duration and $P2Y_{12}$ inhibition intensity.

According to the European Society of Cardiology and the European Bifurcation Club (EBC), the provisional stepwise approach, starting with the implantation of a stent in the MV across the SB, is considered the default strategy for CBLs[7,8]. The EBC recommends a "KISS" (keep it simple and safe) principle, which involves limiting the number of stents used.

MV-only stenting is recommended in most cases with provisional SB stenting, whereas a two-stent approach should be reserved for patients with complex lesions involving large and diseased SBs[7]. The EBC has emphasised DCBs as an area of interest in this scenario, recognising them as a valuable option to preserve a provisional strategy, particularly when the anatomy is suitable (e.g., in Medina 0,0,1 classification). Moreover, the international DCB consensus group has further endorsed the role of DCBs in CBLs[2]. Therefore, in the setting of CBLs, DCBs offer the following potential advantages.

Firstly, DCBs potentially increase the success of a provisional strategy, as compared to plain old balloon angioplasty (POBA)[9]. Secondly, DCBs reduce PCI complexity by respecting the original anatomy of the carina and reducing the need for a two-stent approach, and therefore the incidence of device-related failure. Thirdly, DCBs allow for the possibility of late lumen enlargement[10].

Lastly, SBs are often small vessels (with a diameter ≤2.75 mm), but subtending a non-negligible area of the myocardium, and importantly, DCBs have been repeatedly demonstrated to be non-inferior to DES in the treatment of small vessels[11-14].

How to use DCBs in coronary bifurcations

Before antiproliferative drug delivery to the treated segment, proper lesion preparation is key. Following relevant SB wire protection in accordance with EBC recommendations (reference vessel diameter ≥2.0 mm, >10% of the myocardium supply, ≥73 mm SB length)[15], accurate predilatation towards the MV and/or SB (if diseased) should be performed using a semi- or non-compliant (NC) balloon with a balloon-to-artery ratio of 1:1[2]. In the case of expansion failure of a standard balloon, high-pressure NC balloons, cutting, and/or scoring balloons should be used. In case of severe calcification, calcium debulking strategies (i.e., rotational atherectomy/intravascular lithotripsy) are recommended. For an isolated SB stenosis (Medina 0,0,1), a scoring/cutting

Abbreviations

ACS	acute coronary syndrome	**DES**	drug-eluting stent	**PCI**	percutaneous coronary intervention
BARC	Bleeding Academic Research Consortium	**ISR**	in-stent restenosis	**POT**	proximal optimisation technique
BMS	bare metal stent	**LLL**	late lumen loss	**PTX**	paclitaxel
CBL	coronary bifurcation lesion	**MACE**	major adverse cardiac events	**SB**	side branch
DCB	drug-coated balloon	**NC**	non-compliant	**TLR**	target lesion revascularisation

balloon is preferable to ensure a good predilatation result with controlled dissection and minimal recoil. SB predilatation before MV stenting is generally not recommended but may be useful in case of severe calcification, angulated side branch stenosis, difficult SB wiring, or compromised SB flow after wiring[15]. While it can help to maintain SB flow after MV stent implantation and facilitate rewiring by increasing the ostial SB lumen, it also increases the risk of SB dissection and may complicate further intervention[16].

DCB sizing should be performed at a balloon-to-vessel ratio of 0.8-1:1, with a recommended inflation time of at least 30-60 s to allow proper release of the drug, while inflating at low pressures (6-10 atm). Such pressures should not be exceeded, as the mechanical expansive properties of DCBs can pose a risk of dissection.

Although strong scientific evidence to support specific and standardised cutoffs is currently lacking, according to the consensus documents from the International DCB Consensus Group and the DCB Academic Research Consortium, a residual stenosis <30% (by visual estimation; <40% by quantitative coronary angiography) is considered acceptable following DCB therapy application, as well as non-flow-limiting dissections (not associated with Thrombolysis in Myocardial Infarction <3, prolonged electrocardiographic changes or angina)[2,4]. The role of physiological assessment or intravascular imaging in deciding to apply bailout stenting or not is still under debate, and a common expert consensus is not available yet. However, during provisional stenting, assessment of the jailed SB should be considered in cases of ostial "pinching" to determine the necessity of additional SB intervention[17]. Periprocedural measurements showing normal fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) in the jailed SB have been linked to favourable functional outcomes at follow-up, supporting a conservative management approach. Overall, functional evaluation of the jailed SB has been shown to reduce the need for SB stenting during provisional strategies[18].

LEAVE NOTHING BEHIND

A DCB-only approach to CBLs is appealing, as it theoretically avoids carina shift. The "leave nothing behind" strategy theoretically applies to the entire spectrum of CBLs if the predilatation result is satisfactory. However, evidence supporting the use of a DCB-only approach in *de novo* lesions, beyond small vessels, remains limited. Further studies are needed, particularly in large-calibre vessels and left main disease.

In case of Medina 0,0,1 CBLs with an isolated SB lesion, a simple approach with SB-only treatment can be considered, leaving the MV untouched **(Figure 1, Figure 2A)**.

In case of a disease-free SB (Medina 1,1,0; 0,1,0; 1,0,0), a DCB treatment of the MV across the SB should be considered **(Figure 1)**. In this approach, the ostium of a small, diseased SB may improve during follow-up.

In case of true CBLs (Medina 1,1,1; 1,0,1; 0,1,1), sequential DCB dilatation is recommended, starting in the SB and then in the MV **(Figure 2B, Figure 2C, Figure 3)**. Kissing DCB inflation should be avoided: firstly, this may increase the risk of dissections and perforation in the proximal MV not protected by a stent; secondly, it requires prolonged time in the blood with drug loss; and lastly, the proximal interaction between the two balloons does not enable proper concentric coverage of the vessel, with suboptimal drug delivery to the vessel wall[19].

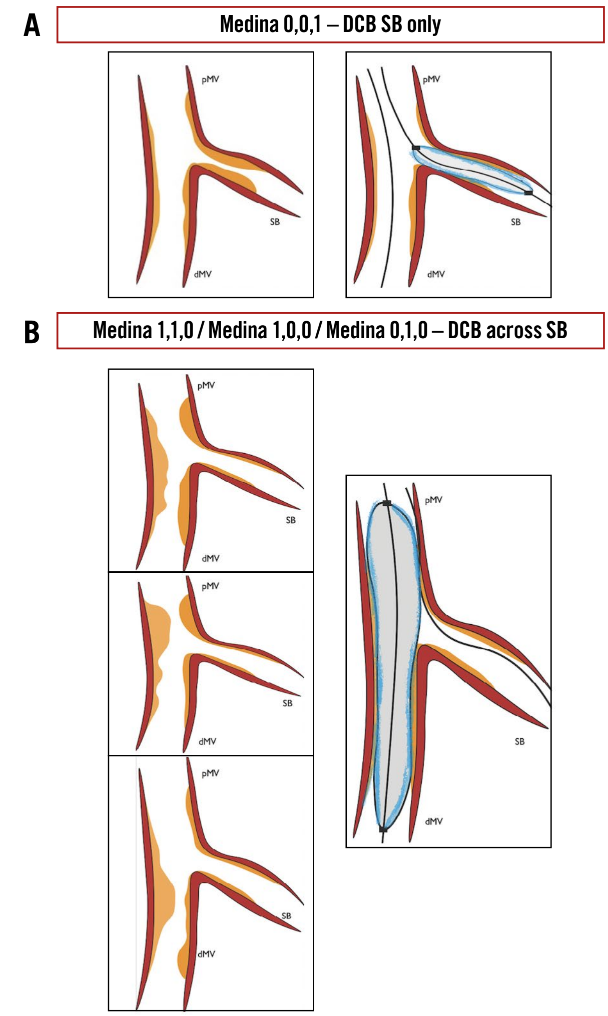

Figure 1. *Coronary bifurcation treatment with DCB only. A) DCB in the SB only is the preferred strategy in an isolated SB stenosis (Medina 0,0,1). Following MV and SB wiring and adequate lesion preparation (scoring and cutting balloons preferred), DCB inflation is applied specifically to the SB, extending the DCB 2 mm into the MV to ensure proper drug concentration in the ostium. B) DCB-only in the MV (DCB across the SB) is the approach that should be used for more complex lesions where both the MV and a small SB are involved. Following lesion preparation, DCB inflation is applied across the SB. DCB-only in both the MV and SB: sequential treatment of the SB first, then the MV with a DCB. In most cases, KBI is avoided. DCB: drug-coated balloon; dMV: distal main vessel; KBI: kissing balloon inflation; MV: main vessel; pMV: proximal main vessel; SB: side branch*

BLENDED APPROACH

The blended/hybrid approach to CBLs inherently integrates the use of DCBs in the provisional DES implantation philosophy, allowing for a reduction in the overall stent burden and

