CORONARY BIFURCATION DISEASE AND BIFURCATION STENTING: A PRACTICAL APPROACH

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ABSTRACT

Approximately 20% of percutaneous coronary interventions (PCIs) are performed to treat coronary bifurcations. PCIs in bifurcation lesions have been associated with lower procedural success rates and worse clinical outcomes than non-bifurcation lesions. In addition, PCIs in bifurcation are renowned for being technically demanding. Indeed, there are several challenges in percutaneous treatment of bifurcation lesions to take into account, including: 1) localisation, size, and angle of bifurcation branches in coronary tree (e.g. left main versus others); 2) disease extension at bifurcation (true versus pseudo-bifurcation lesions); 3) stenting technique; and finally 4) choice of the most appropriate device. Several studies have been published in each of these settings, but therapeutic strategies are still linked mostly to clinical setting and operator experience. In this review, we have summarised the most important aspects and clinical studies on bifurcation lesion treatment with the aim to give the readers a practical approach to bifurcation PCI.

Keywords: Atherosclerotic disease, percutaneous coronary intervention, bifurcation disease.

BIFURCATION DEFINITION AND CLASSIFICATION

The first step in approaching a bifurcation lesion is its identification and definition. The European Bifurcation Club (EBC)[1] has proposed the following practical definition: "A coronary artery narrowing occurring adjacent to, and/or involving the origin of a significant side branch (SB)." Practically speaking, a significant SB is a branch that you do not want to lose during revascularisation. Although there are currently at least six different classifications of bifurcation lesions (where in all of them, a combination of letters and/or digits describes the angiographic position of the lesions in the bifurcation, Figure 1), which require significant efforts for memorisation; the most user-friendly and easy-to-remember is the Medina classification.[2] Such classification consists of recording any narrowing in excess of 50% in each of the three arterial segments of the bifurcation in the following order: proximal main vessel, distal main vessel, and proximal SB. Such classification is the most standardised and utilised nowadays to indicate the presence of a significant stenosis (1) or the absence of stenosis (0). A true bifurcation presenting a significant disease of both main branches (MB) and SB will then be indicated as 1.1.1; 0.1.1; or 1.1.0 Medina class. The main limitation of this classification is the absence of any information on lesion length, especially for the SB, and angiographic features (e.g. presence of calcifications, bifurcation angle). Indeed, the severity of SB and the angle between the two branches have been shown to significantly impact on treatment technique choice and actually on long-term clinical outcome.[3] However, apart from the fact that the presence of quantifiable variables would be recorded under "yes" or "no", the addition of these simple angiographic parameters and possibly others (e.g. eccentric location of the MB lesion, TIMI flow) would negate the simplicity of the Medina classification.

