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Definitions and Standardized Endpoints for Treatment of Coronary Bifurcations

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KEYWORDS

- Academic Research Consortium
- bifurcation
- clinical trials
- endpoints

Abstract

The Bifurcation Academic Research Consortium (Bif-ARC) project originated from the need to overcome the paucity of standardization and comparability between studies involving bifurcation coronary lesions. This document is the result of a collaborative effort between academic research organizations and the most renowned interventional cardiology societies focused on bifurcation lesions in Europe, the United States, and Asia. This consensus provides standardized definitions for bifurcation lesions; the criteria to judge the side branch relevance; the procedural, mechanistic, and clinical endpoints for every type of bifurcation study; and the follow-up methods. Considering the complexity of bifurcation lesions and their evaluation, detailed instructions and technical aspects for site and core laboratory analysis of bifurcation lesions are also reported. The recommendations included within this consensus will facilitate pooled analyses and the effective comparison of data in the future, improving the clinical relevance of trials in bifurcation lesions, and the quality of care in this subset of patients.

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Abbreviations

%DS	diameter stenosis
2D	2-dimensional
3D	3-dimensional
ACS	acute coronary syndromes
Bif-ARC	Bifurcation Academic Research Consortium
CABG	coronary artery bypass graft
CCS	chronic coronary syndromes
CK-MB	creatine kinase-myocardial band
CMR	cardiac magnetic resonance
CT	computed tomography
cTn	cardiac troponin
DAPT	dual antiplatelet therapy
DCB	drug-coated balloon
DES	drug-eluting stent(s)
DMV	distal main vessel
FFR	fractional flow reserve
hs-cTn	high-sensitivity cardiac troponin
IVUS	intravascular ultrasound
LAD	left anterior descending coronary artery
LM	left main coronary artery
LV	left ventricle
MI	myocardial infarction
MV	main vessel
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PMV	proximal main vessel
PMI	periprocedural myocardial infarction
QCA	quantitative coronary analysis
QoL	quality of life
RVD	reference vessel diameter
SB	side branch
SCAI	Society for Cardiovascular Angiography and Interventions
SPECT	single-photon emission computed tomography
TBR	target bifurcation revascularization
UDMI	Universal Definition of Myocardial Infarction
ULN	upper limit of normal
WCE	weighted composite endpoint

Introduction

Historically, a coronary bifurcation lesion has been described as "a coronary artery narrowing occurring adjacent to, and/or involving the origin of a significant side branch (SB)." This description facilitates discussion of when a SB is significant, and thereby when sufficient flow in both vessels should be preserved and secured during treatment.[1]

Historical and on-going studies on the management of bifurcation lesions have primarily focused upon provisional vs upfront 2-stent techniques, and how to optimally perform these to preserve flow in both branches and minimize long-term adverse events **(Supplemental Table 1)**. However, emerging developments in techniques, and devices such as drug-coated balloons (DCB), scoring balloons, dedicated bifurcation devices, and lesion-modification approaches using intravascular lithotripsy, and rotational and directional atherectomy, all now merit assessment in the treatment of bifurcation lesions **(Supplemental Table 2)**. Nevertheless, their management (from patient selection to technical or procedural aspects and the definition of relevant clinical outcomes) requires additional consideration and standardization to enable accurate reproducibility in future dedicated studies, which thus far has not been achieved **(Supplemental Table 3)**. In this regard, we need to clearly define the relevance of a SB, the acute technical/procedural success, and long-term clinical outcomes. These standardized definitions should incorporate, among other details, the angiographic classification, as well as the added value of intravascular imaging, the added value of new noninvasive (image-based) vs invasive methods of functional lesion evaluation, the different types of treatment (medical vs surgical or percutaneous revascularization), and the post-revascularization antiplatelet regimen (type, intensity, duration).

As part of the Academic Research Consortium program, our goal is to create consistent, practical, and reproducible terminology for the methodological approach and endpoints of clinical trials involving coronary bifurcation lesions, thereby improving the clarity of study design and reporting, facilitating pooled analyses and the effective comparison of data in the future. The overall objective is to improve the clinical relevance of trials in bifurcation lesions, hence improving the quality of care in this subset of patients **(Figure 1)**.

Figure 2 depicts the general requirements to be met before undertaking any coronary bifurcation study.

Specifically, this position paper aims to define:

1) A classification for coronary bifurcation lesions from the perspective of symptoms, anatomy, function, and prognosis;
2) The specific technical details relevant to treatment of bifurcation lesions that must be captured;
3) Procedural, mechanistic (anatomical and functional), clinical, and cost-effectiveness endpoints;
4) Patient-, device-, vessel-, and bifurcation-oriented endpoints;
5) Patient-, site-, and central adjudication–reported endpoints;
6) Analytical plan related to intention-to-treat, per- protocol, and as-treated analyses (with the option of sham treatment);
7) Statistical handling of the different methods for analyzing composite endpoints (eg, competing risk, win ratio, negative binomial, Andersen-Gill, Wei-Lin-Weissfel); and
8) Optimal duration of follow-up, considering the study type and objectives.