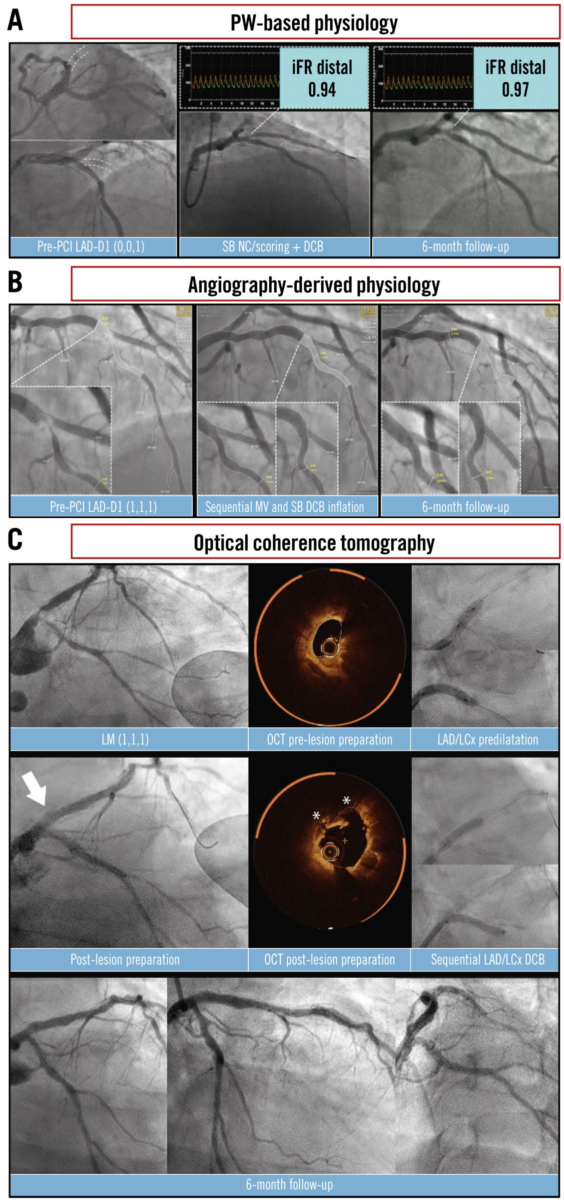

Figure 2. *Coronary physiology and intravascular imaging guidance for a DCB-only approach. A) A case of LAD-D1 CBL (Medina 0,0,1). After wiring both the MV and SB, lesion preparation was performed using a combination of non-compliant and scoring balloons. A 2.5×20 mm sirolimus-coated DCB was inflated in the SB to ensure optimal drug delivery at the ostium. Final physiological assessment with iFR showed a non-ischaemic value (iFR 0.94), which was further confirmed at follow-up (iFR 0.97). B) A case of LAD-D1 CBL (Medina 1,1,1), showing ischaemic values of single-view Murray law-based quantitative flow ratio in both the MV (μFR 0.35) and SB (μFR 0.74). Following successful wiring of both the MV and SB, lesion preparation was performed using a KBI technique with non-compliant balloons. Sequential inflations of paclitaxel-coated DCBs were then carried out in the MV (3.5×30 mm) and SB (2.5×20 mm), resulting in a favourable angiographic and functional outcome, with postprocedural μFR values of 0.86 in the MV and 0.97 in the SB. These results were further confirmed at elective follow-up (μFR 0.91 and 0.93, respectively). C) A case of a calcified left main coronary bifurcation lesion (Medina 1,1,1). OCT revealed circumferential calcium requiring plaque modification. Lesion preparation was performed using orbital atherectomy, followed by non-compliant and cutting balloons. After lesion preparation, OCT confirmed effective calcium modification with visible fractures (asterisks). Sequential inflations of paclitaxel-coated DCBs were then performed in the MV (3.5×15 mm) and SB (3.0×20 mm), resulting in favourable angiographic and OCT outcomes. Elective follow-up confirmed healing of dissections and positive vessel remodelling in both the LCx and LAD. CBL: coronary bifurcation lesion; D1: first diagonal branch; DCB: drug-coated balloon; iFR: instantaneous wave-free ratio; KBI: kissing balloon inflation; LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main; MV: main vessel; NC: non-compliant; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; PW: pressure wire; SB: side branch; μFR: Murray law-based quantitative flow ratio*

providing angiographic and clinical advantages compared to POBA alone. SB treatment with a DCB can be delivered either before or after DES implantation across the SB. In the former case, a DCB is first applied to the side branch, followed by DES implantation in the main vessel, after which the mandatory proximal optimisation technique (POT) is performed **(Figure 3, Figure 4A)**. In case of a suboptimal SB result, the procedure may be continued either with kissing balloon inflation (KBI) and re-POT or POT-side-POT inflations. Theoretically, these further inflations might interact with the antiproliferative drug that has already been delivered to the SB.

In the latter case, DCB treatment is performed as a final step following DES implantation across the SB, POT, SB rewiring and dilatation, DCB application to the SB, followed by optional KBI and mandatory final re-POT **(Figure 4B, Figure 5)**. It has been postulated that such an approach might be associated with suboptimal drug delivery, as the interaction with the DCB and stent struts might lead to drug loss and hamper proper drug delivery to the SB. Furthermore, the deliverability of cutting or scoring balloons, which is inherently limited because of their device profile and mechanical characteristics, is further compromised in the setting of a jailed SB, potentially affecting

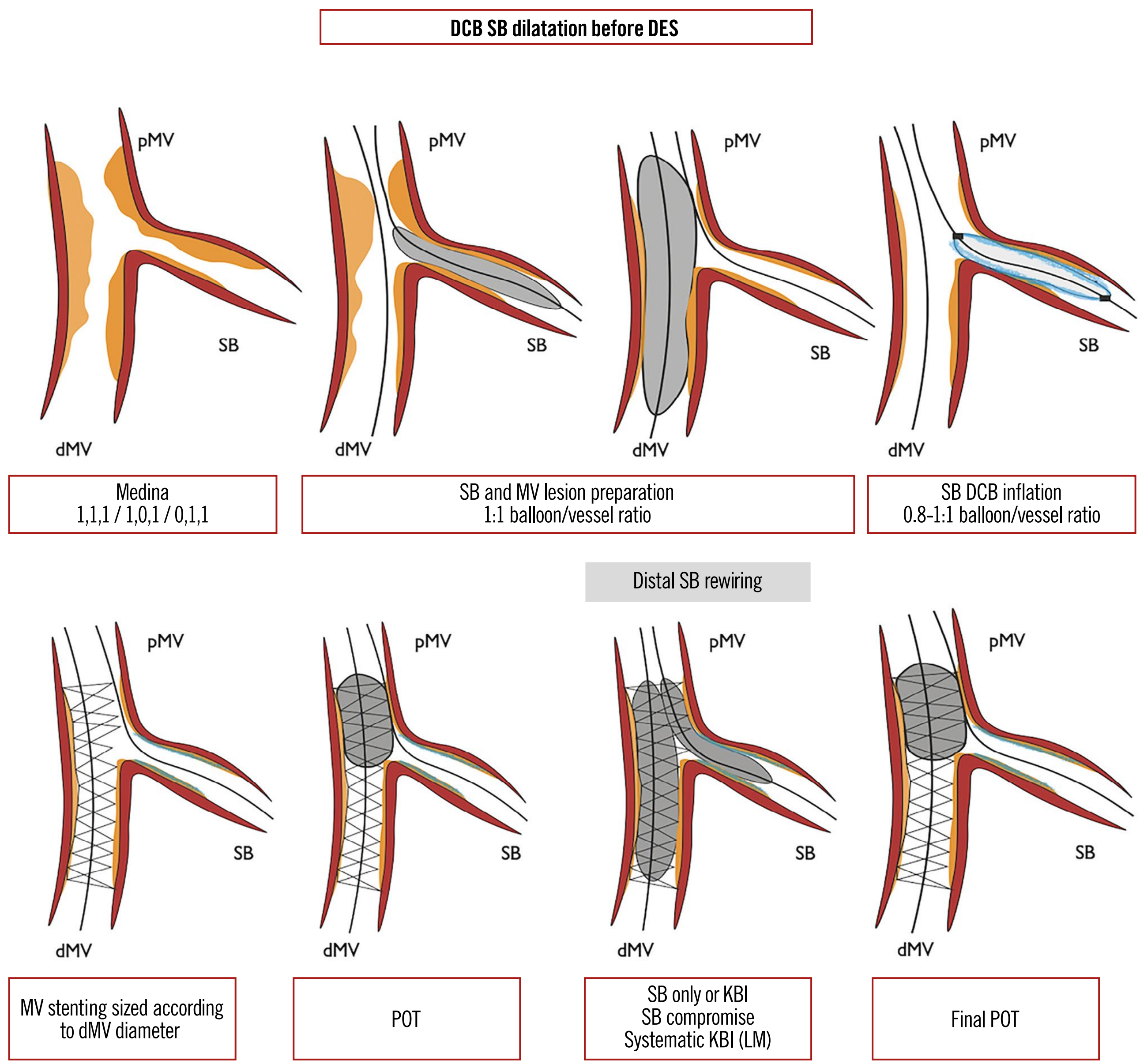

Figure 3. *Side branch treatment with a DCB before provisional DES implantation. In case of a true CBL, DCB inflation towards the SB is performed after lesion preparation in both branches and followed by provisional DES implantation towards the MV. POT is then performed. In case of a suboptimal result (i.e., SB compromise) or a need for systematic KBI (i.e., left main bifurcation), SB distal rewiring is performed, followed by either POT-side-POT or KBI and final POT. CBL: coronary bifurcation lesion; DCB: drug-coated balloon; DES: drug-eluting stent; dMV: distal main vessel; KBI: kissing balloon inflation; LM: left main; MV: main vessel; pMV: proximal main vessel; POT: proximal optimisation technique; SB: side branch*