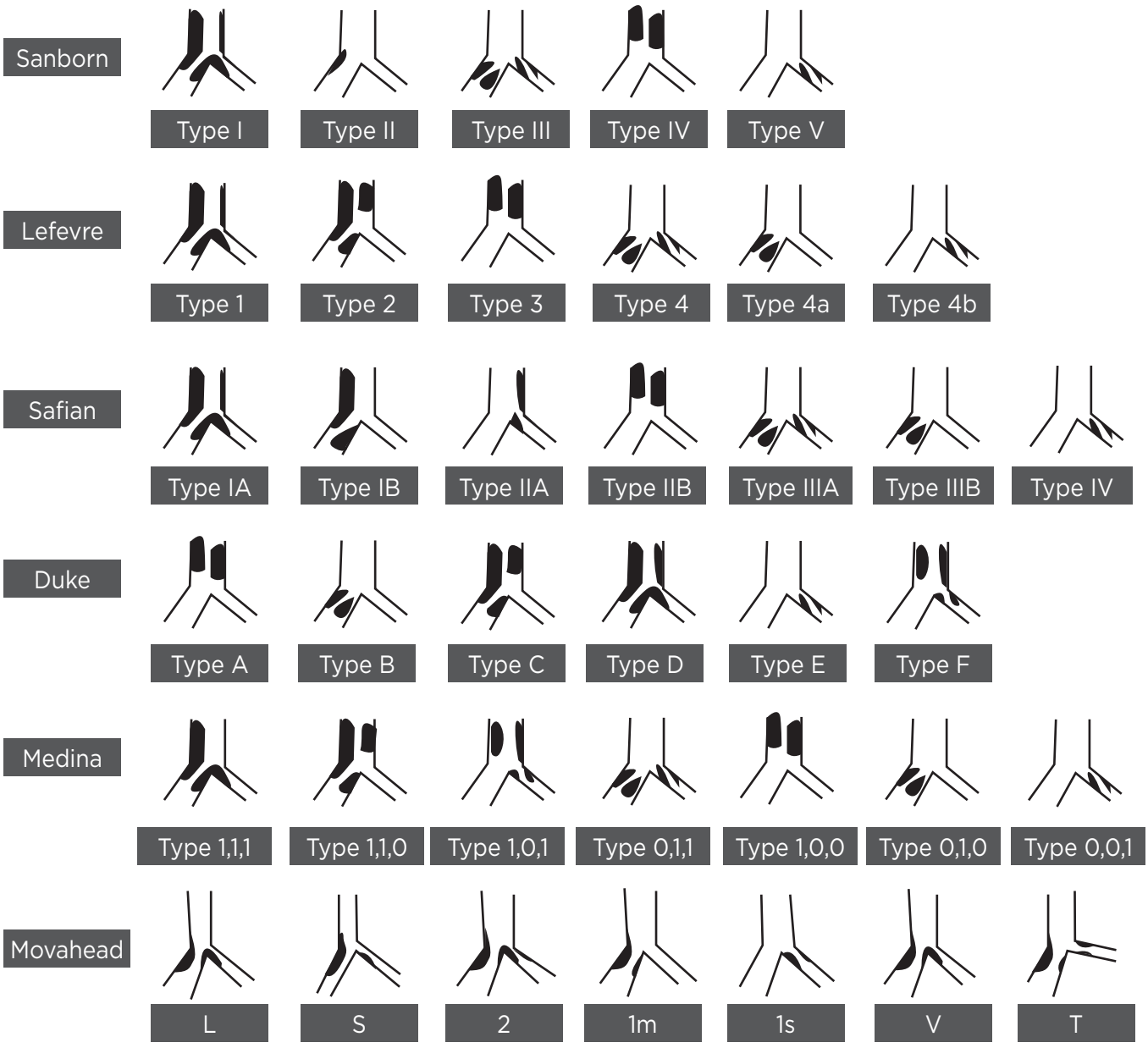

Figure 1: Published classification of coronary bifurcation lesions.

After bifurcation classification, it is very important to consider its localisation in the coronary tree. In this setting, we think that left main coronary artery (LMCA) disease with involvement of distal bifurcation is a different entity than other bifurcation lesion location and should then be approached differently as outlined below in this review.

As stated above, bifurcation lesions could be divided into true bifurcation (Medina 1.1.1; 1.0.1; 0.1.1) where MB and SB are both significantly narrowed (>50% diameter stenosis), and non-true bifurcations, which include all the other lesions involving a bifurcation. This distinction is likely the most important for the choice of the technical approach; indeed, non-true bifurcation should always be treated with a one-stent strategy. On the other hand, in true bifurcation lesion we must consider some anatomical characteristics of the SB such as the length of disease (i.e. localised only to the ostium or extending beyond it), its size (i.e. <2.5 mm), angle (i.e. <70°), and plaque distribution at the level of the carina.

In this setting, a new comprehensive classification of bifurcation lesions that is simple, practical, and inclusive of other important features of coronary bifurcation lesions has been recently published. This classification is based on a system composed of a single prefix (B, for bifurcation lesion) to which up to three main suffixes are added, describing important anatomical features of the lesion:[4]

the proximal segment size (suffix S, for small), atherosclerotic disease burden (one or two-branch disease), and the bifurcation angle (V or T angle). It is known that if the proximal segment is too small (small is defined as less than two-thirds of the sum of the diameters of both branch vessels) the kissing stenting technique cannot be utilised. The second suffix describes the involvement of the disease area of the bifurcation branches, namely, if both ostia at the bifurcation site are involved, the number '2' is used; if the MB only is involved, '1m' is used; and if the SB only is involved, '1s' is used. Thus, a B2 lesion in this classification is a true bifurcation. The bifurcation angle is another important feature of bifurcation lesions. Steep angulations have been found to be associated with higher risk of abrupt vessel closure,[5] SB occlusion,[6] and major adverse cardiac events.[3] In this classification, the third suffix describes the angulation of bifurcation branches: suffix V applies to angles of <70°, and the suffix T applies to angles of >70°. Thus, a B2V lesion is a true bifurcation with an angle <70° between MB and SBs.

A comparison of known classifications, with a detailed algorithmic approach to coronary bifurcation interventions was recently published[7] as a guide to interventional cardiologists for technical decision-making based on lesion characteristics.

