Current Status of Bifurcation Stent Systems

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Abstract

Coronary bifurcation lesions are frequently observed and remain a challenging patient population for successful treatment. Currently, the provisional approach of treatment is considered the first-line method of treatment. Many dedicated bifurcation stents and newer treatment approaches such as drug-coated balloons and bioresorbable scaffolds are also particularly attractive concepts. The aim of this article is to review the current treatment approaches for coronary bifurcation lesions, mainly the dedicated bifurcation stent systems while briefly covering the related topics of provisional and two-stent procedures of treatment and the current status of drug-coated balloons and bioresorbable scaffolds. This article highlights the critical trials involving these strategies. We searched PubMed, Google Scholar, Medline and ClinicalTrials.gov to identify all the relevant trials assessing the safety and efficacy of dedicated bifurcation stent systems, drug-coated balloons vs. other traditionally used coronary stents. A debate still prevails to treat coronary bifurcation lesions optimally. Provisional stenting strategy remains the gold standard for treating a majority of coronary bifurcation lesions, but the two-stent approach can be indicated for some lesions. More long-term follow-up trials are required to concretely define the role of newer treatment approaches such as dedicated bifurcation stents, drug-coated balloons, and bioresorbable scaffolds.

INTRODUCTION

Coronary bifurcation lesions (BIFs) are one of the most exciting and challenging pathologies of the coronary artery. They account for roughly 20% of all percutaneous coronary interventions (PCI) and are connected to lower procedural success and high rates of long-term major adverse cardiac events (MACE) [1, 2]. BIFs are so-referred to lesions occurring at, or adjacent to, a significant division of a major epicardial coronary artery. They vary anatomically, including the dynamic changes occurring during the cardiac cycle and in response to treatment [3]. Every single bifurcation is different. Hence, there is no only strategy applicable to every bifurcation [3]. Noteworthy improvements were made in the recent past regarding the understanding and treatment of BIFs. These include the introduction of drug-eluting stents, use of single stent techniques vs. two-stents, acceptance of a suboptimal result in the side-branch (SB), etc [4].

Approaches to Bifurcation Treatment

The simplified approaches as outlined in the Figure 1 which is related with a low risk of failure and complications.

Provisional Approach

Considerable debate is ongoing over the last few years to ascertain the optimal stenting strategy for treating BIFs. Presently, the use of single-stent strategy (Provisional Strategy) is favored as the first choice of treatment of non-left main (LM) bifurcations in published trials [3, 5]. The reasons for the earlier stated preference is that the formal strategy is quick, easy to perform, safe, and shows similar results to a more complex technique [3]. Two appropriate approaches for provisional stenting are either using a pressure wire to interrogate the SB's lesion or performing kissing balloon inflation (FKI) on all angiographically significant SB lesions at the ostium [3]. However, SB occlusion post stenting of main vessel (MV) is one of the most frequent complications, encountered during bifurcation stenting. It appeared rational to accept that the prominent mechanism behind SB compromise is shifting of plaque from MV to SB (plaque shift) as the burden of plaque in MV and also in SB is the chief risk factor of SB

compromise [6, 7]. Although pre-dilation of the SB may be used, its advantage remains controversial.(8) On the above lines, Lee et al. from the new COBIS II registry investigated SB pre-dilation effects on procedural and long-term outcomes in coronary bifurcation lesions involving the provisional approach. This trial concluded that SB pre-dilation technique improved acute angiographic and procedural findings, but did not advance long-term clinical outcomes in case of actual bifurcation lesions [8].

Two-Stent Approach

There is room to use elective two-stent techniques as well, to treat severely diseased large SB (like LM bifurcation lesions) supplying large area of myocardial volume and complex BIFs (calcified side branches with ostial disease extending 5 mm from carina, sharp angulated origin of side branch where there is anticipated difficulty in recrossing after main vessel stenting) to avoid acute hemodynamic compromise. However, none of these two-stent techniques are proven to be superior to others. To reduce the risk of SB occlusion and to improve patient outcomes, selection of proper bifurcation treatment strategy with the aid of intravascular ultrasound (IVUS) for SB ostium is fundamental [9, 10]. The most commonly used two-stent approaches are double kissing (DK) crush, culotte, mini-crush, V and simultaneous kissing stent (SKS) [3, 11]. As stated earlier, controversies still prevail regarding the use of sophisticated techniques. Currently, optimally performed two-stent techniques by using new-generation drug-eluting stents (DES) may provide similar or even better outcomes vs. the simple provisional methods [12].