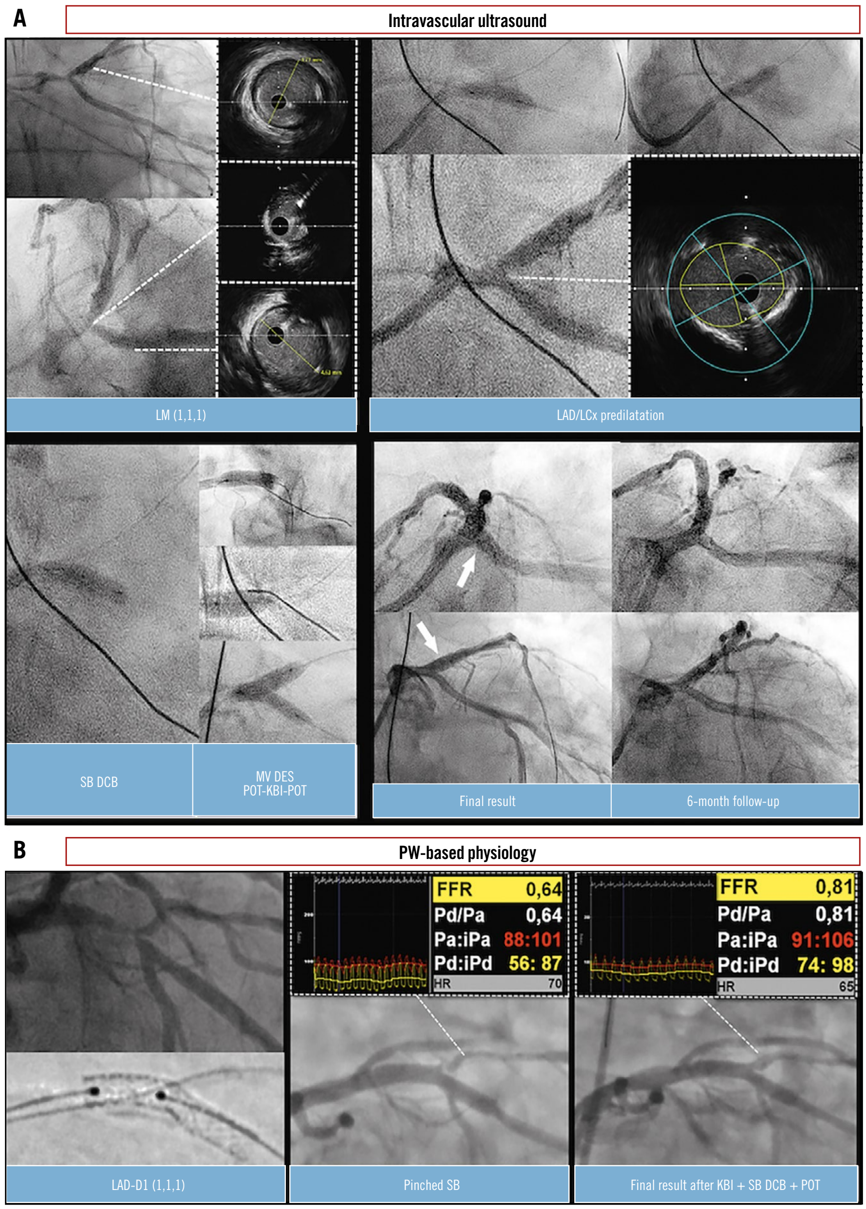

Figure 4. *Coronary physiology and intravascular imaging guidance for a DCB/DES blended approach. A) A case of LM CBL (Medina 1,1,1). IVUS initially revealed a significant stenosis at the ostium of the LCx. Lesion preparation was performed using a 4.0 mm cutting balloon to predilatate the LAD, LCx, and LM. Following predilatation, the IVUS result in the LCx was deemed satisfactory, with restored flow and less than 30% recoil. However, IVUS assessment indicated unacceptable recoil in the LM segment. A 4.0×15 mm paclitaxel-coated DCB was first applied to the LCx for 30 seconds. Subsequently, a provisional DES implantation (5.0×16 mm) was performed from the LM ostium into the LAD. POT was then performed using a 5.5×6 mm NC balloon, followed by KBI (4.0 mm in the LAD, 3.5 mm in the LCx) and final POT. The final angiographic and IVUS results were satisfactory, showing minimal lumen areas of 14 mm² in the LAD, 7.7 mm² in the LCx, and 19.5 mm² in the LM. Three-month follow-up angiography confirmed a durable and favourable result of this blended approach. B) A case of LAD-D1 CBL (Medina 1,1,1). Following lesion preparation of the MV with NC balloons, a DES (3.5×22 mm) was implanted across the D1 using a provisional approach. POT was then performed with a 4.0×8 mm NC balloon. Subsequent angiography revealed a pinched SB with ischaemic FFR values (FFR 0.64) in the D1. After rewiring the SB, KBI was performed using 3.0 mm and 2.5 mm NC balloons, followed by inflation of a paclitaxel-coated DCB (2.5×20 mm) in the SB and the mandatory final re-POT. This strategy resulted in a favourable angiographic outcome and marked functional improvement, with FFR increasing to 0.81. CBL: coronary bifurcation lesion; D1: first diagonal branch; DCB: drug-coated balloon; DES: drug-eluting stent; FFR: fractional flow reserve; IVUS: intravascular ultrasound; KBI: kissing balloon inflation; LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main; MV: main vessel; NC: non-compliant balloon; POT: proximal optimisation technique; PW: pressure wire; SB: side branch*

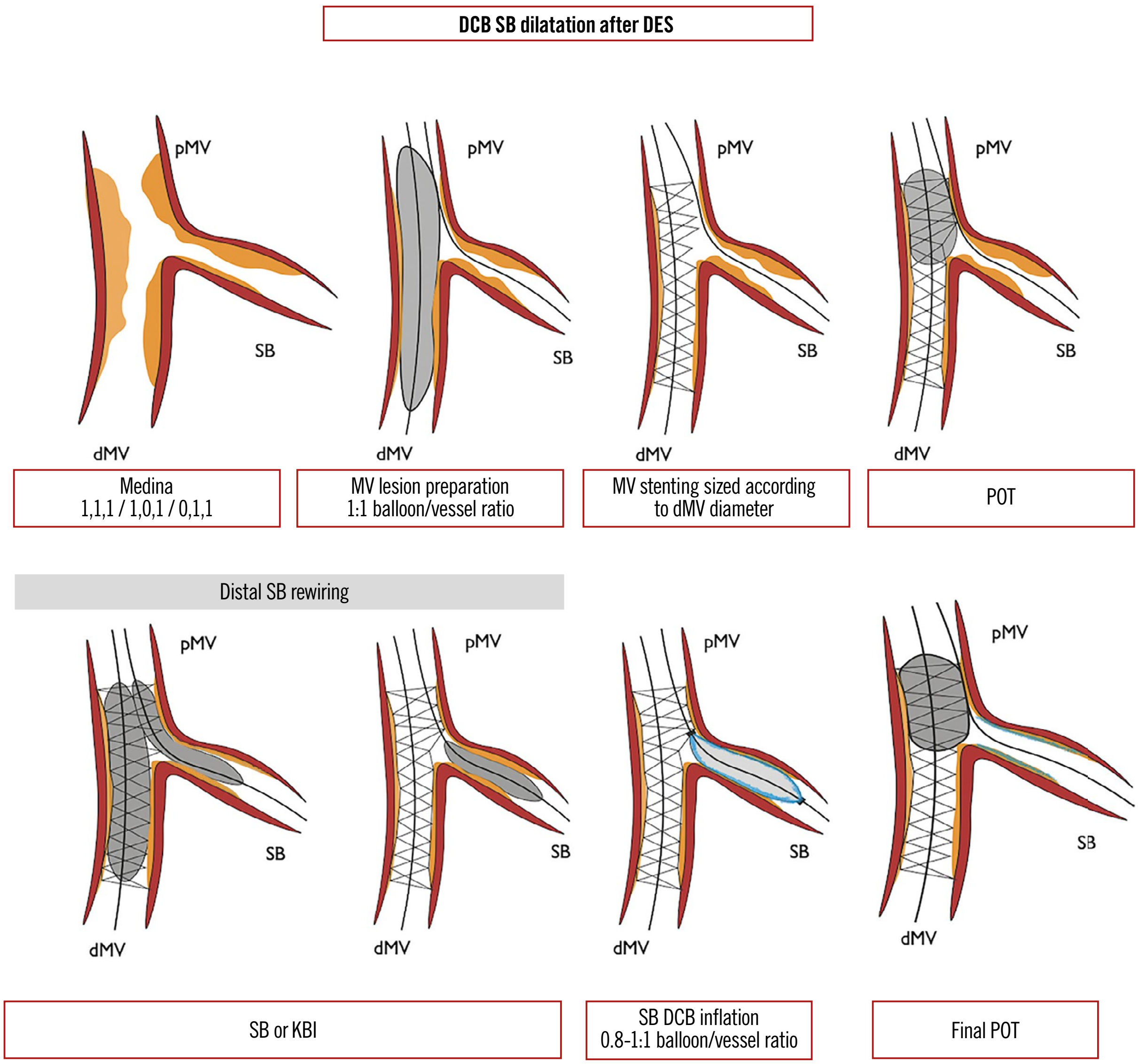

Figure 5. *Side branch treatment with a DCB after provisional DES implantation. In case of a true CBL, DCB inflation towards the SB is performed as a final step following provisional DES implantation across the SB, POT, and SB dilatation to prepare the lesion and open the struts for the DCB. Final POT is mandatory. CBL: coronary bifurcation lesion; DCB: drug-coated balloon; DES: drug-eluting stent; dMV: distal main vessel; KBI: kissing balloon inflation; pMV: proximal main vessel; POT: proximal optimisation technique; SB: side branch*

adequate lesion preparation. It should be noted that the timing and sequence for DCB use in bifurcation PCI remain topics of ongoing debate, as robust evidence to guide these decisions is currently limited. Current recommendations are largely based on expert opinion and clinical experience, emphasising the need for further large prospective randomised studies to establish more definitive guidance.

Available evidence

DCB TO THE MAIN VESSEL (DCB-ONLY STRATEGY)

Few, relatively small studies have investigated the use of DCBs in the treatment of the MV. In a prospective, observational, single-centre study, Schulz et al[20] investigated the feasibility and early safety of a DCB-only (PTX; SeQuent Please [B. Braun]) approach in the management of CBLs. Thirty-nine patients with *de novo* CBLs and an SB ≥2 mm were included; one-third of these cases were left main (LM) bifurcations. Low rates of 4-month angiographic restenosis (3.3% in the SB and 6.7% in the MV) and of major adverse cardiac events (MACE; 7.7%) were observed.

Bruch et al[21], in an observational, multicentre registry, assessed the feasibility of a DCB-only strategy (PTX; SeQuent Please) in the treatment of CBLs of any Medina class with an SB >2 mm. Almost half of all treated bifurcations were Medina type 1,1,1, followed by Medina type 0,1,1. Bailout stenting with a bare metal stent (BMS) was performed in the MV and/or the SB in case of flow-limiting dissections and/or excessive angiographic acute recoil. Overall, 127 patients were enrolled

(130 lesions): 53.8% underwent a DCB-only strategy; in 34.6%, one BMS was implanted in the MV; in 8.5%, a BMS was implanted in the SB; and in 3.1%, two stents (MV and SB) were implanted. At 9 months, the target lesion revascularisation (TLR) rate was 4.6% in the absence of any thrombotic events in the treated vessels, with a MACE rate of 6.2%. PCB inflation in the MV appears to induce beneficial late luminal enlargement, as it does in the SB ostium, as shown using optical coherence tomography (OCT)[22]. Ke et al randomised 60 patients with true bifurcation lesions either to a standard two-stent strategy or DCB-only strategy (PTX; SeQuent Please)[23]. LLL at 12 months was significantly lower with the DCB-only approach both in the MV and the SB (0.05±0.24 mm vs 0.25±0.35 mm; p=0.013 and −0.02±0.19 mm vs 0.11±0.15 mm; p=0.005, respectively), displaying positive remodelling in the SB. In the recent CAGE-FREE 1 randomised clinical trial, DES implantation proved superior to DCB-only PCI (PTX-coated Swide DCB [Shenqi Medical]) for non-complex lesions in an all-comers population. Notably, in subgroup analyses of non-true bifurcations and small vessels, both treatment strategies showed comparable outcomes[24].

