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REVIEW ARTICLE

Drug-Coated Balloons in Percutaneous Coronary Intervention for Complex Bifurcation Lesions

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Abstract

Complex coronary bifurcation lesions represent one of the most demanding challenges in percutaneous coronary intervention (PCI). Despite advances in drug-eluting stent (DES) technology and bifurcation-specific techniques, restenosis and stent-related complications remain more prevalent in bifurcation lesions. Drug-coated balloons (DCBs), which deliver antiproliferative medication without permanent scaffolding, have emerged as a promising tool, particularly for side-branch treatment and stent-less strategies. This comprehensive review examines current evidence, mechanistic rationale, procedural techniques, clinical outcomes and future directions of DCB usage in complex bifurcation PCI.

Keywords: Drug-coated balloons, Coronary bifurcation, Drug-eluting stents, Bifurcation lesions, Provisional stenting.

Introduction

Bifurcation lesions constitute 15–20% of all PCI cases and are associated with higher rates of adverse outcomes due to complex anatomy, plaque distribution, and challenges in maintaining side-branch patency. Traditional strategies such as provisional stenting and two-stent techniques, including DK-crush, culotte, and TAP, though effective, introduce additional metal layers and increase restenosis risk. As the field moves toward physiology- and imaging-guided interventions, DCB therapy is gaining traction for its ability to minimize metallic burden and maintain natural vessel architecture.

Coronary bifurcation lesions and bifurcation classification

A coronary bifurcation lesion is described as a "narrowing of a coronary artery that occurs near and/or involves the origin of a relevant side branch." A side branch (SB) is considered clinically relevant when compromising it could influence the patient's overall aoutcome. For this reason, the determenation of SB significance usually depends on the individual clinical judgement of the interventional cardiologist.

Several systems have been introduced to classify coronary bifurcation lesions, reflecting the wide range of anatomical patterns, technical considerations, therapeutic strategies, and clinical outcomes associated with these lesions. Among them, the Medina classification is the most widely adopted because of its straightforward structure and good reproducibility. This system evaluates whether there is more than 50% diameter narrowing in each of the three key segments of a bifurcation: the proximal main branch (MBP), the distal main branch, and the side branch (SB). Each of these regions is assigned a score of either 0 or 1, in the order MBP–distal main branch–SB. For instance, if the lesion affects the MBP and the SB but not the distal main branch, it is categorized as 1,0,1. In total, seven possible anatomical patterns can be described with this model. Although it is the most commonly used classification, the Medina system has notable shortcomings—such as not accounting for plaque distribution, vessel size, lesion length, bifurcation angles, ostial involvement, or the presence of calcification.

Treatment strategies for bifurcation lesions

The contemporary treatment of coronary bifurcation lesions represents one of the most challenging and

technically demanding arenas within percutaneous coronary intervention (PCI), largely due to the intricate anatomical configuration, heterogeneous plaque distribution, and the complex fluid dynamic interactions that occur at the carina. The central objective of PCI in this subset of lesions is to optimise flow in the main branch (MB), maintain patency and adequate perfusion of the side branch (SB), prevent acute and delayed occlusion of either branch, and achieve long-term clinical durability with minimal restenosis or stent thrombosis. Over the past decade, substantial developments in stent design, intravascular imaging, physiology-guided assessment, and procedural methodology have improved outcomes; however, bifurcation PCI continues to carry higher rates of complications and target vessel failure compared with non-bifurcation lesions.

Current international consensus supports the provisional stenting strategy as the preferred initial approach for the majority of bifurcation lesions. This strategy involves predilatation as needed, followed by stenting of the MB with a contemporary drug-eluting stent (DES), and subsequent evaluation of SB flow, lesion morphology, and clinical relevance. SB treatment—through balloon angioplasty, cutting/scoring balloon use, drug-coated balloon inflation, or selective SB stenting—is performed only in cases of significant flow impairment, severe ostial dissection compromising vessel integrity, or in patients where the SB supplies a sizeable myocardial territory. Multiple randomised studies and meta-analyses have consistently shown that routine two-stent strategies do not provide outcome benefit over provisional stenting in unselected bifurcation lesions, thereby reinforcing a philosophy of procedural minimalism whenever anatomically feasible.