TECHNICAL STRATEGY

Techniques used for treatment of coronary bifurcation lesions must be accurately defined for at least two reasons. First, it is important to compare various techniques with an intention-to-treat (ITT) analysis with respect to success rate, procedure duration, X-ray exposure, volume of contrast media used, and long-term follow-up. Second, impact of elaborate techniques on the outcome can be major.[8] The EBC has strived to include all potential technical strategies by describing four ways of beginning the procedure.[9] This classification can be summarised with the acronym 'MADS' (Figure 2). Each letter of the acronym represents the initial step of first stent placement: M (Main) stent implantation in the proximal main vessel; A (Across) stent implantation across the SB; D (Distal) stent implantation at the ostium or both distal branches; and S (Side) where the SB is stented first with or without protrusion. Each of these families contains several possible techniques with one or two-stent implantation. For example, M as the initial step may be followed by the opening of the stent towards both branches (SKIRT technique),[10,11] with subsequent successive or simultaneous stent placement in one or both distal branches. The second family (A) may be the first and the last step of the procedure but may also be followed by the opening of a stent cell with or without kissing balloon (KB) inflation towards the SB,[12] and, if necessary, by the delivery of a second stent in the SB in a T,[13] or Internal Crush, configuration.[14,15] The third family (D) can start creating a new carina by stent implantation in the proximal segments (simultaneous kissing stent [SKS]).[16,17] A technique of V-stenting configuration can also be achieved by successive delivery of the stents. Thus, each technical approach in bifurcation lesion considers the possibility of one or two-stent utilisation.

This strategic choice is of paramount importance in the treatment of bifurcation lesions. We are aware that for most operators the effectiveness of drug-eluting stents (DES) in reducing restenosis and revascularisation in complex lesions, such as bifurcations, can encourage the utilisation of two stents. However, regardless of technical approach, DES have become the preferred stent platform for treatment of coronary bifurcation. Indeed, many studies showed that DES implantation in bifurcation lesion can increase the risk of stent thrombosis (ST), but this is not clearly linked to two-stent techniques.[9,18,19] There are no solid data to support the supposition that two stents are more thrombogenic than one, that is, provided that correct stent placement has been performed and compliance with antiplatelet therapy is maintained. On the other hand, in the setting of acute myocardial infarction, a two-stent technique has been associated with an increased risk of ST.[20]

Although there is no convincing evidence that discourages using a DES platform and a two-DES strategy in bifurcation lesions, we still feel that a simple technique – if feasible – should always be the preferred one, even in the case of complex lesion subset. In this setting, the recent 5-year follow-up results of the Nordic study[21] demonstrated that the clinical outcomes after simple provisional SB stenting remained at least equal to the more complex strategy of planned stenting of both main vessel and SB. However, it is important to note that the Nordic trial is a small trial, considerably underpowered given the low major adverse cardiac events (MACE) rate found. A properly powered study should include approximately 20,000 patients but an inclusion of this order of