DCB TO THE SIDE BRANCH

Several studies investigated the feasibility and safety of DCBs used for SB treatment in the context of provisional MV stenting. The superiority of DCBs compared to POBA for SB treatment in the context of provisional MV stenting has been confirmed by two meta-analyses[25,26]. In particular, Zheng et al[26] included 934 patients from 10 studies (five randomised controlled trials [RCTs]), showing that DCB treatment of the SB is associated with lower LLL, smaller diameter stenosis and a lower rate of binary restenosis at the elective angiographic follow-up, as compared to POBA. The rate of MACE was significantly lower in the DCB group at 9 months (OR 0.21, 95% CI: 0.05-0.84; p=0.03) and 12 months (OR 0.45, 95% CI: 0.22-0.90; p=0.02). However, DCB treatment was not associated with a reduced incidence of TLF. Notably, several studies providing preliminary evidence in favour of DCB treatment of the SB are hampered by the combined implantation of a BMS to the MV. These data are reported in detail in **Supplementary Appendix 1**. A comprehensive overview of the angiographic outcomes of SB treatment with DCBs as compared to POBA is summarised in **Figure 6**.

DCB TO THE SB BEFORE PROVISIONAL STENT IMPLANTATION IN THE MV

In the pilot, single-arm, observational DEBSIDE trial[27] (n=52 patients), DCB dilatation (PTX; Danubio [Minvasys]) of the SB was performed first, followed by a DES towards the MV and final kissing balloon with plain old balloons. Based on a population of 52 patients, such an approach was seen to be feasible and safe, with a negative LLL (−0.04±0.34 mm) and no restenosis in the SB at the elective angiographic follow-up at 6 months. The incidence of TLR was 10% in the MV and 2% in the SB.

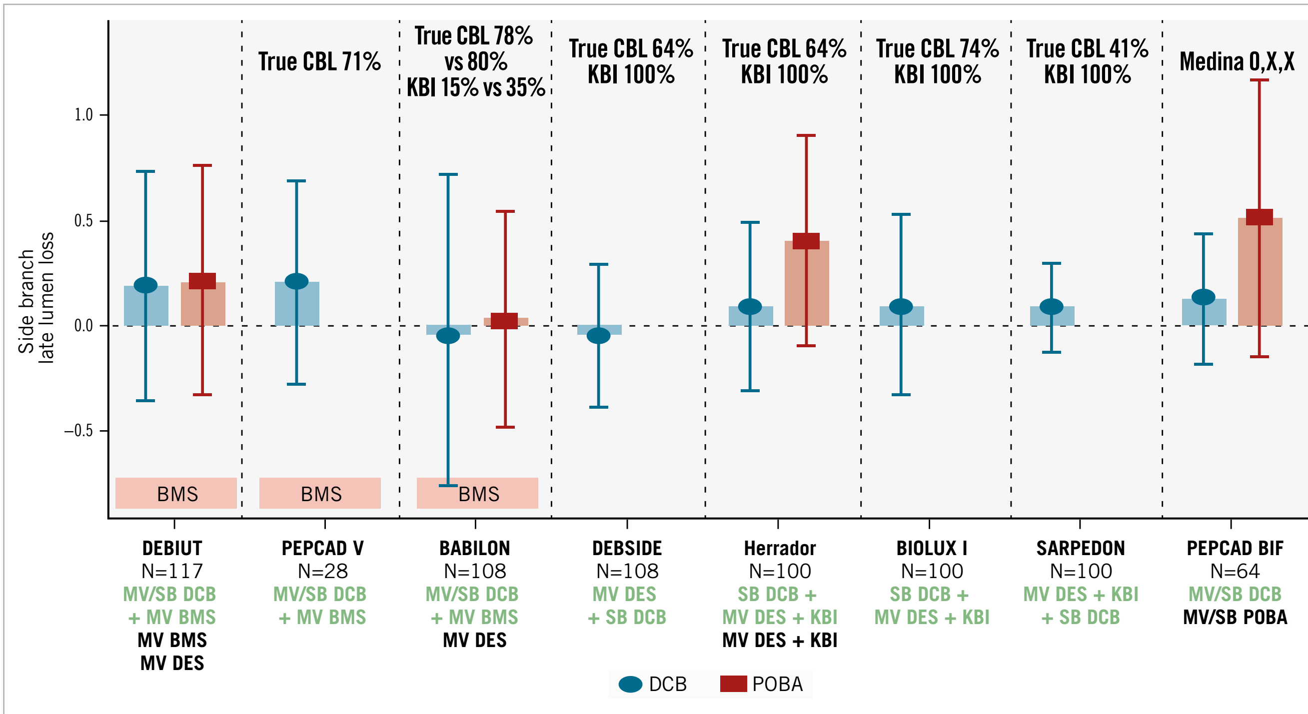

Figure 6. *Angiographic outcomes of SB treatment with DCBs as compared to POBA. Angiographic late lumen loss of the side branch following DCB (blue) or POBA (red) treatment in randomised clinical trials and registries. The rate of true CBL and KBI is reported at the top. The number of patients included, the DCB strategy adopted (green), and the comparator (black) are reported at the bottom. DEBIUT, PEPCAD V, and BABILON combined the use of DCBs and BMS, with DCB inflation both towards the SB and the MV before stent implantation in the MV. BMS: bare metal stent; CBL: coronary bifurcation lesion; DCB: drug-coated balloon; DES: drug-eluting stent; KBI: kissing balloon inflation; MV: main vessel; POBA: plain old balloon angioplasty; SB: side branch*

A similar approach was evaluated in the single-arm, observational BIOLUX-I[28] trial that included 35 patients with CBLs. SB dilatation with a DCB (PTX; Pantera Lux [Biotronik]), performed before MV stenting, was associated with good angiographic LLL (at 9 months 0.10±0.43 mm) and clinical results (12-month vessel-oriented composite endpoint 2.9%). The limitation of the DEBSIDE and BIOLUX-I studies was that there was no control treatment (i.e., POBA or DES in the SB).

DCB TO THE SB AFTER PROVISIONAL STENT IMPLANTATION IN THE MV

Herrador et al[29], in a prospective, observational, non-randomised study including 100 patients, compared treatment of the SB with a DCB (PTX; SeQuent Please) or with POBA, after DES implantation in the MV. The use of a DCB in the SB was associated with better angiographic outcomes, in terms of LLL (0.09±0.40 mm vs 0.40±0.50 mm; p=0.01) and a lower incidence of restenosis (7% vs 20%; p=0.08) at 12 months.

This was confirmed in the single-arm, observational SARPEDON[30] study and further in the PEPCAD-BIF[31], BEYOND[32] and in the recent large DCB-BIF[33] RCTs. In the SARPEDON[30] study, 64 patients were randomised to either a DCB (PTX; SeQuent Please) or POBA treatment of the SB after DES implantation to the MV. The study included only CBLs without disease in the proximal MV (Medina 0; X; X) and mainly included small vessels (mean reference vessel diameter 2.4 mm). DCB treatment in the SB was associated with superior angiographic results at 9 months, both in terms of LLL (0.13±0.31 vs 0.51±0.66; p=0.045) and ISR occurrence (6% vs 26%; p=0.045) as compared to POBA.

The multicentre BEYOND[32] 1:1 RCT (n=222 patients) demonstrated that SB dilatation with DCB (PTX; Bingo [Yinyi Biotech]) after MV provisional stenting in non-left main CBL was associated with superior angiographic results at 9 months (degree of stenosis 28.7±18.7% vs 40±19%; p=0.001), but comparable clinical outcomes (MACE rate 0.9% vs 3.7%; p=0.16) as compared to POBA alone.

The blended use of DCBs and DES in the setting of *de novo* LM true CBLs is particularly intriguing. In a recent real-world multicentre, propensity-matched study including 597 patients, the blended use of a DES+DCB was associated with lower rates of clinically driven TLR (2.91% vs 9.42%; p=0.007), TLF (9.60% vs 17.14%; p=0.026), and stent thrombosis (0.00% vs 2.89%; p=0.030) at 2 years, as compared to a DES-only strategy (provisional stenting or two-stent strategies)[34].

The recent DCB-BIF trial[33] is the largest RCT assessing the clinical performance of SB treatment with DCB in comparison to non-compliant balloons, in true non-complex bifurcation lesions undergoing provisional stenting. Overall, 784 patients with true coronary bifurcation lesions were enrolled and randomised to DCBs (n=391) or NC balloons (n=393). DCB treatment demonstrated superiority compared to non-compliant balloon POBA, by reducing the risk of MACE at 12 months (7.2% vs 12.5%, hazard ratio 0.56, 95% CI: 0.35-0.88; p=0.013), primarily attributed to a reduction in myocardial infarction. No significant differences were observed between groups in procedural success, crossover to a two-stent strategy, all-cause mortality, revascularisation, or stent thrombosis. Interestingly, despite this difference in MI, TLR rates remained similar between the groups. Upon critical review, the higher number of MIs in the non-compliant POBA arm may be attributed to early, predominantly periprocedural events that did not lead to revascularisation. Secondly, the observed benefit of DCBs may stem not only from the pharmacological action of paclitaxel but also from longer balloon inflations, which may reduce acute recoil, dissection, adjunctive procedures, and late restenosis.

Despite several limitations related to heterogeneity in terms of study design, inclusion/exclusion criteria, type of DCBs and DES used, the available evidence supports the use of DCBs in the setting of provisional stenting of CBLs when a balloon dilatation of the SB is planned (i.e., kissing balloon, POT-side-POT). In the setting of LM PCI, the available evidence is still limited. Liu et al retrospectively enrolled 100 patients with true LM bifurcation lesions that were divided into two DES groups (both MV and SB) as well as a DES in MV and DCB in SB group[35]. At the elective angiographic follow-up, the minimal lumen diameter in the left circumflex coronary artery (LCx) ostium was higher in the DES+DCB group than in the two DES groups. LLL was lower in the LCx ostium in the DES+DCB group than in the two DES groups (p<0.05). The incidence of MACE was similar in the two groups. In a substudy of the HYPER trial, 50 patients with true CBLs were treated with the hybrid strategy (i.e., DES in MV and DCB in SB) suggesting that such a blended/hybrid strategy is a safe and effective alternative to two stents in true CBLs[36].

A comprehensive overview of the available studies on DCB treatment for CBLs is provided in **Table 1**, while ongoing clinical trials are reported in **Table 2**.

Specific subsettings

ACUTE CORONARY SYNDROMES

Preliminary data suggest that a DCB-only strategy may be feasible and safe in selected patients with acute coronary syndromes (ACS). Subgroup analyses of large trials and observational registries have shown that, when used after proper lesion preparation, DCBs yield comparable outcomes to DES[37]. In bifurcation settings, DCB use has mainly involved the MV, with limited data specifically addressing SB treatment. Given the potential issues related to thrombus burden and drug delivery, further research is needed to define the optimal use of DCBs in bifurcated lesions during ACS.