Comparison of the Stenting Approaches

Several landmark trials also need to be mentioned here in a more detailed form to evaluate the significance of the two strategies thoroughly (Table 1).

The CACTUS was a prospective, randomized, multicenter study comparing elective "crush" stenting and sole stenting of the MB with provisional side-branch T-stenting with mandatory final kissing-balloon inflation (FKBI/FKI) in true BIFs. In this significant trial, 350 patients from 12 centers in Europe were enrolled. One hundred seventy-seven patients were enrolled in the Crush group, while 173 patients were included in the provisional arm. 94% of the lesions were defined to be true bifurcations out of which 75% lesions were classified as type 1,1,1 as per MEDINA method. It should be noted here that 31% of cases in the provisional group required additional stent implantation. No significant differences were found regarding the primary endpoint at 6-months follow-up: cumulative MACE rate was 15.8% in the Crush group vs. 15% in the provisional group. It should also be noted that the performance of FKI vs. no FKI was associated with a significantly lower incidence of in-hospital and follow-up MI and angiographic restenosis in the MB and the SB in both the groups [13].

Thus, CACTUS demonstrated that a provisional strategy is useful with the additional necessity to implant a second stent in the SB for nearly 1/3rd patients [13]. To conclude, CACTUS supports the usual recommendation of using provisional stenting for coronary bifurcation lesions [4].

The prospective randomized NORDIC trial provided more definite evidence for using either one-stent or two-stent technique with DES to treat bifurcation lesions. This landmark trial compared the strategy of stenting both the MB and SB vs. the provisional stenting of the MB only with sirolimus-eluting stents. The operator was required to attempt the FKI technique for all SB stenting cases at the end of the method. MACE after six months was the primary endpoint of the trial, which was not significantly different in both the groups after six months. After eight months, the combined angiographic endpoint of diameter stenosis > 50% of MV and occlusion of the SB was found in 5.3% in the provisional main branch stenting group and 5.1% in the two-stent group. To conclude, this trial suggests that the simple provisional stenting strategy used was associated with reduced procedure and fluoroscopy times and lower rates of procedure-related biomarker elevation. The study again highlights that most of the bifurcations can be treated with a provisional stenting strategy with an optional second stent. Also, a planned two-stent approach should be used for treating lesions with a large SB (like left main bifurcation) (Table 2) [14]. However, two-stent techniques are chosen more frequently for LM bifurcation than for non-LM lesions due to ischemic myocardial volume, which would be risk by adverse events [9]. In the DKCRUSH-V randomized trial, a planned DK crush two-stent strategy reduced target lesion failure (16.9% vs. 8.3%; P = 0.005) and stent thrombosis (4.1% vs. 0.4%; P = 0.006) compared with a provisional stenting for unprotected left main distal bifurcation lesions through 3-year follow-up [11].

To conclude, the success of the procedure itself is more dependent for positive long-term clinical outcomes than the type of stenting, underlining the greater importance of augmenting the preferred technique than the choice of method [9].

Dedicated Bifurcation Stents (DBS)

Rationale for DBS

As noted, the treatment approach for bifurcation PCI with either single or two stents is confusing, challenging and is subjected to several drawbacks. Hence, to overcome these deficiencies, some advanced stents dedicated for treating bifurcation lesions are now available. These newly available dedicated stents can be broadly classified as per below-mentioned Table 3.

The below mentioned Table 4 explains the unique

design features along with the details of safety and effectiveness of currently known dedicated bifurcation stents to treat coronary bifurcation lesions.