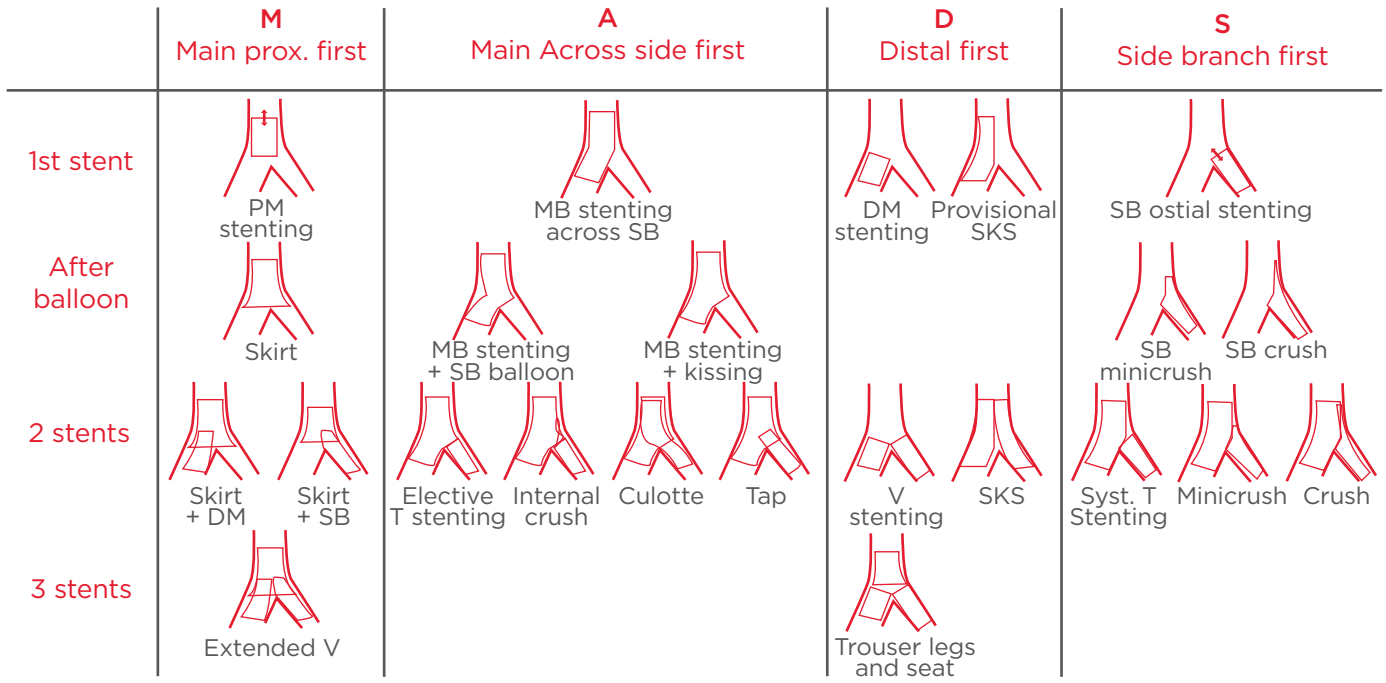

Figure 2: MADS classification of different bifurcation treatment techniques.

magnitude would not be feasible in the complex lesion subset of a bifurcation study. Furthermore, ischaemia testing was not performed in the trial, and there were no objective data to compare relief of ischaemia; however, MACE was adjudicated by a blinded events committee and should not have been influenced by the open design of the study. Finally, the study included only first-generation DES and this is another major limitation that must be kept in mind[21] (Table 1).

Several other studies[17,20,22-27] demonstrated that routine stenting of both branches offers no clear advantage over a provisional strategy of stenting MB only with balloon angioplasty of the SB. However it is also important to consider that, if it is true that there are bifurcations requiring one stent as a default treatment and a second stent when the result is suboptimal, then there are also bifurcation lesions in which two stents need to be implanted as an ITT from the beginning (indeed, approximately 30% of true bifurcation lesions require two stents and this percentage is about 50% for LMCA). Again, the distinction of these strategies is linked to SB relevance, extension of disease, and territory distribution of the involved vessels. The preliminary assessment by the operator of clinical relevance of SB disease for the patient's symptoms and disease burden in SB (ostial versus disease extending from 10 to 20 mm or more distally) is fundamental to perform a tailored approach for each bifurcation. Practically, in bifurcation lesions the objective is to conclude the procedure with both branches open ('keep it open' strategy), associated with an optimal stenting result in the MB.

Furthermore, an optimal angiographic result with minimal residual stenosis in SB may not be physiologically important if the operator utilises fractional flow reserve (FFR) examination[28] to assess the final result. Thus, we believe that each bifurcation is different and no single strategy can be applied to every situation.

In practice, two wires should be placed in most bifurcations for protecting SB from closure as a result of plaque shift or stent struts during MB stenting. Moreover, the SB wire facilitates rewiring. In the French multicentre TULIPE study,[29] the absence of this jailed wire was associated with a greater rate of re-interventions during follow-up. Two stents as ITT should be the technique used when the disease in the SB extends beyond the ostium and when the SB diameter and territory of distribution are relatively large. In all other conditions, SB provisional stenting should be the procedure of choice.

If SB is either very small for stenting or functionally irrelevant, we feel that the best strategy, after

Table 1: Published randomised controlled trials in bifurcation disease.

Study	No. Patients	Two-Stent strategy	Type of DES	Thienopyridine duration, mo	Intention to treat	Angio follow-up (months)	Clinical follow-up (months)
Pan et al.	91	Any	SES	12	Yes	6	11
Colombo et al.	85	Any	SES	3	No	6	6
NORDIC	413	Any	SES	6-12	Yes	8	6
Ferenc et al.	202	T-stenting	SES	6-12	Yes	9	12, 24
BBC ONE	500	Crush or Culotte	DES	9	Yes	-	9
CACTUS	350	Crush	SES	6	Yes	6	6, 12
DK-CRUSH2	370	DK-Crush	DES	12	Yes	8	6, 12

Adapted from Louvard et al.[53]

stenting MB, is to avoid rewiring or post-dilating SB. Conversely, when SB is suitable for treatment but disease is localised only to the ostium, the preferred strategy is the provisional technique: after stenting MB, the operator should rewire SB, remove the jailed wire, and perform final kissing inflation (FKI). If the result remains unsatisfactory (suboptimal result, plaque shift with >75% residual stenosis or TIMI flow grade <3, in a SB >2.5 mm) or SB balloon dilation is complicated by a flow-limiting SB dissection, then SB stenting should be performed. Finally, if SB is suitable for stenting and presents a diffuse disease beyond the ostium, we prefer a two-stent strategy as ITT.[30]

