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# Research Progress of Drug-Coated Balloons in the Treatment of Coronary Bifurcation Lesions

**Xing Huang, Ying Huang***

Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: *1640515024@qq.com

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## Abstract

Coronary bifurcation lesions are anatomically complex and remain challenging in percutaneous coronary intervention (PCI), particularly in side-branch (SB) management and the prevention of in-stent restenosis (ISR). Drug-coated balloons (DCBs) based on the concept of "leave nothing behind" allow localized delivery of antiproliferative agents and inhibit neointimal hyperplasia, which offer novel therapeutic strategies for bifurcation lesions. This review summarizes the principles of DCB technology and the current evidence supporting their application in coronary bifurcation lesions, to inform optimal intervention procedures.

## Keywords

Coronary Bifurcation Lesion, Drug-Coated Balloon, DCB, PCI

## 1. Introduction

Coronary bifurcation lesions account for approximately 15% - 20% of percutaneous coronary intervention procedures (PCI) and remain technically challenging due to complex anatomy [1]. Anatomical factors, including lesion location, bifurcation angle, vessel size, and plaque distribution, play a critical role in determining procedural complexity and clinical outcomes, thereby leading to increased risks of procedural failure, periprocedural complications, and long-term restenosis. At present, Drug-eluting stents (DES) remain the cornerstone of interventional therapy for coronary bifurcation lesions, with commonly used techniques including single-stent and double-stent strategies. While lots of studies have compared these two strategies, evidence suggests that both of them present advantages and limitations, failing to establish a standard strategy for all bifurcation lesions [2] [3]. Drug-coated balloons (DCBs), based on the concept of "leaving nothing behind",

provide a novel therapeutic pathway to optimize outcomes in these complex lesions.

## 2. The Rise of DCB

While DES revolutionized the prevention of in-stent restenosis (ISR) by effectively inhibiting neointimal hyperplasia, the long-term safety of scaffolds became a focal point of concern in the early 2000s. It was suggested that the prolonged release of anti-proliferative agents and the presence of permanent polymer matrices could impair endothelial healing and trigger chronic local inflammation, potentially increasing the risk of late adverse events [4].

In 2003, Scheller *et al.* [5] first reported a stent-free approach for anti-proliferative agents delivery to prevent restenosis. Building on the observation that local blood flow velocity decreases following contrast injection, the study employed iopromide as a carrier to enhance the retention and absorption of paclitaxel at the target site. The findings revealed that even brief exposure of vascular smooth muscle cells to the paclitaxel-iopromide combination could achieve sustained antiproliferative effects. Additionally, this stent-free delivery method resulted in a significant reduction in restenosis rates in the porcine coronary models. These pivotal experiments suggested that prolonged drug release may not be a prerequisite for inhibiting restenosis, fundamentally challenging the prevailing understanding of restenosis prevention. Scheller introduced a paclitaxel-coated balloon in another study [6], demonstrating its superior efficacy compared to an uncoated balloon in restenosis prevention. Following this landmark study, the safety and efficacy of drug-coated balloons have been extensively validated. DCB applications have evolved from ISR to de novo lesions in both small and large vessels, as well as complex coronary bifurcation lesions.

## 3. Advantages of DCBs in Bifurcation Lesions

DCBs are semi-compliant balloons coated with anti-proliferative agents. During the brief period of balloon inflation, the anti-proliferative agents can rapidly penetrate the vessel wall and effectively inhibit the proliferation and migration of smooth muscle cells, which interrupts the progression of atherosclerosis.

Technologically, DCBs possess characteristics that differentiate them from DSE. Firstly, the uniform coating of anti-proliferative agents across the entire balloon surface ensures homogenous and continuous drug delivery throughout the lesion segment. In contrast, DES release drugs only from metallic struts, resulting in inferior spatial consistency within the vascular wall. Secondly, DCBs leave no permanent implants, which preserves the native vessel architecture and physiological compliance. This feature reduces late neointimal hyperplasia and stent-related adverse events, while also offering the potential to simplify and shorten dual antiplatelet therapy [7].