Table 1. Results of Provisional vs. Two-Stent Technique

Reference Study	Year	Number of Patients		FU (in Months)	Adjusted Hazard Ratio/Comparative Rates (%)						
		Provisional	Double		MACE	Death/MI	Death	MI	TVR	All-Cause Death	TLR
Palmerini, et al. [15]	2008	456	317	24	0.48 (0.33–0.69) P = 0.001	0.38 (0.17–0.85) P = 0.018	---	---	---	---	---
Toyofuku, et al. [16]	2009	261	119	36	---	---	0.61 (0.34–1.08) P = 0.09	---	0.32 (0.18–1.21) P < 0.01	---	---
Kim, et al. [17]	2011	234	158	36	0.89 (0.22–0.67) P < 0.001	---	0.77 (0.28–2.13) P = 0.62	0.38 (0.19–0.78) P = 0.008	0.16 (0.05–0.57) P = 0.005	---	---
Song, et al. [18]	2014	509	344	36	0.42 (0.28–0.63) P < 0.001	0.48 (0.25–0.93) P = 0.03	0.30 (0.11–0.81) P = 0.02	0.41 (0.18–0.95) P = 0.04	0.47 (0.32–0.69) P < 0.01	---	---
Behan, et al. [19] **BBC ONE NORDIC**	2016	447	443	60	---	---	---	---	---	2.9% vs. 5.9% (P = 0.17) 5.9 vs. 10.4 (P = 0.10)	---
D'Ascenzo, et al. [20]	2016	178	87	120	60% vs. 66%, p>0.05	---	34% vs. 43%, P > 0.05	9% vs. 14%, P > 0.05	---	---	19% vs. 25%, P > 0.05
Chen et al. [11]	2019	242	240	36	16.9% vs. 8.3%, P = 0.005	5.0% vs. 3.3%, P = 0.37	---	5.8%vs. 1.7%, P = 0.017	---	---	10.3% vs.5.0%, P = 0.029

MACE: Major Adverse Cardiac Events; MI: Myocardial Infarction; TLR: Target Lesion Revascularization; TVR: Target Vessel Revascularization.

Table 2. Preferred Strategy to Treat Bifurcation Lesions as Per Lesion Characteristics [9]

Preferred Strategy (Lesion characteristics)
Provisional
1) Immaterial stenosis at the ostial LCX with MEDINA classification 1, 1, 0 or 1,0,0
2) Small LCX <2.5 mm in diameter
3) Little LCX, right dominant coronary system
4) A wide angle between LAD and LCX
5) No concomitant disease or only focal disease in LCX
Two-stent approach
1) Significant stenosis at the ostial LCX with MEDINA classification 1, 1, 1 or 1, 0, 1 or 0, 1, 1
2) Large LCX ≥2.5 mm in diameter
3) Diseased left dominant coronary system
4) Narrow-angle between LAD and LCX
5) Concomitant diffuse disease in LCX

LAD: Left Anterior Descending; LCX: Left Coronary Circumflex

Table 3. Classification of Current DBS [4]

Purpose of Stents	Some Available Stents	Significance
Stents for provisional SB stenting that enable or maintain access to the SB after MB stenting and do not need re-crossing of MB stent struts	Petal (boston scientific), invatec (invatec), antares (trireme), y-med sidekick (y-med Inc.), nile croco (minvasys), multilink frontier, (abbott vascular)	Sanctions the second stent placement on the SB, if required
Side-branch stenting followed by MB stent implantation in the bifurcation and requiring re-crossing	Sideguard (Cappella Inc.), Tryton (Tryton medical), Axxess plus (Devax)	Sideguard and Tryton are developed to treat the SB first. They need re-crossing into the SB after MB stenting. The Axxess plus is planted in the proximal MB at the level of the carina and does not need re-crossing into the SB but may require the additional implantation to treat some BIFs completely