When SB intervention becomes necessary, the interventional cardiologist must select an appropriate technique based on the bifurcation angle, plaque distribution, vessel size discrepancy, and anticipated interaction between stent struts and carina behaviour. Classical T-stenting remains suitable for near-orthogonal bifurcation take-off angles, enabling precise ostial coverage with minimal protrusion. In more complex anatomies—especially those characterised by oblique angles or eccentric plaque at the SB ostium—overlapping strategies such as T-and-protrusion (TAP), culotte stenting, or one of the crush-based approaches may be selected. The crush family of techniques includes mini-crush, step-crush, and the double-kissing (DK) crush technique, each offering increasing levels of scaffolding precision at the expense of procedural complexity. The DK crush technique, in particular, has gained traction following multiple randomised trials demonstrating superior angiographic patency and lower target lesion failure in left main (LM) bifurcations, although the technique requires meticulous execution, including dual rewiring and two mandatory kissing balloon inflations. Final kissing balloon inflation (KBI) remains a central procedural manoeuvre at the conclusion of many two-stent techniques and may also be performed following provisional SB treatment. Although KBI improves stent geometry in bench simulations and facilitates more symmetrical expansion at the carina, clinical data regarding its long-term benefit remain inconsistent. Some studies suggest modest reductions in SB restenosis, whereas others demonstrate no clinically meaningful improvement, raising the possibility that the utility of KBI may depend on specific anatomical or procedural variables rather than being universally advantageous.

Despite ongoing refinements in technique, planned two-stent strategies are employed in a minority of cases. Extensive evidence indicates that, for most bifurcations, these approaches do not confer superior outcomes relative to provisional stenting. A large meta-analysis of multiple randomised trials comparing provisional strategy with routine two-stent implantation identified no significant difference in death, stent thrombosis, restenosis, or target vessel revascularisation, even though the two-stent group experienced a higher incidence of both early and late myocardial infarction. These findings underscore a critical principle in bifurcation PCI: increased procedural complexity may introduce additional risk without necessarily improving clinical outcomes.

Nevertheless, important exceptions exist. Subgroup analyses consistently suggest that certain patients with true bifurcation lesions—defined by simultaneous, significant stenosis in both MB and SB—particularly when the SB diameter is large or the SB lesion is long, may benefit from a planned two-stent approach. This is especially relevant in LM bifurcations or severely calcified anatomies, where the consequences of SB loss are clinically significant and the probability of SB compromise during a provisional strategy is high. In such patients, techniques such as DK crush or culotte may offer more predictable scaffolding and long-term patency.

The EBC TWO trial provided further clarity by examining outcomes in true bifurcations with large-calibre SBs. The trial demonstrated no difference between a provisional T-stent approach and a culotte two-stent strategy in the primary composite endpoint of death, myocardial infarction, or target vessel revascularisation at 12 months. These findings further reinforce the principle that routine complexity does not necessarily improve outcomes, even in anatomically challenging cases. Complementing this, long-term analyses from the NORDIC I and BBC ONE trials revealed that patients undergoing provisional stenting experienced significantly lower 5-year mortality compared to those treated with culotte, crush, or classical T-stenting. Furthermore, a large meta-analysis encompassing nearly 7,000 patients indicated a higher incidence of late stent

thrombosis in patients treated with planned two-stent techniques, likely attributable to increased metal burden, layered struts at the carina, and difficulty achieving optimal final strut apposition.

Beyond stent strategy, the role of intravascular imaging has become increasingly prominent in bifurcation PCI. Optical coherence tomography (OCT) and intravascular ultrasound (IVUS) enable precise evaluation of plaque morphology, vessel dimensions, carina shift, and stent expansion, providing essential information that cannot be reliably obtained from angiography alone. Imaging-guided PCI has demonstrated reductions in stent malapposition, underexpansion, and target lesion failure, particularly in LM bifurcations. Physiological assessment using fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) further refines SB treatment decisions, as many angiographically significant SB stenoses are functionally non-ischaemic and do not require stenting.

Optimisation techniques such as the proximal optimisation technique (POT) have transformed bifurcation PCI by addressing geometric mismatches between the proximal and distal MB. POT improves stent apposition, restores circular lumen geometry, facilitates easier SB rewiring through distal struts, and reduces the risk of carina shift. In combination with KBI and sequential dilatation strategies (POT–side branch–POT), POT has become a cornerstone of contemporary bifurcation practice, serving both mechanical and physiological functions.

Despite these advances, long-term outcomes after bifurcation PCI remain inferior to those observed in simple lesions, highlighting a persistent need for improved stent designs, enhanced imaging algorithms, and more predictable procedural strategies. Emerging technologies, including artificial intelligence–assisted OCT interpretation, computational modelling of carina behaviour, and dedicated bifurcation stent platforms, may further refine the interventionalist's ability to tailor treatment. Drug-coated balloons (DCBs) have also shown promise for SB ostial disease by avoiding additional metal layers and decreasing long-term restenosis, although evidence remains heterogeneous and their role continues to evolve.