In coronary bifurcation lesions, DCBs provide several distinct clinical advantages. In the management of coronary bifurcation lesions, DCBs offer distinct

clinical advantages. Anatomically, as blood flow bifurcates from the proximal MV into the distal MV and SB, the hemodynamic milieu undergoes profound alterations. The carina typically experiences higher wall shear stress compared to the lateral walls, rendering it naturally resistant to atherosclerosis. However, the cage-like scaffolding created by DES implantation can induce carina shift and introduce metallic struts that disrupt laminar flow patterns. Such mechanical interference generates zones of pathological low shear stress, which subsequently stimulate neointimal hyperplasia and restenosis [8]. In contrast, DCBs preserve the native vascular geometry and the physiological compliance of the carina. By eliminating metallic interference, DCBs facilitate the restoration of laminar flow and minimize the risk of carina displacement, thereby optimizing the long-term biological stability of the bifurcation. Most side branches (SB) are small vessels, but they often supply myocardial territories of pivotal functional significance. The PICCOLETO II trial [9] demonstrated that DCBs are non-inferior to DES in the LLL of de novo small vessels treatment. (0.04 mm vs 0.17 mm, $P_{non\text{-}inferiority} = 0.001$; $P_{superiority} = 0.03$). It was demonstrated that DCBs are non-inferior to DES in the treatment of de novo small vessels. Besides, the use of DCBs in the side branches can improve the procedural success of provisional stenting, reduce the need for bailout stent implantation, simplify procedural complexity, and minimize radiation exposure for both patients and clinicians. Critically, DCBs maintain the original anatomy and hemodynamics of the carina. Furthermore, for in-stent restenosis (ISR) within bifurcations, DCBs limit metallic burden and avoid "stent-in-stent" layering, which preserves access for re-interventions in the future. Based on available clinical evidence, the European Bifurcation Club and international expert consensuses have endorsed the clinical value of DCBs in bifurcation PCI [10]-[12].

## 4. Available Evidence

### 4.1. DCB in Combination with Stents

Adhering to the "keep it safe and simple" principle, the European Bifurcation Club recommends provisional stenting as the primary strategy for most non-complex bifurcation lesions, with DCBs serving as an optimized adjunct for SB management [13]. Consequently, the hybrid DCB-DES strategy has become one of the most commonly adopted approaches in bifurcation lesions. In this hybrid strategy, DES implantation in the main vessel (MV) provides robust mechanical scaffolding to maintain luminal patency and stabilize the plaque burden, while DCB is applied in the SB to suppress neointimal hyperplasia.

#### 4.1.1. Side Branch DCB Inflation Following Main Vessel Stenting

The hybrid strategy, which balances structural support with the "leave nothing behind" philosophy, has been validated as safe and feasible by multiple prospective studies. The prospective, multicenter DEBSIDE study [14] evaluated the hybrid strategy in 50 patients with coronary bifurcation lesions except 0,0,1 type lesions according to Medina classification( a 3-digit binary code indicating stenosis

≥ 50% in the proximal main vessel, distal main vessel, and side branch. 1 = stenosis, 0 = no stenosis [15]). The procedural success rate was 100%. At 6-month follow-up, late lumen loss (LLL) in the SB was −0.04 ± 0.34 mm. Only one patient (2%) experienced myocardial infarction, and four patients (8%) underwent non-clinically driven target lesion revascularization (TLR), resulting in an overall major adverse cardiovascular events (MACE) of 10% with no cardiac deaths reported. In the BIOLUX-1 study [16], 35 patients (74.3% true bifurcation lesions, defined as involving a stenosis ≥ 50% in both the MV and the SB, specifically Medina 1,1,1, 1,0,1, or 0,1,1) were treated with everolimus-eluting stents in the MV combined with paclitaxel-coated balloons in the SB. Intravascular ultrasound (IVUS) assessment at 9 months revealed a side-branch LLL of −0.03 ± 0.22 mm. Furthermore, the 12-month composite endpoint (cardiac death, target-vessel myocardial infarction, and clinically driven target-vessel revascularization) occurred in 5.7%, with no definite stent thrombosis observed. Another prospective study [17] involving 45 patients with de novo true bifurcation lesions (Medina 1,1,1 or 0,1,1) reported an 88.9% procedural success rate, with bailout stenting required in 11.1% of SB. During the 6-month follow-up, the rate of target lesion failure was only 2.2%, with no cardiac death, target-vessel myocardial infarction, or side-branch thrombosis.