BIFs: Bifurcation Lesions; MB: Main Branch; SB: Side Branch

Table 4. Brief Information on Currently Available DBS

DBS System	Company	Unique Design Features and Mechanism	Concerned Clinical Trial	Available Clinical Trial Results or Conclusion of the Trial	Reference
Y-Med Sidekick	Y-Med, USA	1) Low-profile 6F guide compatible SDS 2) SDS integrates an MB fixed-wire platform with a rapid-exchange steerable guidewire that preserves SB access 3) Available in 3 models with different exit ports as per the lesion	The first-in-man clinical study, Ischinger, et al. 2007	Device success rate – 80%, additional stent Requirement – 40%, 1 MACE reported in a short-term FU	[4]
Multilink Frontier	Abbott Vascular, USA	Balloon expandable, two balloons with simultaneous kissing inflation, two guidewire lumens, integrated-tip design	Frontier stent multicentre registry	Device Success – 91%, Procedural Success – 93%. In-hospital MI in 2 patients following SB occlusion Late loss - 0.84–0.55 mm, Overall bifurcation restenosis rate 44.8%, At 6-months FU, TLR – 13.3% and MACE – 17.1%	[4]
Antares	TriReme Medical, USA	Single balloon and inflation, rapid exchange, peel away lumen for the second wire	TOP	---	[21]
Xience™ SBA/FRONTIER BMS	Abbott Vascular, USA	Double balloon and wire, single inflation, everolimus elution	FRONTIER stent registry	Procedural success rate >90%, (Refer to data of Multilink Frontier)	[21]
Invatec, Twin-Rail™	Invatec, Italy	Dual balloon, a single inflation	Lefevre	Angiographic success – High, Device Success – 75%. TLR at seven months – 14.3%, In conclusion, a trend for higher device success and better safety profile with the Twin-Rail vs. single balloon SDS was reported.	[4,21]
Minvasys Nile Croco®	Minvasys, France	Dual balloon, two catheters, Paclitaxel elution in the newer generation	Del Blanco et al.	Nile Croco Study demonstrated high performance and safety of Nile Croco stent system in treating bifurcation lesions, with a high procedural success rate and low prevalence of MACE.	[21, 22]
Taxus Petal (AST Petal)	Boston Scientific, USA	Dual balloon, dual wire, single inflation, Paclitaxel elution	Ormiston et al.	Successful implantation occurred in 89.3% of patients. On a per-device basis, 73.5% of deployments were successful. The primary endpoint occurred in one patient. TVR was 11.1%, TLR was 7.4%, and through 1-year, there were no deaths, Q-wave MIs, or stent thrombosis. In-segment late loss was 0.47 + or - 0.45 mm (proximal MB), 0.41 + or - 0.57 mm (distal MB), and 0.18 + or - 0.39 mm (SB) as observed in 21 patients.	[21, 23]
Stentys	Stentys, USA	Single wire, second, separate wire needed for SB, self-expandable, Paclitaxel elution in the newer generation	OPEN-1, Cortese et al., APPOSITION III	OPEN I demonstrated excellent procedural success with a relatively low MACE and competitively low LLL in both MB and SB at six months. Stentys demonstrated good intermediate procedure-related results with low AE rates at mid-term FU as per Cortese, et al. Stentys was termed safe and feasible also in case of PCI-STEMI with acceptable 1-year cardiovascular event rates, improving with post-dilation in APPOSITION III	[21, 24, 25]
Tryton Side Branch Stent™	Tryton Medical, USA	Single balloon, single wire	Tryton Side Branch study, Genereux, et al.	The Tryton Confirmatory Study along with TRYTON Pivotal RCT supports the safety and effectiveness of Tryton SBS for treating BIFs involving large SBs	[21, 26]
Cappella Sideguard®	Cappella Medical Devices, Ireland	Single balloon, single wire, self-expandable, nitinol-based	Mamas, et al.	The stent can be used to treat complex BIFs and is not affected by limitations stated with standard methods.	[21, 27]
Devax AXXESS™	Devax, USA	Single wire, self-expandable, Biolimus A9 elution	DIVERGE, Triantafyllis et al., Borgia, et al.	Firstly, DIVERGE confirmed the safety and efficacy of AXXESS stent to treat BIFs. Then, Triantafyllis et al. stated that percutaneous revascularization of complex BIFs with the AXXESS stent is safe, providing excellent results at long-term, especially in non-LM lesions. Recently, the feasibility of AXXESS to treat true double coronary bifurcation lesions was also reported	[21, 28, 29]
Medtronic Bifurcation Stent	Medtronic, USA	Dual balloon, dual wire, single inflation	BRANCH	BRANCH demonstrated the Medtronic Bifurcation Stent to be safe and effectively deployable to treat a plethora of BIFs with good clinical outcomes	[21, 30]
BiOSS Expert	Balton, Poland	Final kissing balloon inflation, paclitaxel elution	POLBOS I	MACE rates were comparable. TLR was higher with BiOSS Expert. A more aggressive protocol generated better outcomes	[31]
BiOSS LIM	Balton, Poland	Final kissing balloon inflation (FKBI), sirolimus elution	POLBOS II	MACE and TLR were comparable between BiOSS LIM and rDES. Cumulative MACE and TLR were also comparable at 12-month FU, FKBI subgroup of BiOSS LIM demonstrated significantly lower restenosis rates	[32]