TECHNICAL STRATEGY FOR LM BIFURCATION DISEASE

The LM is responsible for supplying ~75% of the left ventricular (LV) cardiac mass in patients with right dominant type or balanced type and 100% in the case of left dominant type. As a result, severe LM disease will reduce flow to a large myocardium territory, placing the patient at high risk for life-threatening events. The LM is generally divided into three anatomic regions: the ostium or origin of the LM from the aorta, a mid-portion, and the distal portion. The LM differs from the other coronary arteries in its relatively greater elastic tissue content, which can explain elastic recoil and high restenosis rate following balloon angioplasty. The segment of the LM that extends beyond the aorta displays the same layered architecture as that of the other coronary arteries. Atherosclerotic lesions tend to form at specific regions of the coronary vasculature where there is a low shearstress area. In the LM bifurcation, intimal atherosclerosis is accelerated primarily in an area of low shear stress in the lateral wall, close to the left anterior descending artery (LAD) and left circumflex artery (LCx) bifurcation. Thus, the carina is frequently free of disease and this can explain the reason why single-stent strategy (provisional stenting) can be successfully performed in patients with no or moderate disease by angiography.

In a systematic review and meta-analysis of 1,278 patients published by our group,[31] we have shown that treating unprotected (U)LMCA lesions with DES is associated with a 5.5% (3.3–7.7%) risk of death, a 16.5% (11.7–21.3%) MACE rate, and a TLR rate of 6.5% (3.7–9.2%). Distal LM disease is a predictor of MACE and TLR; however, it is the presence of high-risk features that predicts death. Our review also shows that most series have reported low rates of ST (0–2%), apart from the Price et al.[32] group (4%). Data about safety and efficacy of PCI compared with coronary artery bypass grafts (CABG) in patients with LMCA disease have been further summarised in two important meta-analyses, published in 2011.

These two papers reviewed a total of 1,611 patients[6,11,33,34] randomised in the LEMANS,[35] SYNTAX left main cohort,[36] PRECOMBAT,[37] and a study by Boudriot et al.,[38] and reached similar conclusions; the primary endpoint of 1 year MACE was non-significantly different in the PCI cohort

compared with the CABG cohort (14.5% versus 11.8%; OR 1.28; 95% CI: 0.95-1.72; p=0.11). As in each of the individual studies analysed, the rate of stroke was lower in the PCI group than in the CABG group (0.1% versus 1.74%; OR 0.15; 95% CI: 0.03-0.67; p=0.013), whilst higher rates of target vessel revascularisation (TVR) were observed in the PCI cohort (11.4% versus 5.4%; OR 2.25; 95% CI: 1.54-3.29; p<0.001). Thus, according to such evidence, we can assert that PCI is comparable to CABG for the treatment of ULMCA with respect to the composite of major adverse cardiovascular or cerebrovascular events at 12-month follow-up, as well as having a lower risk of stroke and a higher risk of TVR.

These differences should be kept in mind by operators in the clinical decision-making process when evaluating the choice of best treatment according to the patient's risk profile. However, the best suggestion that we can give to the readers for safely performing PCI in LM stem is careful patient selection. There are four important areas to consider when selecting patients for LM PCI: 1) knowing the data from literature and guidelines; 2) evaluating the patient in terms of clinical presentation (stable, functional class, ACS, STEMI, shock); 3) evaluating the patient in terms of clinical characteristics (age, diabetes, renal function, cognitive status, valvular disease, carotid disease, previous cardiac intervention, other co-morbidities, EuroSCORE); 4) reviewing the angiographic characteristics of the patient (LV function, LM anatomy [distal/non-distal lesion, calcification, bifurcation angle, diseased LCx ostium, trifurcation], mitral valve disease, number of lesions, diffuse disease, complexityof additional lesions [length, calcifications, bifurcations], chronic total occlusion - particularly right coronary artery [RCA] total occlusion - diffuse calcified and porcelain aorta, possibility of complete or incomplete revascularisation, number of stents needed, overlapping, SYNTAX score); 5) knowing the own local centre experience; 6) knowing the evolution of techniques and the different technology for PCI and CABG.