Compared to conventional angioplasty, the hybrid strategy provides superior anatomical and clinical benefits for SB management. The BEYOND study [18] enrolled 222 patients with non-left main coronary bifurcation lesions. Following successful DES implantation in the MV, patients were randomized (1:1) to receive either paclitaxel-coated balloons or regular balloon angioplasty in the SB. At 9-month follow-up, compared with the regular balloon angioplasty group, the DCB group demonstrated significantly lower target lesion stenosis (28.7% vs 40.0%, $P_{superiority} < 0.0001$) and LLL (−0.06 mm vs 0.18 mm, $P < 0.0001$). There were no significant differences between the groups in terms of major adverse cardiac and cerebral events (MACCE). In the DCB-BIF trial [19], 784 patients with true bifurcation lesions(67.9% involving the left anterior descending; 15.2% involving the distal Left Main) were randomized to either the DCB group or the non-compliant balloon group. At 1-year follow-up, the incidence of the composite endpoint (cardiac death, target-vessel myocardial infarction, and clinically driven target-vessel revascularization) was significantly lower in the DCB group (7.2% vs 12.5%, P = 0.013). The difference was caused by a reduction in target-vessel myocardial infarction, which was potentially related to a longer period of balloon inflation in the procedure and the anti-proliferative effects of DCBs. No significant differences were observed between the groups in cardiac death, all-cause mortality, revascularization, or stent thrombosis. A systematic meta-analysis [20] demonstrated that, compared to non-drug-coated balloons, DCBs in the SB significantly reduced LLL and diameter stenosis. Regarding clinical endpoints, DCBs were associated with a significant reduction in MACE at 6 or 9 months. Notably, several studies reported negative values of LLL in the DCB-treated side branches, which

suggests that the hybrid strategy provides additional luminal gain by promoting positive vascular remodeling.

Liu *et al.* [21] compared the hybrid strategy with the double-stent strategy for true left main (LM) bifurcation lesions. In the double-stent strategy group, the crush technique was performed predominantly (62%), followed by the culotte technique (18%), the T-stenting technique (18%), and the V-stenting technique (2%). The final kissing balloon inflation was performed on all patients. The immediate post-procedural coronary angiography showed no significant differences between the two groups in terms of minimal lumen diameter or luminal stenosis in the MV. Although the hybrid strategy group exhibited a smaller minimal lumen diameter and a higher degree of residual lumen stenosis of side-branch ostia after the procedure, the 6-month follow-up revealed superior mid-term vascular remodeling with the hybrid strategy. Specifically, luminal stenosis (16.71% vs 32.09%, $P = 0.002$) and LLL (−0.17 mm vs 0.43 mm, $P < 0.001$) of the SB, and LLL (0.09 mm vs 0.17 mm, $P = 0.037$) of the MV were all smaller in the hybrid strategy group than those in the double-stent strategy group. There were no statistical differences observed in the 1-year incidence of lumen restenosis or MACE between the two groups.

To mitigate long-term complications associated with permanent metallic stents, combining DCBs with bioresorbable scaffolds (BRS) represents a promising, fully resorbable intervention strategy. Following scaffold resorption, the lesion is expected to regain the native anatomical integrity and physiological hemodynamics. In a multicenter retrospective study [22] including 40 patients with coronary bifurcation lesions, involvement of the left anterior descending artery, left circumflex artery, right coronary artery, and left main was observed in 57.5%, 27.5%, 20%, and 2.5% of cases, respectively. Notably, a proportion of patients presented with multivessel bifurcation disease. All patients were treated with BRS implantation in the MV combined with paclitaxel-coated balloon angioplasty in the SB. During a mean follow-up of 15 months, only one patient required target vessel revascularization, and no cardiovascular death or thrombosis was observed. Although current evidence is limited to case reports and small-scale observational studies, the combination of BRS and DCBs appears to show favorable safety in bifurcation lesions, providing a rationale for future randomized controlled trials.