DIABETES MELLITUS

Diabetic patients often present with complex, diffuse disease and higher restenosis risk, especially in small vessels and bifurcations. Although no RCTs have specifically investigated DCB use in bifurcation PCI in diabetic patients, the stent-sparing nature of DCBs and their favourable outcomes in small vessels suggest they could be beneficial in this high-risk population. Dedicated studies are needed to confirm this hypothesis.

HIGH BLEEDING RISK

DCB-based strategies are particularly appealing in HBR patients due to the potential for stent-free revascularisation and DAPT de-escalation[38,39]. In bifurcation lesions, using DCBs in the SB or within hybrid strategies can help minimise stent length and reduce the bleeding risk associated with prolonged DAPT. Observational data and the recent REC-CAGEFREE II trial[40] support the safety of abbreviated

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Table 1. Randomised clinical trials and registries on the use of DCBs in CBLs.

Study name, year	Study reference	Design	DCB	Comp	n	Inclusion	DCB treatment strategy	Predilatation, %	Intravascular imaging, %	KBI, %	POT, %	Bailout stenting	Primary endpoint	Angiographic follow-up (*p*-value)*	MACE (*p*-value)	TLR (*p*-value)
DEBIUT, 2012	NCT00857441	1:1:1 RCT Open-label, superiority Multicentre Core lab CEC Provisional T Arms: MV DCB+BMS and SB DCB MV BMS+POBA SB MV DES+POBA SB	DIOR[a]	PES	117	CCS, UA, ischaemia *De novo* (DS 50-100%) RVD >2.5 mm in MV >2 mm in SB	Direct DCB dilatation in MV and SB	-	-	100	-	10 vs 5 vs 5 (0.68)	6M LLL	6M MV LLL 0.58±0.65 vs 0.60±0.65 vs 0.13±0.45 (0.87) SB LLL 0.19±0.55 vs 0.21±0.57 vs 0.11±0.43 (0.92) Restenosis 24 vs 28 vs 15 (0.79)	12M 20 vs 29 vs 17 (0.32)	12M 20 vs 27 vs 15 (NS)
BABILON, 2014	NCT01278186	1:1 RCT Open-label, non-inferiority Multicentre Provisional T Arms: MV DCB+BMS and SB DCB MV DES+POBA SB	SeQuent Please[b]	EES	108	CCS, UA, ischaemia *De novo* (DS 50-100%) RVD >3 mm in MV >2 mm in SB	Direct DCB dilatation in MV and SB	-	-	26	-	7.8 vs 8.9 (1.0)	6M LLL	9M MV LLL 0.31±0.48 vs 0.16±0.38 (0.15) SB LLL −0.04±0.76 vs 0.03±0.51 (0.98) Restenosis MV/SB: 13/6 vs 1.8/3.6 (0.027/0.67)	9M 17.3 vs 7.1 (0.11)	9M 15.4 vs 3.6 (0.045)
PEPCAD V, 2011	46	Observational, prospective Dual centre Pilot Core lab CEC Single arm: MV DCB+BMS and SB DCB	SeQuent Please[b]	-	28	CCS or UA or ischaemia *De novo* (DS >70% or >50% with ischaemia) RVD 2.5-3.8 mm in MV 2-3.5 mm in SB Lesion length <20 mm	Direct DCB dilatation in MV and SB	-	-	8	-	14.3	9M LLL	9M MV LLL 0.38±0.46 SB LLL 0.21±0.48 Restenosis MV/SB: 3.8/7.7	9M 10.7	9M 3.8
Herrador, 2013	29	Comparative, observational, non-randomised cohort Single centre Autonomous QCA Provisional T Arms: MV DES and SB DCB MV DES	SeQuent Please[b]	TAXUS[c]	100	DS >50% in MV and SB RVD >2.5 mm in MV >2.5 mm in SB SB lesion length <10 mm	Direct DCB dilatation in SB	-	97 (IVUS)	100	-	-	12M LLL	12M MV LLL 0.49±0.6 vs 0.62±0.7 (0.39) SB LLL 0.09±0.4 vs 0.4±0.5 (0.01) Restenosis MV/SB: 12/7 vs 18/20 (0.44/0.08)	12M 11 vs 24 (0.76)	12M 12 vs 20 (0.16)

DEBSIDE, 2015	27	Observational Multicentre Core lab CEC Provisional T Single arm: SB predilatation followed by MV DES and KBI and final SB DCB	DANUBIO[d]	Nile PAX[d]	52	CCS or UA or ischaemia RVD 2.5-3.5 mm in MV 2-3 mm in SB SB lesion length <6 mm	DCB final dilatation in SB (after provisional T)	MV 100 SB 80	-	80	-	Excluded	6M LLL	6M MV LLL 0.54±0.6 SB LLL −0.04±0.34 Restenosis MV/SB: 0/0	6M 10	6M 8
BIOLUX-I, 2015	28	Prospective Multicentre Pilot Single arm: DCB dilatation to SB and DES to MV, final KBI with POBA	Pantera Lux[e]	-	35	DS >50% RVD 2-4 mm in MV	DCB for SB treatment after predilatation	MV 97	-	100	-	11.4	9M LLL	9M MV LLL 0.28±0.59 SB LLL 0.10±0.43 Restenosis MV/SB: 0/0	12M 6	12M 2.9
SARPEDON, 2015	30	Prospective, observational cohort Single centre Autonomous QCA Single arm: DCB in SB after provisional DES and KBI	Pantera Lux[e]	-	58	*De novo* DS >50% in MV or SB RVD >2.25 mm in MV >2 mm in SB	-	-	8.6 (IVUS)	-	-	Excluded	6M LLL	6M MV LLL 0.21±0.35 SB LLL 0.09±0.21 Restenosis MV/SB: 4/6	12M 19	12M 5.2
Schulz, 2014	20	Prospective, observational Single centre Single arm: DCB in SB, MV, SB/MV	SeQuent Please[b]	-	39	*De novo* after appropriate predilatation with 0.8/1:1 balloon (DS <30% MV, <75% SB) RVD Any	-	100	-	-	-	12.8	4M ISR	4M Restenosis MV/SB: 6.7/3.3	4M 7.7	4M 7.7
PEPCAD-BIF, 2016	31	1:1 RCT Prospective Multicentre Provisional DES After successful predilatation (recoil <30%, diss <C), randomisation to arms: SB DCB SB POBA	SeQuent Please[b]	POBA	64	CCS or UA, ischaemia *De novo* Medina 0,0,1 or 0,1,1 RVD 2.0-3.5 mm in SB SB lesion length <10 mm	DCB for SB treatment after predilatation	100	-	-	-	0	9M LLL	9M LLL 0.13±0.31 vs 0.51±0.66 (0.045) ISR 6 vs 26 (0.045)	-	-
Okutsu, 2022	47	Observational Single centre Direct coronary atherectomy+DCB LM 59% Autonomous QCA/IVUS/OCT	SeQuent Please[b]	-	25	*De novo* true CBLs of proximal left coronary RVD >3 mm in MV >2 mm in SB	-	-	96 (OCT)	-	-	5	In-hospital MACE	3M LLL 0.2±0.6	0	0
DCA/DCB, 2020	48	Retrospective registry Multicentre Direct coronary atherectomy+DCB in bifurcation LM 81%	SeQuent Please[b]	-	129	Major CBLs (SB >2 mm) suitable for DCA delivery RVD >2 mm in SB	-	-	-	-	-	-	12M TVF	6-15M LLL 0.29±0.51 ISR 2.3	12M TVF 10.9	12M 3.1

Table 1. Randomised clinical trials and registries on the use of DCBs in CBLs (cont'd).

Study name, year	Study reference	Design	DCB	Comp	n	Inclusion	DCB treatment strategy	Predilatation, %	Intravascular imaging, %	KBI, %	POT, %	Bailout stenting	Primary endpoint	Angiographic follow-up (*p*-value)*	MACE (*p*-value)	TLR (*p*-value)
BEYOND, 2020	32	Prospective RCT Multicentre DCB vs POBA in non-LM bifurcations after provisional with DES in MV (1:1 randomisation after predilatation) Arms: SB DCB SB POBA	Bingo PCB[f]	POBA	222	CCS or UA, ischaemia, old MI *De novo* CBLs with SB DS >70%, <50% after predilatation RVD 1.25-5 mm in SB Lesion length <40 mm	DCB for SB treatment after predilatation	MV 93.2 SB 82.9	-	100	-	0	9M DS	9M DS 28.7±18.7 vs 40±19 (0.001 superiority)	9M 0.9 vs 3.7 (0.16)	-
Ke et al, 2023	23	RCT Single centre True CBLs Arms: DCB-only PCI Two DES	SeQuent Please[b]	DES	60	*De novo* true CBLs Medina type 1,1,1; 0,1 1; 1,0,1 RVD >2.25 mm in SB	DCB-only strategy for true CBLs after predilatation	100	-	63	-	0	12M LLL	12M MV LLL 0.05±0.24 vs 0.25±0.35 (0.013) SB LLL −0.02±0.19 vs 0.11±0.15 (0.005)	0	12M 10%
SPARTAN-LMS, Gunawardena et al, 2023	49	Retrospective, propensity-matched Single centre DCB-only vs DES in LM	SeQuent Please[b]	DES	148	Primary lesion treated in the LM	DCB-only strategy for LM	-	64.9 (OCT/IVUS)	-	-	1	All-cause mortality	-	-	34M 7.3 vs 8.3 (0.86)
Uskela et al, 2023	50	Retrospective Single centre Single arm: DCB-only in LM	Paclitaxel DCB	-	66	-	-	-	-	-	-	-	12M MACE	-	12M 24	12M 6
Liu et al, 2022	51	Retrospective Single centre LM PCI Arms: DES in MV + DCB in SB 2 DES strategy	Bingo[f] paclitaxel+iohexol matrix	DES	85	LM >50% DS	SB DCB (LCx) in the treatment of left main bifurcation lesions	100	28 (IVUS)	100	100	-	12M MACE	LLL DES+DCB vs 2DES LM 0.09 vs 0.17 (0.037) LAD 0.16 vs 0.16 (0.385) LCx −0.17 vs 0.43 (0.001)	12M 10	12M 9
Her et al, 2016	22	Prospective Single centre Single arm: DCB-only in isolated SB	SeQuent Please[b]	-	16	-	-	-	-	-	-	-	9M SB ostial lumen area (OCT)	-	-	-
Vaquerizo et al, 2016	52	Prospective Single centre Single arm: DCB-only in isolated SB	DIOR[a]	-	49	CCS with ischaemia *De novo* Medina 0,0,1 RVD >2 mm in SB	DCB for SB treatment after predilatation	100	-	-	-	14.3	12M MACE	7-8M LLL 0.32±0.73	12M 16	12M 14
Bruch et al, 2016	21	Prospective Multicentre Single arm: DCB-only vs DCB+BMS	SeQuent Please[b]	BMS	127	CCS and ischaemia, UA Any Medina RVD >2 mm in SB	DCB treatment after predilatation	MV 86.9 SB 73.8	-	-	-	46	9M TLR	9M ISR 4.5 vs 5.5	9M 6.6 vs 6.1	9M 4.5 vs 3.6