A patient presenting with good LV function, non-distal and non-calcified LM stenosis, ostial LM lesions and mid-shaft LM lesions, and very few additional lesions on the other coronary vessel has been shown to have excellent outcomes following LM stenting. Conversely, a patient with heavy calcified LM disease, reduced LV function, diabetic (particularly if insulin-dependent), with multivessel disease (particularly with low EuroSCORE), and/or distal LM bifurcation lesion with reduced LV function or with occluded RCA or with additional complex lesions on the other coronary vessels (high SYNTAX score), is definitively a better surgical candidate. Finally, a recently published score, the NERS Score II system - which consisted of seven clinical and nine angiographic variables – demonstrated, for values ≥19, an enhanced MACE sensitivity and specificity (84.0% and 76.0%, respectively), significantly higher compared with the SYNTAX score. A NERS Score 2 ≥19 was the only independent predictor of cumulative MACE (hazard ratio: 3.27; 95% CI: 1.86 to 5.23; p≤0.001) and ST (OR: 22.15; 95% CI: 12.47-57.92; p≤0.001) at follow-up after LM stenting.[39]

DEDICATED BIFURCATION STENT AND NEW TREATMENT DEVICES

There is still a debate regarding the choice of the best device, including the new dedicated bifurcation stents, the bioresorbable scaffolds (BRS), and drug eluting balloons (DEB), and including adjunctive procedures such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), and FFR for assessing the best approach and the results in the interventionalist armamentarium to treat bifurcation lesions.

As stated before - unless clinically contraindicated - DES should always be utilised. Conversely, the safety and efficacy of dedicated stents are still under evaluation. The main advantage of most dedicated bifurcation stents is to allow the operator to perform the procedure on a bifurcation lesion without the need to rewire the SB. Dedicated bifurcation stents can be broadly divided into three categories (Table 2):

1. MB dedicated devices (Stentys self-expanding stent, Stentys SA; Axxess Plus, Devax, Irvine, CA, USA).

2. SB dedicated devices (e.g. Sideguard, Cappella Inc., Auburndale, Massachusetts; Tryton, Tryton Medical, Newton, Massachusetts). The Tryton and Sideguard are designed to treat the SB first and require re-crossing into the SB after MB stenting for FK.

3. MB and SB dedicated devices: the Medtronic coronary Y-stent (Medtronic, Minneapolis, MN), The Taxus® Bifurcation Stent System (Boston Scientific

Corporation; Natick, MA), Antares® Coronary Stent System (TriReme Medical, Inc., Pleasanton, CA), Abbott Vascular Side Branch Access (more commonly referred to as Xience SBA) stent (Abbott Vascular, Redwood City, CA), Y-Med sideKicK™ (Y-Med, Inc., San Diego, CA), Invatec Twin- Rail™ (Invatec S.r.l., Italy), and Minvasys Nile Croco® (Minvasys, Gennevilliers, France).

The Axxess Plus stent was the first available on the market of dedicated bifurcation devices designed to elute an anti-restenostic drug (Biolimus A9). The Axxess Plus stent is a self-expanding, nickel-titanium, conically-shaped stent that is placed at the level of the carina. Recently, results of the 3-year follow-up of the Diverge Trial have been published, demonstrating the good safety of this dedicated stent in terms of cumulative MACE.[40] However the lack of randomised, long-term clinical studies for this class of dedicated devices makes their utilisation a niche in the percutaneous management of bifurcation disease.

Table 2: Characteristics of dedicated stents.

Stent	Stent Material	Drug-Eluting	GCS	Stent Delivery System	Mechanism of Stent Expansion
Devax AXXESS™	Nitinol	Biolimus A9	7F	Single wire rapid exchange system	Self expandable
Stentys bifurcation stent	Nitinol	No/Yes*	6F	Single wire rapid exchange system (second wire needed for SB access)	Self expandable; balloon to open access to SB
Tryton Side Branch Stent™	Cobalt chromium	No	6F	Single balloon, single wire rapid exchange system	Balloon expandable
Cappella Sideguard®	Nitinol	No	6F	Single balloon, single wire rapid exchange system	Balloon deployed; self-expandable
Medtronic coronary Y-stent	Cobalt alloy	No	6F	Double balloon, dual wire, single catheter	Balloon expandable (single inflation)
Taxus® bifurcation stent	Platinum alloy	Paclitaxel	7F	Double balloon, dual wire, side exchange catheter	Balloon expandable (single inflation)
Antares® coronary stent	Stainless steel	No	6F	Single balloon, rapid exchange system, with second wire in peel-away lumen	Balloon expandable (single inflation)
Abbott Vascular side-branch access stent	Cobalt chromium	Everolimus	7F	Double balloon, dual wire, joined mandrel tip; MB rapid exchange and SB over-the-wire	Balloon expandable (single inflation)
Y-Med sideKicK™	Cobalt chromium	No	5F	MB fixed wire platform with rapid exchange steerable SB wire	Balloon expandable
Invatec Twin-Rail™	Stainless steel	No	6F	Double balloon, dual rapid exchange, single catheter	Balloon expandable (single inflation)
Minvasys Nile Croco®	Cobalt chromium	No/Yes*	6F	Double balloon, dual rapid exchange system, with 2 independent catheters	Balloon expandable