#### 4.1.2. Side Branch DCB Inflation before Main Vessel Stenting

In the provisional stenting strategy, following the stents are implanted in the MV, the side-branch ostia may become narrow due to the carina and plaque shift, which increases the technical difficulty of the re-crossing of guidewires and DCBs through the stent struts, but also risks compromising the integrity of the drug coating due to mechanical shearing against the metallic struts during balloon delivery. Herrador *et al.* [23] investigated a bifurcation PCI sequence in which a DCB was applied to the SB prior to stent implantation in the MV. At 12-month follow-up, angiographic outcomes in the DCB group were superior to those in the plain balloon group, with a MACE rate of 12%. In another study [24] focusing on true

coronary bifurcation lesions, the majority of patients (89.9%) were treated using a side-branch-first approach. During follow-up, this strategy was associated with side-branch lumen enlargement, as well as low rates of MACE (2.9%) and all-cause mortality (0.7%). These findings suggest that the side-branch-first approach is also safe and effective. However, it is noteworthy that carina shift induced by main-vessel stenting may lead to re-narrowing of the previously treated side-branch ostium. In the study by Herrador *et al.* [23], it was recommended that patients who underwent a side-branch-first strategy undergo kissing balloon inflation following DES implantation in the MV. When the SB showed an unsatisfactory angiographic result after inflation, which is defined as residual stenosis > 50% or flow-limiting dissection, bail-out stenting was expected to be performed. Specifically, the DCB group received a bare-metal stent that is shorter than the previously used DCB, while the conventional balloon group received a DES. The incidence of bail-out stenting was 10% in the DCB group, compared with 4% in the conventional balloon group. To date, there are no available studies evaluating the effect of different procedural sequences in the bifurcation PCI.

### 4.2. DCB-Only

The DCB-only strategy refers to a stent-free interventional strategy in which the MV and/or SB lesions are only treated with DCBs, perfectly representing the concept of "leave nothing behind" in the treatment of coronary bifurcation lesions. Some studies have reported low rates of restenosis and adverse clinical events in simple bifurcation lesions, but the long-term safety and efficacy of this strategy at high-risk, complex cases remain to be validated through large-scale randomized controlled trials in the future. Schulz *et al.* [25] performed the DCB-only intervention in 39 bifurcation lesions, one-third of which involved the left main artery. Angiographic follow-up at 4 months revealed a low restenosis rate of 10% and a TLR rate of 7.7%. Additionally, a total of 130 bifurcation lesions, 74.6% of which were true bifurcations and 46.2% classified as Medina 1,1,1, were enrolled in an international multicenter registry [26]. All patients initially underwent DCB-only treatment, and bailout stenting was reserved only for cases with flow-limiting dissections or severe elastic recoil. Remarkably, 53.8% of patients were successfully treated with DCB alone without stents. At 9-month follow-up, the DCB-only subgroup exhibited a TLR rate of 4.5% and a MACE rate of 6.1%, with no thrombotic events.

In the bifurcations with ostial side branch or distal main branch lesions (Medina 0,0,1; 0,1,0; or 0,1,1), the DCB-only strategy demonstrates superior maintenance of vessel patency compared to plain old balloon angioplasty (POBA). In the PEPCAD-BIF trial [27], 64 bifurcations not involving the proximal main branch were randomly assigned to treatment with the DCB or the uncoated balloon. Angiographic follow-up at 9 months revealed that the DCB group achieved significantly lower LLL (0.13 mm vs 0.51 mm, P = 0.013) and binary restenosis rates (6% vs 26%, P = 0.045) compared with the uncoated balloon group.

In more complex true bifurcation lesions, the DCB-only strategy has also shown

favorable angiographic and clinical endpoints compared with the double-stent strategy. Ke *et al.* [28] randomized 60 patients with non-left main true bifurcation (Medina 1,1,1; 1,0,1; 0,1,1) to either the DCB-only group or the double-stent group. The double-stent techniques, including DK-crush, DK-culotte, or T-stent, were performed at the operator's discretion. Baseline of anatomical characteristics, including bifurcation angle, degree of stenosis, and lesion length, were similar in the two groups. During the procedure, a higher incidence of non-flow-limiting dissections was observed in the DCB-only group. However, at the 1-year follow-up, LLL in both the MV and SB was significantly lower in the DCB-only group (LLL in MV: 0.05 mm vs 0.25 mm, P = 0.013; LLL in SB: −0.02 mm vs 0.11 mm, P = 0.005). There were no statistical differences in perioperative or 1-year cumulative MACE between the two groups.