EASTBOURNE-BIF, 2024	NCT03085823	Substudy Prospective, observational Multicentre Single arm: DES in MV and DCB in SB or DCB-only	MagicTouch[g] sirolimus+ phospholipid	-	194	Bifurcation lesion from EASTBOURNE registry	DCB for SB treatment after predilatation	-	-	-	-	19	12M TLR	-	12M 8.8	12M 4.2
Kasbaoui et al, 2023	53	Prospective, observational Single centre Single arm: DES in MV and DCB in SB	AGENT[c] paclitaxel+acetyl tributyl citrate	-	45	ACS or CCS with ischaemia *De novo* true CBL Medina 1,1,1; 0,1,1 RVD 2-3.5 mm in SB	DCB for SB treatment after predilatation	-	-	-	-	11.1	6M TLF	6M ISR 2.2	-	6M 2.2
Ikuta et al, 2022	54	Prospective, observational Multicentre Single arm: DES in MV and DCB in SB	SeQuent Please[b] paclitaxel +iobromide	-	138	-	DCB for SB before MV stenting	-	-	-	-	-	12M ISR	12M SB LLL −0.14±0.43 ISR 8	12M 2.9	12M 3.6
Pan et al, 2022	34	Retrospective, propensity-matched, observational Single centre DES in LM bifurcation Arms: Hybrid (DCB + DES) DES-only strategy (provisional stenting or two-stent strategies)	SeQuent Please[b] paclitaxel +iobromide		597	CCS or UA *De novo* coronary lesions (diameter stenosis >50%) at the LM bifurcation Medina 1,0,1; 0,1,1; or 1,1,1 RVD >2.0 mm in SB	DCB for SB treatment after predilatation	100	43 (IVUS)	95	-	3.5	24M TLF	12M MV LLL 0.25±0.48 vs 0.22±0.42 (NS) SB LLL 0.13±0.42 vs 0.42±0.62 (0.001)	-	12M 2.9 vs 9.4 (0.007)
Liu et al, 2022	35	Retrospective, observational Single centre LM PCI Arms: DES in MV and DCB in SB Two DES	Bingo[f]	2-stent strategy	100	True LM bifurcation	DCB for SB treatment after predilatation	100	28 (IVUS)	100	-	-	6M LLL	6M SB LLL −0.17 vs 0.43 (0.001) SB ISR 7 vs 30 (0.093)	6M No difference	6M 6 vs 12 (0.485)
DCB-BIF, 2025	33	1:1 RCT Open-label superiority Multicentre Core lab CEC *De novo* true CBLs Medina 1,1,1; 0,1,1; or 1,0,1 DCB vs POBA for SB in provisional strategy with DES to MV Arms: DCB NC balloon POBA	PCB	POBA	784	CCS or ACS RVD >2.5 mm in MV >2.5 mm in SB Lesion length <10 mm	DCB for SB treatment after predilatation	MV 96.4 SB 18.5	27 (OCT/IVUS)	97	86 vs 89	3.8 vs 3.3	12M MACE	-	12M 7.2 vs 12.5 (0.013)	12M 1.3 vs 1.5 (NS)

*LLL given in mm; restenosis and diameter stenosis given as %. [a]Eurocor Tech; [b]B. Braun; [c]Boston Scientific; [d]Minvasys; [e]Biotronik; [f]Yinyi Biotech; [g]Concept Medical. ACS: acute coronary syndrome; BMS: bare metal stent; CBL: coronary bifurcation lesion; CCS: chronic coronary syndrome; CEC: clinical events committee; comp: comparator; DCA: direct coronary atherectomy; DCB: drug-coated balloon; DES: drug-eluting stent; diss: dissection; DS: diameter stenosis; EES: everolimus-eluting stent; ISR: in-stent restenosis; IVUS: intravascular ultrasound; KBI: kissing balloon inflation; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LLL: late lumen loss; LM: left main; M: month; MACE: major adverse cardiac events; MI: myocardial infarction; MV: main vessel; NC: non-compliant; NS: non-significant; OCT: optical coherence tomography; PCB: paclitaxel-coated balloon; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; POBA: plain old balloon angioplasty; POT: proximal optimisation technique; QCA: quantitative coronary angiography; RCT: randomised controlled trial; RVD: reference vessel diameter; SB: side branch; TLF: target lesion failure; TLR: target lesion revascularisation; TVF: target vessel failure; UA: unstable angina

Table 2. Ongoing clinical trials on the use of DCBs in CBLs.

Identifier (ClinicalTrials.gov)	Status	Study title	Study design	Inclusion criteria	Exclusion criteria	Outcomes	Reference vessel	DCB	DES	Target sample size	Follow-up
NCT05222061	Unknown	A Study of Drug Coated Balloon For Treating the Side Branch in Complex Bifurcation Lesions (STENT-FREE)	Prospective, single blinded, randomised (DCB vs balloon)	True bifurcations (1,1,1; 0,1,1; 1,0,1), MV diameter >2.5 mm Ischaemic symptoms, ischaemia	STEMI <72H, cardiogenic shock, CTO, >2 other lesions to be treated, SS <32, LM, ISR, LVEF <30%	12M LLL for MV and SB 3, 6, 12M MACE, death, ST, ISR, TLR, TVR, angina, angio success (DS residual <30% TIMI 3), fluoroscopy time	MV >2.5 mm	Any	No DES	80	12M
NCT04896177	Recruiting	Sirolimus DCB in Coronary Bifurcation Lesions	Prospective, randomised (sirolimus vs paclitaxel), non-inferiority, open label	*De novo* bifurcation with SB DS >70%, no expectation to implant stent to SB, no DCB to MV Evidence of ischaemia Residual stenosis <50% in SB after pretreatment and TIMI 3	Shock, SVHD, haemorrhagic diathesis, STEMI <7D, NYHA IV, HTx, creatinine >3, life expectancy <12M, ISR, LM	9M DS in target lesion branch Success rate; 9M ISR, LLL; 1, 6, 12, 24M TLR, TVR, TLF	RVD 2.0-4.0 mm	Shenzhen Salubris SCB vs Yinyi Biotech	No DES	280	24M
NCT03820622	Unknown	The Safety and Efficacy of DIOR Balloon in Coronary Bifurcation Lesions (BEYOND-II)	Prospective multicentre, randomised (DIOR[a] vs BINGO[b] PCB), open label, non-inferiority	Stable/UA, old MI, no contraindication to CABG One or two true bifurcations (1,1,1; 1,0,1; 0,1,1) in different epicardial vessels Residual MV >70% or 50% with symptoms and SB >50% (visual estimation), MV <20% after stent while SB >70% after stent	MI <1W, shock, NYHA III-IV, LVEF <35%, GFR <30 mL/min/1.73 m², haemorrhagic diathesis, PCI or PAD <12M, allergies, life expectancy <12M MV or non-target lesion LM or 3VD, SB is triple bifurcation, MV within 3 mm from ostium, SB disease >26 mm or a stenosis >90% is <5 mm, SB aneurysm, CTO, moderate-severe calcification Residual DS <50% TIMI 3, no angio complications and no dissections type C-F	9M LLL Device success, clinical success; 1, 6, 9, 12M DOCE, POCE, death, MI, TLR, TVR, LLL of SB, MLD of SB, ABR	SB RVD 2.5-4 mm and length <26 mm	DIOR[a] paclitaxel vs BINGO[b] paclitaxel	No DES	220	12M
NCT04403048	Not yet recruiting	Drug Coated Balloon for Side Branch Treatment vs. Conventional Approach in True Bifurcation Coronary Disease: PRO-DAVID	Prospective, randomised (standard provisional vs DCB provisional), parallel, open label	CCS, UA, NSTEMI suitable for PCI, in CCS ischaemia *De novo* bifurcation involving side branch (1,1,1; 1,0,1; 0,1,1), SB RVD ≥2.5 mm and lesion length >5 mm, LM SB DS >70%, non-LM SB DS >90%, SB length ≥73 mm In LAD-D, SnuHscore ≥2	STEMI <72H, CTO, SS >32, TIA/stroke <6M, LVEF <30%, shock, SVHD, creatinine >2, allergies Thrombus, severe calcification, ostial, graft, CTO, ISR or restenosis <4 mm, previous stent <15 mm from lesion	12M MACE 12-36M MACE, angiographic success, procedural success, 12M lesion thrombosis, 9M LLL, bailout stenting or inadequate predilatation, fluoroscopy time/dose, contrast, 6-9M rate of lumen gain >20%	SB RVD ≥2.5 mm, SB length >5 mm	Any	Any	800	36M
NCT04641468	Unknown	Clinical Efficacy and Safety of a Prospective, Multicenter Drug Coated Balloon for Left Main Artery Disease in China	Prospective, open label, observational (DCB alone combined with retracted DES if necessary)	*De novo* lesion with myocardial ischaemia, LM bifurcation 0,1,0; 0,0,1, DS >70% or <30% in distal LM (visual estimation), RVD 2-4 mm	Shock, haemodynamic instability, LVEF <35%, allergies, stents implanted in LM, GFR <30 mL/min/1.73 m², life expectancy <12M	12M MACE 12M TLR, revascularisation	RVD 2-4mm	Any	Any	30	12M
NCT04753827	Completed	"L-Sandwich" Strategy in the True Coronary Bifurcation Lesions	Prospective, randomised (strategy 1=2 DES bifurcation-culotte/DK crush, 2=DES MV+DCB SB, 3=DES MV, DES SB >5 mm from ostium, DCB ostium), open label, parallel assignment	Bifurcation with SB disease >25 mm	SB <2.5 mm Shock, life expectancy <12M, allergies, severe calcification	6M LLL (MV or SB) 6M TLF	SB >2.5 mm	Any	Any	90	6M