Taken together, current best evidence supports a stepwise, anatomy-driven approach to bifurcation PCI. The provisional strategy remains the cornerstone of treatment, balancing procedural simplicity with excellent long-term outcomes. Two-stent techniques, although vital in certain anatomically complex or clinically high-risk scenarios, should be reserved for lesions where the risk of SB loss is high or the vessel calibre demands more robust scaffolding. As imaging-guidance, physiology-based decision-making, and stent technology continue to advance, the interventional management of bifurcation lesions will likely become even more refined, offering a more predictable path toward optimal outcomes for this historically challenging subset of coronary disease.

The role of Drug- Coated Balloons (DCB) in the treatment of bifurcation lesions : clinical perspectives and current evidences

Drug-coated balloons (DCB) have increasingly gained attention as a potential alternative or adjunctive therapy in the management of bifurcation lesions, particularly in scenarios where conventional drug-eluting stents (DES) may be associated with higher risks of restenosis, stent malapposition, or metal-layer–related late failure. DCB are based on semi-compliant balloon platforms coated with an antiproliferative agent—most commonly paclitaxel due to its high lipophilicity and ability to rapidly penetrate the vessel wall; sirolimus-based DCB, although less lipophilic, have recently been engineered with carrier technologies enabling effective tissue uptake. Upon inflation, typically maintained for 30–90 seconds depending on the specific device, the drug is promptly transferred to the vessel wall, exerting antiproliferative effects without leaving a permanent implant. As such, DCB therapy uniquely combines immediate luminal gain achieved by prior lesion preparation with long-term suppression of neointimal hyperplasia, all while avoiding the biometallic burden associated with stent implantation.

Before DCB deployment, adequate lesion preparation is crucial. DCB are not intended to serve as primary debulking or lesion-modifying devices; rather, they require optimal predilatation using standard semi-compliant balloons, high-pressure non-compliant balloons, or lesion-modifying technologies such as cutting, scoring, or, in heavily calcified lesions, atherectomy. A satisfactory angiographic result—defined by minimal dissection (usually type A/B), no flow limitation, and acceptable residual stenosis—constitutes the prerequisite for DCB application. When these conditions are met, prolonged balloon inflation facilitates homogeneous drug transfer, achieving durable antiproliferative activity while eliminating the risk of late and very late stent thrombosis, metal fatigue, stent fracture, or neoatherosclerosis. Importantly, the absence of a permanent scaffold reduces the reliance on prolonged dual antiplatelet therapy (DAPT), often making DCB a valuable option in high bleeding risk patients.

The clinical evidence supporting DCB use is strongest in the setting of in-stent restenosis (ISR). The early landmark PACCOCATH ISR I trial first introduced the concept, demonstrating the superiority of paclitaxel-coated balloons over plain balloon angioplasty in the management of bare-metal stent (BMS) restenosis. Subsequent studies confirmed that DCB not only reduce neointimal proliferation but also outperform repeat paclitaxel-eluting stents in BMS ISR at both short- and long-term follow-up. In contrast, the data

surrounding DES ISR remain more heterogeneous. Trials such as PEPCAD-DES showed DCB to be superior to plain old balloon angioplasty (POBA) in restenotic DES lesions, while the ISAR-DESIRE 3 study demonstrated non-inferiority between DCB and paclitaxel-eluting stents with respect to death, myocardial infarction, and target lesion thrombosis. Nonetheless, newer-generation DES continue to challenge DCB in certain settings; for instance, the RIBS V study demonstrated improved outcomes—including significantly lower target lesion revascularisation (TLR)—with second-generation everolimus-eluting stents compared with DCB in BMS ISR. However, it is essential to recognise that relatively few randomised studies exist in this domain, and heterogeneity in lesion preparation, balloon technologies, and stent generations limits broad generalisability.

A meta-analysis synthesising data from both observational and randomised studies compared DES, DCB, and POBA for the management of DES ISR and reported comparable reductions in TLR for DES and DCB, while emphasising that DCB avoid the drawbacks of an additional stent layer, reduced vessel compliance, and cumulative metal burden. Acknowledging these findings, the European Society of Cardiology (ESC) Guidelines on myocardial revascularisation recommend DCB for the treatment of ISR—whether following BMS or DES—with a Class I recommendation and level of evidence A.

Beyond ISR, DCB have shown promise in selected native coronary settings, including small-vessel disease, where stent implantation may be technically challenging, associated with higher restenosis rates, or simply unnecessary. Studies such as the BELLO trial demonstrated favourable outcomes with DEB compared with DES implantation in vessels smaller than 2.5 mm, underscoring the potential of DCB to provide adequate lumen preservation with lower long-term restenosis risk when vessel caliber constrains stent expansion.