GCS: guilding catheter size (French); MB: main branch; SB: side-branch.
*paclitaxel is eluted in newer stent iteration.
Devax Inc., Lake Forest, CA; Stentys, Inc., Princeton, NJ; Tryton Medical, Durham, NC; Cappella Medical Devices, Galway, Ireland; Medtronic, Minneapolis, MN; Boston Scientific, Natick, MA; TriReme Medical, Pleasanton, CA; Abbott Vascular, Redwood City, CA; Y-Med, San Diego, CA; Invatec, Italy; Minvasys, Gennevilliers, France.
Adapted from Movahed.[54]

Recently, bioresorbable vascular scaffold (BVS) adoption introduced a unique potential in the treatment of coronary lesions, as they provide temporary vessel scaffolding and then slowly disappear, thereby allowing for the restoration of the vessel wall physiology and vasomotion. Initial preclinical and clinical results appear promising but data are limited to simple lesions, and there is no evidence in the context of randomised control trials that would allow direct comparison of the efficacy of the BVS with the effectiveness of new-generation DES. Albeit the feasibility of using BVS in bifurcation lesions is unknown, a recent study by Colombo and co-authors,[41] utilising an *in-vitro* arterial model, including main-vessel stenting with ballooning of the SB with low-pressure final kissing balloon inflation through the BVS struts (Absorb everolimus-eluting BVS - Abbott Vascular, Santa Clara, California), T-stenting, and crush and culotte procedures, demonstrated that intervention of bifurcation lesions using BVS appears feasible.

DEB technology can represent a potential alternative to DES to prevent restenosis. There are several commercially available DEB in Europe with different carriers and paclitaxel as the active drug. The potential advantage of DEB utilisation in bifurcation lesions is that there is no distortion of the original anatomy of the bifurcation, but there is a reduction of strut deformation, lower risk of polymer fracture, and finally, homogeneous administration of the drug to the vessel wall. In this setting, the potentially homogeneous drug delivery to the vessel wall is indeed one of the more frequently stated advantages of DEB over DES,[42,43] as opposed to a very spatially defined delivery due to release from the comparably narrow stent struts (surface coverage of <20%), as reported by Hwang et al.[44] However, a recent *in vitro* study by Seidlitz and co-authors[45] suggested that it seems crucial to carefully design coatings to avoid vast drug losses during the advancement to the site of expansion, while at the same time allowing for sufficient transfer upon expansion against the vessel wall. The results of the study further indicate that using a micro-pipetting technique with tightly folded balloons may lead to an inhomogeneous distribution of coatings with little coating located deep within the folds. This finding, which is contradictory to common assumptions about this dosage form, emphasises the necessity to further characterise device performance *in vitro*, and indirectly implies an inhomogeneous drug distribution also with paclitaxel-eluting balloon.

In the bifurcation clinical setting, the DEBIUT study failed to demonstrate angiographic superiority of DEB (Dior - Eurocore GmbH, Bonn, Germany) as compared to bare metal stents (BMS), with similar late luminal loss and binary restenosis rates in both treatment groups; DES showed better angiographic results than both DEB and BMS; the reduced duration of dual antiplatelet therapy to 3 months appeared to be safe in combination with DEB and BMS.[46] Finally, it is important to keep in mind that DES implantation in coronary bifurcation lesions is an off-label indication, and DES utilisation in large, real-world registries is associated with higher event rates compared with on-label use of DES, which is consistent with a higher-risk clinical and lesion profile. However, event rates with off-label use of DES are lower compared with off-label use of BMS.[47]

IMAGING AND FUNCTIONAL GUIDE IN BIFURCATION TREATMENT

Intravascular imaging constitutes an important contribution to treatment for bifurcation disease, assisting in the evaluation of: 1) longitudinal plaque distribution; 2) plaque composition; 3) mother and daughter vessel reference diameters; 4) precise stent landing zone analysis; and 5) SB ostium analysis (diseased or not), and after for: 1) stent expansion and apposition; 2) SB ostium assessment; 3) final vessel sizes (stent over or under-expansion); and 4) proximal or distal dissection. IVUS has major spatial resolution and seems preferable, improving the safety of coronary bifurcation stenting using DES;[1] however, a recent retrospective Italian registry published by our group did not associate it with significant clinical benefits.[48]