NCT04242134	Active, not recruiting	Drug-coating Balloon Angioplasties for True Coronary Bifurcation Lesions	Prospective, 1:1 randomised (DCB provisional=NC SB dilatation, DCB dilatation SB, KB with NC, POT vs provisional DES), parallel, single blinded	CCS with ischaemia, UA, MI >7D Bifurcation 0,1,1; 1,0,1; 1,1,1, RVD ≥2.5 mm in MV and SB (visual estimation), DS ≥50%, SB lesion <10 mm, ostium SB DS >70% after stenting	STEMI <7D, allergies, life expectancy <12M, ISR, CTO, severe calcification	12M MACE 12M all-cause death, CD, MI, TLR/TVR, ST Angiographic success, procedural success, crossover	RVD ≥2.5 MV and SB	Paclitaxel DCB	Any	784	12M
NCT04918615	Active, not recruiting	Compare Sirolimus Coated Balloon Catheter With Paclitaxel Coated Balloon Catheter in De Novo Coronary Bifurcated Lesions (PROMISE-BIF)	Prospective, multicentre, randomised (DCB vs DCB in the treatment of SB in bifurcation) non-inferiority	SB with *de novo* lesion ≥70% with no expected stent implantation No DCB on main vessel (KB before DCB) Residual stenosis after predilatation ≤30% (TIMI 3)	SB severely calcified and not properly predilated ISR Dissection type ≥C after predilatation/KB or restenosis >30% LVEF <30%, GFR <30 ml/min/1.73 m^2	9M DS% side branch 9M LLL SB, immediate success; 1, 6, 12, 24M DOCE, POCE, TLR, TVR, MI, ST	SB 2.0-4.0 mm; LL ≤40 mm	Sirolimus[d] vs Paclitaxel[b]	No DES	234	24M
NCT04842838	Not yet recruiting	Comparative Clinical Study of Drug coating Balloon Strategy and Drug-eluting Stent Strategy (Kissing-DCB)	Prospective, randomised (DCB vs DES), parallel assignment, single blinded	Evidence of ischaemia Bifurcation (1,1,1; 1,0,1; 0,1,1) MV RVD 2.5-4 mm, SB ≥2 mm, MV DS ≥70% and SB ≥50% After predilatation, DS <30%, dissection type A-C	MV or SB require more than one device More than 1 non-target lesion requiring intervention Distance between non-target and target <10 mm LM bifurcation ISR or severe calcification STEMI or NSTEMI <7D Shock, LVEF <35%, GFR <30 mL/min/1.73 m^2, allergies	12M TLF, NACE Technical success, procedural time, 1, 6, 24, 36M TLF, TLR, TVR BARC 2-5, ST	MV RVD 2.5-4 mm, SB RVD ≥2	Any	Any	1,000	12M
NCT03223974	COMPLETED	Clinical Trial on Safety and Efficacy of Drug-coated Balloon in Treatment of Coronary Bifurcation Lesions (BJDCB-BIF)	Prospective, randomised clinical trial (DCB vs DES)	CCS, UA or MI >7D Bifurcation (0,1,1-1,1,1-1,0,1), MV RVD 2.5-3.5 mm and length <30 mm, SB RVD 2-3 mm and length <22 mm. DS >70% or 50% with ischaemia After predilatation, no dissection type C-F, DS <30%, TIMI 3 Distance with residual stenosis to be treated >10 mm Only one DCB or DES to be used for MV and SB	MI <7D, LVEF <30, NYHA III-IV, SVHD, life expectancy <12M, allergies, severe liver or renal failure, stroke <6M, GI bleeding Thrombosis, graft, CTO, LM or 3VD to treat	9M LLL 1, 6, 9, 12, 24M DOCE, and ischaemia-driven revascularisation	MV RVD 2.5-3.5 and length <30 mm SB RVD 2-3 and length <22 mm	Any	Any	80	24M
NCT01009996	Withdrawn (funding issues)	Efficacy Study of Kissing Drug-Eluting Balloons in Coronary Bifurcation Lesions (KISSING DEBBIE)	Observational cohort prospective	*De novo* bifurcation RVD 2.25-4.0 mm	LM, MI <48H	9M LLL Procedural success, 9M ISR, 3, 6, 9, 12M MACE	RVD 2.25-4.00 mm	Any	Any	-	12M

Table 2. Ongoing clinical trials on the use of DCBs in CBLs (cont'd).

Identifier (ClinicalTrials.gov)	Status	Study title	Study design	Inclusion criteria	Exclusion criteria	Outcomes	Reference vessel	DCB	DES	Target sample size	Follow-up
NCT05731687	Recruiting	Bifurcation PCI With a Hybrid Strategy With Drug Eluting Balloons Versus a Stepwise Provisional Two-stent Strategy (Hybrid DEB)	Randomised controlled trial and registry	Significant *de novo* bifurcation lesion (MV and SB diameter ≥2.5 mm, DS of the MV ≥70% and of the SB ≥50% or in intermediate stenosis FFR ≤0.80 or iFR ≤0.89) Stable coronary artery disease or stabilised acute coronary syndrome Age ≥18 years Acceptable candidate for treatment with a DES	Unstable clinical condition Previous PCI with stent implantation in the target lesion(s) Known comorbidity with a life expectancy of <2 years Active bleeding requiring medical attentions (BARC >2 at index PCI) Pregnancy Unable to provide consent for any other reason Participation in another stent or drug trial Known hypersensitivity or allergy to aspirin, clopidogrel, ticagrelor, prasugrel, cobalt chromium, sirolimus, excipients with phospholipid or related origins	Composite of all-cause death, periprocedural or spontaneous MI, TVR Procedural success, MACE, TVF, major bleeding, contrast volume used, probable and definite ST, major intraprocedural complications, radiation exposure, procedural time, procedural costs, percentage of stent expansion in proximal and distal MV and SB, final minimal lumen and stent area after stenting, dissections	MV and SB diameter ≥2.5 mm	Concept Medical	Supraflex[e]	-	12M
NCT06166459	Not yet recruiting	Yao Strategy for the Treatment of de Novo Medina 0,1,0 or 0,0,1 Bifurcation Lesion	Single group assignment, open label	Subjects 18-80 years old *De novo* native lesion, Medina type 0,1,0/0,0,1 bifurcation lesion Reference diameter of the target vessel 2.75-4.00 mm, length <40 mm Subjects willing to participate in the study, sign informed consent form, and accept clinical follow-up	DS of adjacent branch vessel ostium ≥50% STEMI Stents implanted within 10 mm proximal or distal to the target lesion Aneurysm within 10 mm proximal or distal to the target lesion Target vessel distortion or severe calcification lesion, so balloon catheter fails to pass Previous CABG Evidence for extensive thrombus within target vessel Evidence of heart failure by at least one of the following: (a) most recent LVEF ≤35%, or (b) current heart failure defined as dyspnoea at rest (NYHA Class IV assessed day of procedure), or (c) Killip class ≥2 (post-STEMI patients) Life expectancy of ≤1 year Stroke, peptic ulcer, or gastrointestinal bleeding within the past 6 months Severe renal failure (eGFR <30 ml/min/1.73 m^2), failure to comply with angiography conditions Intolerance to aspirin and/or clopidogrel or ticagrelor or has contraindications Intolerance or allergy to heparin, contrast agent Patients participating in the clinical trial of another drug or device without reaching the time limit of primary endpoint Not applicable to be enrolled by investigators due to other reasons	9M LLL 12M MACE	Diameter of the target vessel 2.75-4.00 mm, length <40 mm	Any	Any	200	12M

NCT06045039	Recruiting	Clinical Efficacy of Stent-balloon-stent (SBS) Technique in the Treatment of Coronary Bifurcation Lesions	Prospective, cohort	Myocardial ischaemia, such as coronary angiography, including patients with stable angina pectoris, unstable angina pectoris, asymptomatic myocardial ischaemia and acute MI (>24 hours). All bifurcation lesions Medina 1,1,1 or 0,1,1 with an RVD in the SB ≥2.5 mm by visual estimation and had to meet DEFINITION criteria of complex bifurcations Tolerate long-term antiplatelet therapy	Severe surgical contraindications Life expectancy <12M Previously undergone stent implantation or surgical CABG for related lesions Severe hepatorenal insufficiency Heart failure patients with NYHA Class ≥III Scheduled for surgery requiring antiplatelet medication interruption within 6 months Need for chronic oral anticoagulation Any clinical condition that may interfere with medication compliance or long-term follow-up Pregnant or breastfeeding women	Target lesion failure rate Cardiac death 3-12M TVMI 6-12M Clinically driven TLR 6-12M Minimum lumen area and lumen stenosis rate 6-12M	RVD in the SB ≥2.5 mm	Any	-	200	12M
NCT02276846	Unknown	Palpitate-Eluting Balloon Angioplasty in the Treatment of Coronary Bifurcation Lesion Evaluated by OCT (PEBCBLO)	Prospective, observational (efficacy of PCB SeQuent Please[c] in SB after MV treatment with EXCEL stent)	CCS or UA or documented ischaemia *De novo* bifurcation with DS >70% in both branches or >50% if ischaemia	MI <48H, NYHA IV, shock, SVHD, life expectancy <12M, stroke <6M, GFR <30 mL/min/1.73 m², post-transplantation, thrombus, multilesion treatment outside bifurcation Previous stent <15 mm lesion, DES <9M/BMS <3M, graft, CTO, ISR, allergies	9M LLL 9M MACE, procedural success	LAD/LCx RVD 2.5-4.0 mm, length <30 mm D1/D2 OM RVD 2.0-3.5 mm, length <30 mm	SeQuent Neo[c]	EXCEL[f]	30	9M

[a]By Eurocor Tech; [b]by Yinyi Biotech; [c]by B. Braun; [d]by MicroPort; [e]by SMT; [f]by JW Medical Systems. 3VD: three-vessel disease; ABR: angiographic binary restenosis; BARC: Bleeding Academic Research Consortium; BMS: bare metal stent; CABG: coronary artery bypass graft surgery; CBL: coronary bifurcation lesion; CCS: chronic coronary syndrome; CD: cardiovascular death; CTO: chronic total occlusion; D: day; D1: first diagonal branch; D2: second diagonal branch; DCB: drug-coated balloon; DEB: drug-eluting balloon; DES: drug-eluting stent; DOCE: device-oriented composite endpoint; DS: diameter stenosis; eGFR: estimated glomerular filtration rate; FFR: fractional flow reserve; GFR: glomerular filtration rate; GI: gastrointestinal; HTx: heart transplantation; iFR: instantaneous wave-free ratio; ISR: in-stent restenosis; KB: kissing balloon; LAD: left anterior descending artery; LCx: left circumflex artery; LLL: late lumen loss; LM: left main; LVEF: left ventricular ejection fraction; M: month; MACE: major adverse cardiovascular events; MI: myocardial infarction; MLD: minimal lumen diameter; MV: main vessel; NACE: net adverse clinical events; NC: non-compliant; NSTEMI: non-ST-elevation myocardial infarction; NYHA: New York Heart Association; OCT: optical coherence tomography; OM: obtuse marginal; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; POCE: patient-oriented composite endpoint; POT: proximal optimisation technique; RVD: reference vessel diameter; SB: side branch; SCB: sirolimus-coated balloon; SNuH: size, number, highest; SS: SYNTAX score. ST: stent thrombosis; STEMI: ST-segment elevation myocardial infarction; SVHD: single ventricle heart disease; TIA: transient ischaemic attack; TIMI: Thrombolysis in Myocardial Infarction; TLF: target lesion failure; TLR: target lesion revascularisation; TVF: target vessel failure; TVMI: target vessel myocardial infarction; TVR: target vessel revascularisation; UA: unstable angina; W: week

antiplatelet regimens following DCB treatment, although their applicability specifically to bifurcated anatomy remains to be fully validated.