A growing area of interest is the application of DCB in bifurcation lesions. In these complex anatomical settings, DCB offer theoretical and practical advantages, particularly for the SB. The avoidance of additional metal layers at the carina circumvents the geometric distortions and strut layering problems commonly encountered with two-stent strategies. DCB use in bifurcations—most commonly for SB ostial disease following a provisional MB stenting strategy—enables drug delivery without imposing a rigid scaffold that might impair MB optimisation or complicate subsequent rewiring. Moreover, the lack of a permanent implant reduces the occurrence of SB metallic jailing, thus minimising the risk of late SB ostial restenosis and facilitating more physiological vessel healing.

Evidence in this setting remains emerging but increasingly promising. Several observational studies and small randomised comparisons have reported lower SB restenosis rates with DCB compared with conventional balloon angioplasty, and in some cases comparable outcomes to SB stenting, particularly when meticulous lesion preparation and final optimisation techniques such as POT (proximal optimisation technique) are performed. Furthermore, in left main bifurcations where SB patency is critical and where additional stent layers may significantly impair long-term outcomes, the concept of DCB-only or hybrid strategies continues to be explored.

In summary, DCB represent an important and evolving therapeutic option in the management of ISR, small-vessel disease, and increasingly, bifurcation lesions. Their capacity to deliver potent antiproliferative therapy without permanent implantation offers unique advantages in terms of long-term vessel physiology, reduced stent-layer complexity, and flexibility in subsequent interventions. While DES remain the standard of care in many scenarios, expanding evidence supports a complementary role for DCB in the contemporary bifurcation PCI toolbox. As technology advances and sirolimus-based platforms continue to improve drug transfer efficiency, the clinical scope of DCB is expected to grow, with future trials likely to further clarify their optimal indications and procedural integration.

Several studies have evaluated the efficacy and safety of DCB in bifurcation lesions, building on prior evidence from in-stent restenosis (ISR) and small-vessel disease.

PEPCAD V Registry: This prospective, multicentre, single-arm trial enrolled 28 patients with bifurcation lesions. Predilatation was performed using a DCB in both MB and SB, with bare-metal stent (BMS) implantation in the MB only if TIMI flow was <2 or MB stenosis exceeded 50% (14.3% of patients). Procedural success was 100%, and at 9 months, restenosis rates were 3.8% in the MB and 7.7% in the SB. These outcomes compared favorably with restenosis rates reported after DES implantation in other studies (e.g., 4.6–6.7% MB and 13.2–14.7% SB in the CACTUS study; 0.6–5.1% MB and 11.5–19.2% SB in the Nordic study).

DEBIUT Trial (2012): This multicentre, randomised study enrolled 117 patients and compared three strategies:

- DCB in both MB and SB with BMS in the MB,
- BMS in the MB with POBA in the SB,
- Paclitaxel-eluting DES in the MB with conventional balloon in the SB.

The angiographic outcomes were similar between the DCB+BMS and BMS-only groups, but inferior to DES in the MB. Nevertheless, binary restenosis at 6 months and major adverse cardiovascular event (MACE) rates at 12 months were comparable across all groups, suggesting that DCB pretreatment provided no additional advantage over DES.

BABILON Trial

This study evaluated DEB pretreatment before BMS implantation in the MB and demonstrated worse angiographic and clinical outcomes at 9 months compared with DES-only therapy.

DEBSIDE Trial

This trial specifically assessed the role of DCB in the SB after MB DES implantation using the novel DANUBIO balloon. In 52 patients, the study reported excellent angiographic results, very low complication rates, and only one TLR at 6 months.

SARPEDON Study

This study further confirmed the feasibility of SB DCB after MB DES implantation. Angiographic outcomes were favorable, and restenosis rates remained low, although the 1-year MACE rate was 19%.

PEPCAD-BIF Trial

A multicentre randomised study including 64 patients with bifurcation lesions compared DCB versus POBA in the SB after MB stenting. Only 5 patients required SB stenting as a bail-out. The DCB group demonstrated significantly lower restenosis rates (6% vs. 26% in POBA), reduced TLR, and improved angiographic endpoints (p=0.045).

The above studies highlight several key points regarding DCB use in bifurcation lesions:

- DCB can safely deliver antiproliferative therapy to the SB ostium without the need for stent implantation.
- When used following provisional MB stenting, DCB reduce restenosis and TLR compared with plain balloon angioplasty.
- In carefully selected patients, DCB may offer outcomes comparable to more complex two-stent strategies, while avoiding additional metal layers and procedural complications.

Conclusion

DCB represent a promising tool in the management of coronary bifurcation lesions, particularly for SB treatment following MB stenting. They combine effective local drug delivery with preservation of vessel architecture and reduced long-term risk associated with permanent implants. While DES remain the standard for most MB lesions, DCB provide a valuable adjunctive or alternative therapy for SB ostial disease, particularly in small vessels, ISR, or patients at high bleeding risk. Ongoing research and larger randomised trials are warranted to further clarify their optimal role and long-term efficacy in bifurcation PCI.

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