### 4.3. DCB for Bifurcation Restenosis

Bifurcation lesions are associated with a high risk of restenosis due to factors such as metallic overlap, stent deformation, and abnormal shear stress, making the treatment more challenging than that of single-vessel lesions. Compared with DES, DCBs leave no permanent implants, which reduces the risk of geometric distortion related to metal overlap while preserving access for future reintervention.

Toru Naganuma *et al.* [29] compared DCBs with DES for the treatment of bifurcation ISR. A total of 167 bifurcation ISR were included. Despite the DCB group presenting with higher baseline EuroSCOREs, a greater proportion of true bifurcation, and a higher prevalence of multiple stent layers (resulting from stenting for a previous ISR), there were no significant differences between the two groups in MACE or TLR during a 2-year follow-up. It was suggested that DCB is non-inferior to DES for managing complex bifurcation ISR. Notably, patients with multiple stent layers in the DCB group experienced a remarkably high TLR rate of 54.1%. Multivariate Cox regression analysis identified multiple stent layers and true bifurcation lesions as independent predictors of MACE. Conversely, the choice of treatment strategy (DCB or DES) was not a decisive factor for long-term outcomes. The results indicate that anatomical complexity plays a dominant role in the long-term endpoints of bifurcation ISR.

Another study [30] focusing on LM bifurcation ISR demonstrated that the incidence of MACE in the DCB group was comparable to that in the DES group during 2-year follow-up (25% vs 25.5%, P = 0.96). Furthermore, a retrospective study by Lee *et al.* [31] revealed that the rate of MACCE was similar between the two groups, and the DCB group exhibited a lower incidence of cardiovascular mortality (0% vs 10.7%, P = 0.02) compared to the DES group. These findings collectively suggest that the application of DCB for left main bifurcation ISR is both safe and feasible.

### 4.4. Sirolimus-Coated Balloons for Bifurcation Lesions

Recently, rapamycin analog-based DCBs, especially sirolimus-coated balloons,

have emerged as a focal point of clinical research. Traditional DCBs primarily employ Paclitaxel, a highly lipophilic agent that binds specifically to tubulin heterodimers, stabilizing microtubule structures and inducing mitotic arrest to inhibit the proliferation of vascular smooth muscle cells. In contrast, Sirolimus reversibly inhibits the kinase activity of mammalian target of rapamycin complex 1 (mTORC1), leading to cell-cycle arrest at the G1 phase [32]. In addition, Sirolimus exerts potent anti-inflammatory properties by downregulating chemokine expression, thereby potentially retarding the progression of atherosclerosis [33]. Compared with paclitaxel, Sirolimus exhibits minimal interference with endothelial function due to lower toxicity and pro-inflammatory potential, which is advantageous for the promotion of early re-endothelisation. Nevertheless, the comparatively low lipophilicity of sirolimus restricts its penetration into the vessel wall, thus limiting its clinical application in earlier-generation DCBs. Advances in drug-coating technologies, including nanotechnology, biodegradable polymeric microspheres, and microporous balloon platforms, have substantially enhanced the local bioavailability of sirolimus through optimized drug release kinetics, making sirolimus an increasingly attractive agent for next-generation DCBs [34]-[36].

The SPACIOUS trial [37] is the only randomized controlled study to date that directly compared sirolimus-coated balloons (SCB) with paclitaxel-coated balloons (PCB) for the treatment of coronary bifurcation lesions. A total of 230 patients with non-left main true bifurcation lesions underwent successful drug-eluting stent implantation in the MV and were subsequently randomized in a 1:1 ratio to treatment with either a SCB or a PCB for the SB. At 9-month follow-up, the SCB demonstrated a significantly lower rate of binary restenosis (4.4% vs 12.8%; P = 0.043) compared with the PCB group. No significant differences were observed between the two groups with respect to LLL, net lumen gain, or 1-year clinical outcomes. Cox regression analysis showed that treatment with SCBs was not associated with an increased risk of adverse clinical events in patients with bifurcation lesions.