The detailed assessment of the bifurcation by OCT pre-intervention may aid tailoring the treatment strategy. The expected ability to assess the risk of carina shift or SB closure may influence the decision to protect a SB with a wire and whether or not to pre-dilate it. The exact determination of vessel dimension and distribution of the disease in the bifurcation segment could influence the decision of whether to plan a simple or a complex approach up-front, ensuring adequate coverage of all diseased areas where needed. A final OCT pullback after a complex bifurcation procedure often points to areas of under-expansion, malapposition, or an excessive amount of free floating struts, which are not visible on angiography and can be corrected with additional high-pressure

post-dilation or KB inflation. In addition, high-speed optical frequency domain imaging (OFDI) can be used to create 3D reconstructions of implanted stent structures with excellent quality and at high resolutions. Utilising this technique, OCT may be used to guide the procedure preserving SB patency without compromising the MB, obtaining the optimal vessel dimensions and reducing malapposition of stent struts and the amount of unplanned floating struts. Although not available in all centres, 3D OCT would be of great help for the operator, providing insight into the take-off of SBs as well as aiding in the understanding and planning of optimal treatment strategy.[49,50]

FFR is a pressure-derived flow index, which represents the amount of flow reduced by a specific stenosis. FFR-guided revascularisation strategy is known to be better than angiography-guided revascularisation in various lesion subsets. In particular, FFR can give useful information for the interventional decision-making process of small SB with an angiographically-significant ostial lesion after MB stenting, which may not be functionally significant by FFR analysis. FFR can be used in bifurcation, appearing feasible, safe, and effective.[1,34] In this setting, Koo and co-authors[28] demonstrated that a suboptimal angiographic result in SB after MB stenting should not be an indication to perform SB stenting. In this study, 94 jailed SB were evaluated by FFR and the conclusions can be summarised as follows: no lesions with a quantitative coronary angiography (QCA) percentage stenosis <75% had an FFR <0.75, and among those with a percentage stenosis >75%, only 27% were functionally significant. Moreover, no TVR occurred in those with percentage stenosis <75%, suggesting that most of these lesions do not have functional significance and should not be treated despite 'critical' angiographic appearance.

A particular aspect that needs to be addressed is the utilisation of FFR for LM disease. Although LMCA disease was an exclusion criteria within the DEFER and FAME trials, FFR has nevertheless been used for evaluation of the physiological significance of indeterminate ULMCA lesions. However, a number of important caveats of this approach warrant further consideration. At present, there are a lack of randomised data from larger multicentre studies confirming the long-term safety of this approach. Also, it remains debatable as to whether an FFR <0.75 versus an FFR of <0.80 should be regarded as the appropriate ischaemic threshold.

Some authors suggest the complementary use of IVUS to assess LMCA severity if the LMCA FFR is between 0.80 and 0.85.[51] At least 50-60% of ULMCA lesions involve distal bifurcation, often with significant involvement of the ostia of both daughter branches. Therefore, an FFR pullback should be undertaken starting within both daughter branches to localise the most significant distribution of disease across the region bordering the distal LMCA segment and ostia of both daughter branches. FFR readings across the LMCA segment will be influenced by the presence of lesions within distal coronary segments as well as the amount of functional myocardial territory supplied by these lesions. It is important to keep in mind that stenoses within the LAD or LCx territories will artificially increase the FFR measured across the LMCA stenosis,[52] and therefore, PCI to these lesions would unmask the true haemodynamic significance of the stenosis within the LMCA segment.

In conclusion, based on the current available level of evidence, we recommend the use of FFR for the assessment of (angiographic indeterminate) isolated ostial or midshaft LMCA stenoses in patients who are considered more appropriate candidates for coronary arterial bypass grafting. In those patients with distal/bifurcation LMCA lesions and in those with diffuse/distal coronary arterial disease, we strongly recommend the liberal use of IVUS. Furthermore, in those patients considered likely candidates for ULMCA PCI, IVUS remains crucial for assessing the degree of lumen compromise and the extent, distribution, and morphology of plaque, as well as for the immediate post-procedural quantification of stent deployment.

CONCLUSION

Coronary bifurcation disease is a very challenging subset in interventional cardiology. A provisional approach with MB stenting is the preferred choice in most bifurcations lesions but it is very important to select the most appropriate approach for each bifurcation based on anatomical variables and operator experience. Regardless of strategy choice (one versus two stents), DES have dramatically improved the long term outcomes and should be the preferred device. We believe that the future prospective is primarily related to the development and refinement of dedicated bifurcation stents, which may simplify the procedure by adapting to the complex anatomy of bifurcation disease, and, at the same time, improving the long-term clinical

outcomes. BVS represents the last frontiers in the treatment of bifurcation disease and those devices may indeed offer the unique opportunity to simplify the procedure with a 'cross-over' approach, since the SB will be jailed for only a few months.

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