INTRACORONARY IMAGING AND PHYSIOLOGY FOR DCB-BASED PCI IN CBLS

Intracoronary imaging (ICI) provides a more detailed assessment of vessel size, plaque composition, morphology, and characteristics, thereby enabling optimised lesion preparation, as compared to angiography alone. Although current guidelines recommend the use of ICI (Class I, Level of Evidence A recommendation) in complex DES-based PCI[41], its role in DCB PCI has been underevaluated until recently. OCT is often preferred because of its high resolution, especially in detecting subtle dissections, thrombus, or incomplete lesion preparation, while IVUS allows for accurate measurement of the vessel wall and plaque burden[4]. The ULTIMATE III trial recently demonstrated improved angiographic outcomes with IVUS-guided DCB PCI compared to angiographic guidance alone, resulting in improved acute gain and reduced 7-month LLL (–0.10±0.34 mm vs 0.03±0.52 mm; p=0.025) and improved minimal lumen diameter and diameter stenosis[42]. Furthermore, recent evidence suggests that medial dissections are needed for better outcomes after DCB-only PCI, probably due to the effect of dissection *per se* on vascular remodelling and because they might facilitate better drug transfer to the vessel wall[43].

In the setting of CBLs, intracoronary imaging and coronary physiology can assist in refining the Medina classification and in guiding the decision to perform bailout stenting when residual stenosis or angiographic dissections are present. Although specific thresholds (e.g., minimal lumen area or dissection severity) for bailout stenting after DCB treatment are yet to be established, ICI can provide valuable guidance in borderline or ambiguous cases. SB ostial narrowing frequently appears to be angiographically significant after MV stenting, yet functional assessment often shows no ischaemia. Physiological tools such as FFR or non-hyperaemic pressure ratios (NHPRs) can help identify functionally non-significant lesions and support SB deferral. In a pivotal study by Koo et al, FFR assessment of jailed SB lesions following MV stenting revealed that many angiographically significant stenoses were not haemodynamically relevant, thus supporting a physiology-guided approach to avoid unnecessary interventions[44]. To date, no prospective, dedicated clinical studies have assessed the role of invasive, pressure wire or angiography-based coronary physiology in guiding DCB treatment. Retrospective observational data suggest that a distal coronary-to-aortic pressure ratio (Pd/Pa) cutoff value of 0.90 may indicate optimal lesion preparation prior to DCB application[45].

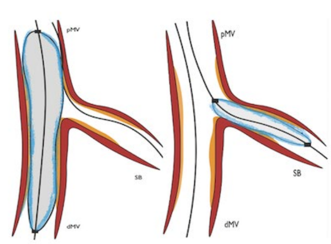
Conclusions

The use of DCBs for SB treatment of coronary bifurcation lesions is a novel approach, allowing for a reduction

EuroIntervention — Central **Illustration**

Drug-coated balloons for coronary bifurcation lesions: techniques, advantages, pitfalls, and state-of-the-art.

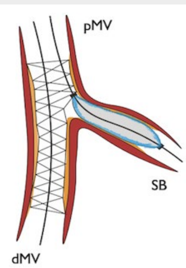
LEAVE NOTHING BEHIND



Advantages
- Efficient and sustained drug delivery
- No polymers or permanent implants
- Preserves vessel geometry and SB access
- DAPT de-escalation

Avoid DCB KBI
- Suboptimal delivery of the drug
- Proximal interaction of the two balloons
- Higher risk of dissection

BLENDED in the PROVISIONAL pathway



Advantages
- ↑ use of provisional vs 2-stent strategy
- ↓ stent burden
- Avoids issues related to polymer and strut crushing
- Allows SB late lumen enlargement

DCB to the SB after DES implantation
- Suboptimal drug delivery due to strut interference
- Limited deliverability in jailed SB

WHAT DO WE KNOW?
- DCB for SB treatment seems to be reasonable and supported by clinical and angiographic data and RCTs
- The use of PCB + BMS is inferior to new-generation DES
- The use of PCB + DES showed promising results in real-world registries
- "DCB-only strategy" is feasible and safe in case of Medina 0,X,X lesions

MORE DATA NEEDED
- RCTs used different study protocols, methods, and devices
- RCTs were relatively small, with no routine POT and a low KBI rate

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BMS: bare metal stent; DCB: drug-coated balloon; DES: drug-eluting stent; dMV: distal main vessel; KBI: kissing balloon inflation; PCB: paclitaxel-coated balloon; pMV: proximal main vessel; POT: proximal optimisation technique; RCT: randomised controlled trial; SB: side branch in the overall stent burden and fulfiling a provisional approach to CBLs **(Central illustration)**. The blended/hybrid approach, which combines DCBs with DES, has demonstrated promising results in observational and randomised studies. Additionally, the "DCB-only strategy" has proven to be both feasible and safe for SB-only CBLs. DCB treatment appears to be more efficient than POBA to prevent restenosis in the SB. However, it is important to note that, so far, RCTs have used heterogeneous study protocols and techniques, methods, and devices, have rarely included true CBLs, and have been small in terms of sample sizes.

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Conflict of interest statement

B. Scheller is a shareholder of InnoRa GmbH. A. Banning reports speaker fees from Abbott; and received a research grant from Boston Scientific. F. Ribichini reports research grants from Philips and Abbott. R. Scarsini reports speaker fees from Abbott; and research grants from Philips and Abbott. S. Fezzi reports consultancy fees from Boston Scientific, Teleflex, and Shockwave Medical. T. Rissanen reports consultancy fees from Boston Scientific, Abbott Laboratories, Cordis, Biotronik, and B. Braun. The other authors have no relevant conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. DCB technologies and armamentarium.

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Supplementary data

Supplementary Appendix 1. DCB technologies and armamentarium.

Paclitaxel (PTX) remains one of the most used coating drugs, with a typical dose between 2 and 3.5 μg/mm2. PTX is a lipophilic drug that rapidly penetrates cell membranes, binds to microtubules, and inhibits cell division, migration, and proliferation. Its lipophilicity ensures swift cellular uptake, even tissue penetration, and homogeneous distribution, resulting in sustained effects on smooth muscle cells, with a prolonged persistence of the cytotoxic action[4]. Various matrices and excipients, such as iopromide and urea, have been employed to enhance drug dissolution, release, and adherence to the vessel wall. Shellac, a natural resin, and combinations like shellac with vitamin E have also been explored to improve drug delivery. Concerns about the theoretical harm of PTX cytotoxicity, compared to -limus molecules have been raised, based on stents development data. However, paclitaxel DCBs have been shown to be safe for use in both coronary and peripheral arteries[4].

Sirolimus is a reversible mammalian target of rapamycin (mTOR) inhibitor, that primarily acts at the G1 to S phase junction, inhibiting cell proliferation. Limus-eluting DCBs release sirolimus or its analog, biolimus, which are designed for enhanced lipophilicity and efficient local drug delivery. Various coating technologies are utilized for sirolimus-based DCBs, including Nanoluté™, CAT™, and SeQuent SCB. These technologies encapsulate sirolimus in phospholipids, employ micro-reservoirs for controlled release, or use crystalline coatings to achieve persistent drug tissue concentrations.

DCB and BMS in MV

Several studies investigating the performance of DCB PCI in the setting of CBLs are hampered by the combination of DCBs with BMS in the MV treatment. In the PEPCAD-V (n=28; PTX; Sequent Please, Braun, Melsungen, Germany) the angiographic LLL of DCB followed by BMS implantation in the MV was 0.38 ± 0.46 mm, with a single TLR and two late stent thrombosis. Such “blended” strategy, including combined pre-dilatation of MV and SB with DCBs followed by BMS to the MV, was seen to provide inferior results compared to DES use towards MV with POBA to the SB, both in the BABILON (n=108; PTX; Sequent Please, Braun, Melsungen, Germany) and DEBIUT [2] (n= 117; PTX; Dior, Eurocor GmbH, Bonn, Germany) studies.

DCB to the SB before BMS implantation in the MV

In the pilot PEPCAD-V the feasibility and safety of a combined DCB treatment towards MV and SB, followed by the implantation of a BMS in the MV were investigated. At nine months, the angiographic LLL was 0.38 ± 0.46 mm in the MV and 0.21 ± 0.48 mm in the SB. A single TLR was performed, while two late BMS thrombosis occurred.

The DEBIUT was a 1:1:1 RCT that compared a first strategy including the combined DCB treatment of both MV and SB, followed by BMS implantation in the MV, a second one with BMS implantation in the MV and POBA in the SB, and a third one with paclitaxel-DES in the MV and POBA in the SB. Based on a population of 117 patients, the study demonstrated superiority of the DES-based approach. DCB treatment (PTX; Dior, Eurocor, Bonn, Germany) towards the SB showed acceptable angiographic result at 6 months, as compared to POBA in the DES arm (LLL 0.19±0.55 vs 0.11±0.43 mm; p value= 0.001).

Similarly, in the 1:1 RCT BABILON (n=108) study, the use of everolimus DES in the MV with POBA towards the SB was superior compared to the combined pre-dilatation with DCBs (PTX; SeQuent Please, Braun, Melsungen, Germany) followed by BMS in the MV. Although the use of DES in the MV was superior to the strategy with DCB followed by BMS, the use of a DCB in the SB was associated with a similarly low LLL in comparison to the POBA group (−0.04 ± 0.76 mm vs 0.03±0.51, respectively), along with a low restenosis rate (6%) at 9-month follow-up.