AE: Adverse Event; BIFs: Bifurcation Lesions; FKBI/FKI: Final Kissing Balloon Inflation; FU: Follow-up; MACE: Major Adverse Cardiac Events; MB: Main Branch; MI: Myocardial Infarction; rDES: Recent Drug-Eluting Stents; LLL: Late Lumen Loss; PCI-STEMI: Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction; SB: Side Branch; SDS: SideKick dedicated system; TLR: Target Lesion Revascularization; TVR: Target Vessel Revascularization.

Table 5. Effectiveness of Drug-Coated Balloons in Coronary Bifurcation Lesions [5]

Trial	No. of Patients (n)	Treatment	DCB Used	Main Results
PEPCAD V	28	DCB in both branches + BMS in MB	Sequent Please	LLL: 0.38 ± 0.46 mm (MB) and 0.21 ± 0.48 mm (SB)
DEBUIT	117	BMS in MB (37 patients) DCB in both branches + BMS in MB (40 patients) DES in MB (40 patients)	Dior I	In-segment LLL: -0.49 ± 0.85 mm -0.41 ± 0.60 mm -0.19 ± 0.64 mm, respectively, (p = 0.001)
BABILON	108	DCB in both branches + BMS in MB (52 patients) DES in MB (56 patients)	Sequent Please	In-segment LLL: -0.31 ± 0.48 mm -0.16 ± 0.38 mm (p = 0.150)
BIOLUX-I	35	DES in MB and DCB in SB	Pantera Lux	SB LLL 0.10 ± 0.43 mm
DEBSIDE	50	DES in MB and DCB in SB	Danubio	SB LLL -0.04 ± 0.3 mm
SARPEDON	58	DES in MB and DCB in SB	Pantera Lux	MV and SB LLL were 0.21 ± 0.35 mm and 0.09 ± 0.21 mm, respectively
FASICO Registry [33]	34	DCB+DES on the same vessel in 26.5% patients. Hybrid approach SCB + stent on another vessel in 14.7% patients	Magic Touch, sirolimus	TLR and MACE in 3 patients No adverse events were observed in patients treated for de novo lesions or BMS restenosis. This DCB (sirolimus) demonstrated high immediate technical performance and adequate short-term efficacy and safety
Sgueglia, et al. [34]	12	BMS in MB followed by kissing DCB	SeQuent Please. In.Pact Falcon. New Dior. Pantera Lux	No MACE, ISR reported

BMS: Bare-Metal Stent; DCB: Drug-Coated Balloon; DES: Drug-Eluting Stent; ISR: In-Stent Restenosis; LLL: Late Luminal Loss; MACE: Major Adverse Cardiac Events; MB: Main Branch; MV: Main Vessel; SB: Side Branch