Currently, PCBs remain the most widely utilized DCB type in clinical practice and are recommended as the preferred DCB type in international expert consensus documents [11] [12]. In contrast, the evidence-based clinical data for SCB are still in the cumulative phase. Particularly in complex situations such as coronary bifurcation lesions, the long-term efficacy and safety profile of SCBs requires further validation through high-quality randomized controlled trials with long-term follow-up.

## 5. DCB-Based Strategy Selection

DCB-based strategies for coronary bifurcation lesions include the DCB-only approach and the hybrid strategy combining DES with DCB. The decision to implant a stent depends on multiple factors, such as the anatomical location of the lesion, lesion characteristics, vessel diameter, and the extent of the myocardial territory supplied.

For LM bifurcation lesions, safety remains the paramount consideration. Thus, clinical practice prefers either a double-stent or DES-DCB hybrid strategy. Evidence for the DCB-only approach in this high-risk territory remains limited, as most studies exclude LM bifurcation lesions.

For non-LM bifurcations, available studies have not yet performed head-to-head comparisons across different anatomical sites (such as left anterior descending-diagonal branch or left circumflex-obtuse marginal branch bifurcations) to define the optimal application site for DCBs. Consequently, treatment decisions are primarily driven by specific lesion characteristics. Based on angiographic findings, it is generally straightforward to distinguish between true and non-true bifurcation lesions. The Chinese Expert Consensus suggests the DCB-only approach for non-true bifurcations, whereas the hybrid strategy is recommended for true bifurcations. The Asia-Pacific consensus proposes that, following optimal lesion preparation, a DCB-only approach may also be considered in true bifurcation lesions if angiographic results are acceptable, which is defined as the absence of flow-limiting dissections, residual stenosis ≤ 30% in MV, and residual stenosis≤50-70% in SB [12]. According to the European Bifurcation Club expert consensus, the provisional stenting strategy is recommended for non-left main coronary bifurcations, specifically those classified as non-true bifurcations or true bifurcations with SB lesion length > 10 mm [38]. Although DCB represents an attractive therapeutic modality, robust evidence supporting the hybrid strategy or DCB-only approach remains insufficient. Furthermore, several technical intricacies, including SB selection criteria and the optimal integration of final kissing balloon inflation or re-POT, remain unresolved [10]. In contrast, the German Consensus Group suggests a more tailored approach: if pre-dilation of the MV and SB results in thrombolysis in myocardial infarction (TIMI) < 3 or dissection, the implantation of DES is mandatory. Conversely, the DCB-only strategy is considered a feasible alternative provided that satisfactory angiographic outcomes are achieved in both the MV and SB [39]. This consensus divergence fundamentally reflects the ongoing debate in interventional cardiology between prioritizing immediate anatomical expansion and pursuing long-term physiological remodeling, driven by differing clinical philosophies and evidence interpretations.

## 6. Conclusion and Future Perspectives

Coronary bifurcation interventions remain technically challenging and are associated with a relatively high incidence of procedural complications, and no universally accepted optimal interventional strategy has been established. However, several important issues still limit the widespread adoption of DCBs. In the hybrid strategy combining DES and DCBs, the impact of the treatment sequence of the MV and SB on vascular remodeling and clinical outcomes remains unclear. The safety of the DCB-only strategy in complex bifurcation lesions is supported by very limited evidence. Moreover, although new-generation sirolimus-coated balloons have been increasingly introduced into clinical practice, data are limited,

particularly in coronary bifurcation lesions. In addition, most available clinical studies have short follow-up durations (≤1 year), which is insufficient to adequately assess the long-term effects of DCB treatment on late restenosis, late thrombosis, and vascular remodeling. High-quality, large-scale randomized controlled trials are urgently warranted to standardize clinical protocols for drug-coated balloons in the treatment of coronary bifurcation lesions.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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