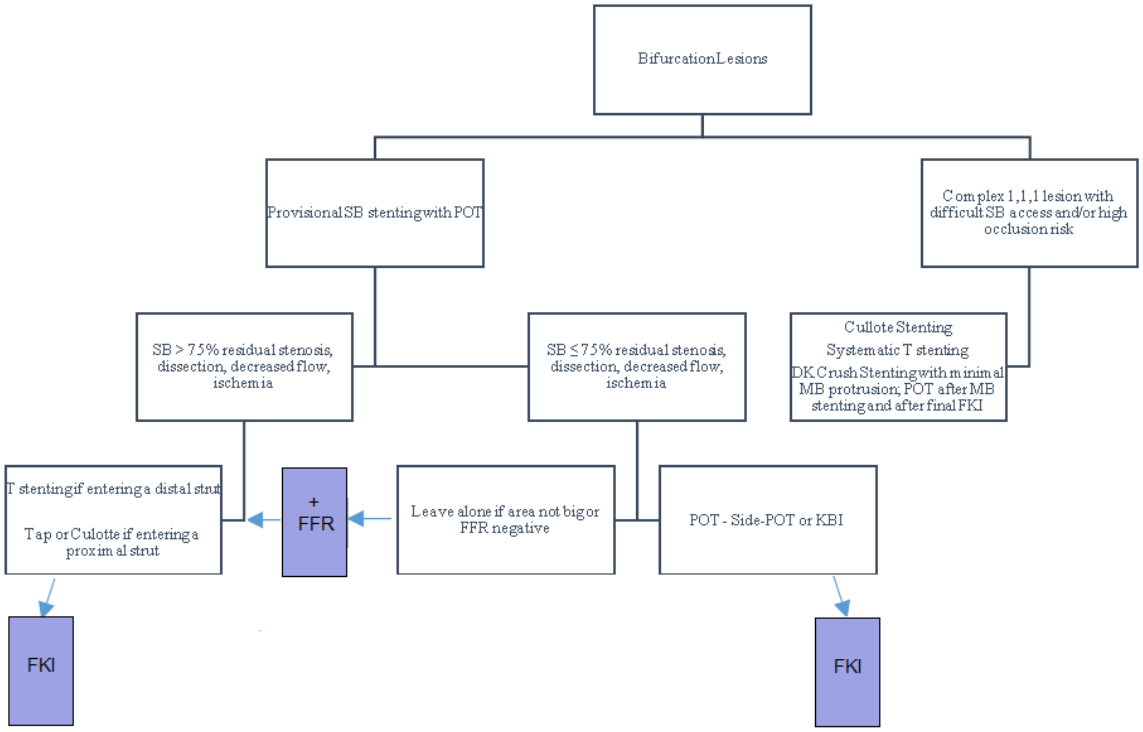

Figure 1. Simplified Approach to Treat BIFs [1]. FFR: Fractional Flow Reserve; FKI: Final Kissing Balloon; POT: Proximal Optimization Technique; SB: Side Branch

Other Available Techniques for Treating Bifurcation Lesions

Use of Drug-Coated Balloons to Treat BIFs

Drug-coated balloons (DCB) are a comparatively new technology, permitting the release of anti-proliferative agent discarding the concept of a permanent prosthesis. These are proved to be useful to treat in-stent restenosis and shown promise also to treat de novo small coronary vessel disease [5]. However, currently, the data available to determine its exact value remains scarce. Also, these data often demonstrate conflicting results. The DCB was termed superior to the plain old balloon angioplasty in managing the SB post stent deployment in the main branch as per the PEPCAD-BIF trial. Contrary to this, DCB in both MB and SB was inferior to DES as per DEBUIT and BABILON trials (Table 5) [5].

Use of Bioresorbable Vascular Scaffolds to Treat BIFs

Bioresorbable Scaffolds (BVS) were introduced as a newer paradigm for coronary artery disease treatment

permitting temporary vessel support and drug delivery. However, precise recommendations involving the use of BVS for treating bifurcation lesions are lacking due to their initial avoidance in addressing the subset of this patient population [35].

Also, a number of disadvantages are linked with the use of BVS at bifurcation lesions. Firstly, the free use of the device in patients presenting with bifurcations, arrive at the cost of distressingly high rates of early device thrombosis. Also, BVS has thicker and broader struts than metallic stents, rendering a more bulky device. There are also constraints on post-dilation techniques, which are crucial elements of modern bifurcation PCI, as polymeric struts may break more easily, limiting their expansion capacity [5].

DISCUSSION AND CONCLUSION

Coronary bifurcation lesions are still challenging as far as their treatment is concerned. The provisional one stent approach involving the stenting of the main branch seems to be a suitable first-line treatment approach for most bifurcation lesions. Still, some lesions require two-stent approach. The enhanced outcomes with the currently available DES for bifurcation lesions suggest the ready use of the systemic two-stent approach.

Also, the dedicated bifurcation stent introduces a new treatment approach consisting of state-of-the-art technologies into cath labs but requires skilful expertise to handle the intricate design of these systems. However, long-term data from large volume trials are necessary before reaching a definite recommendation for their use. Preliminary results with newer devices such as drug-coated balloons and bioresorbable vascular scaffolds are also impressive but lack sufficient data in treating bifurcation lesions.

Conflicts of Interest

The author has no conflict of interest to declare.

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