1. Anatomical definitions and classification of coronary bifurcation lesions

1.1. DEFINITION

Bifurcation Academic Research Consortium (Bif-ARC) endorses the coronary bifurcation definitions of the last European Bifurcation Club consensus **(Table 1, Figure 3)**.[2]

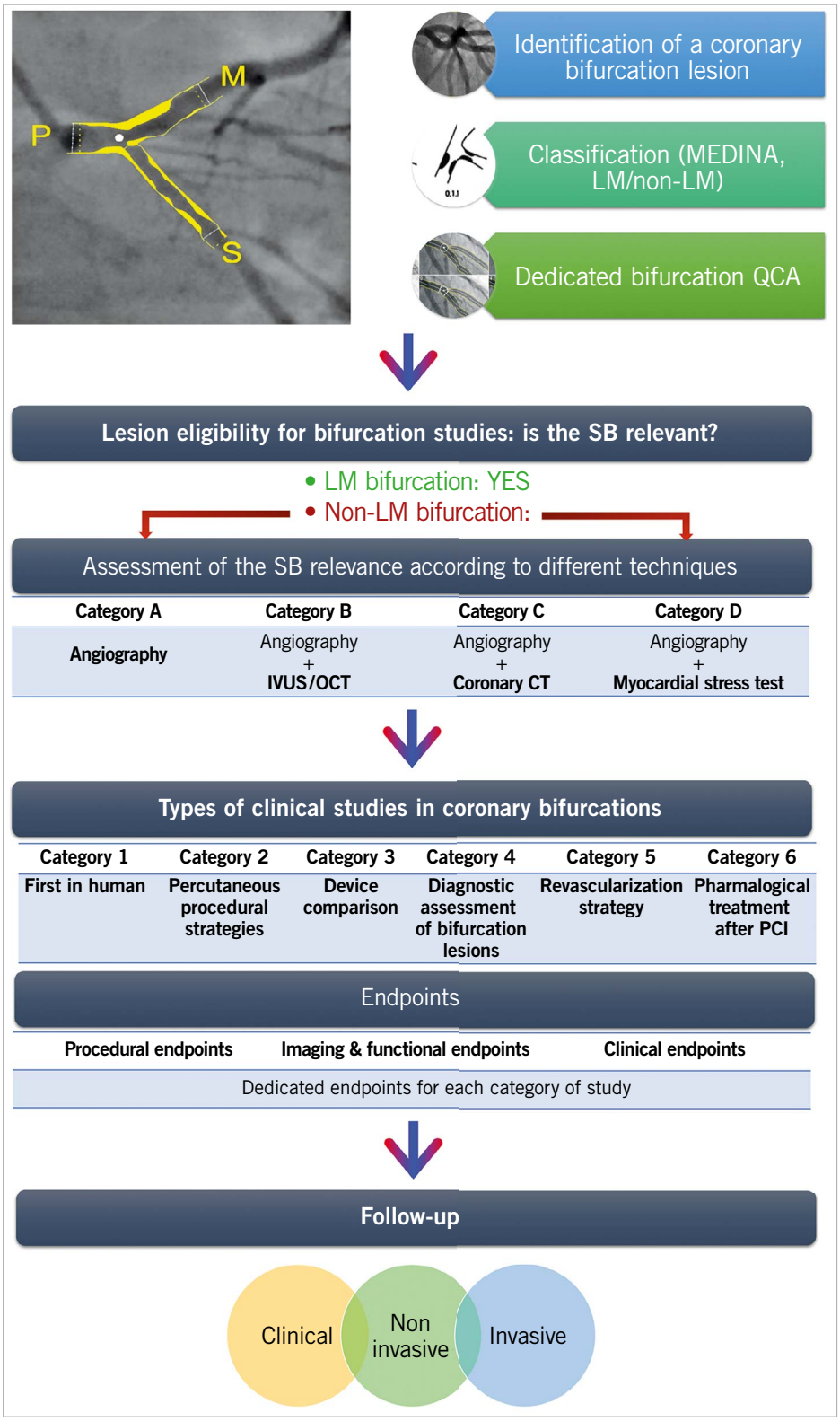

Figure 1. *Summary of Bif-ARC Recommendations. After identifying a bifurcation lesion, this should be classified according to MEDINA classification and the left main (LM) involvement. Dedicated bifurcation quantitative coronary analysis (QCA) is strongly advised to be used by sites and core laboratories for quantitative assessment. To evaluate the eligibility of the lesion in a bifurcation trial, its side branch (SB) should be proven to be clinically relevant through different diagnostic techniques according to their availability in the center and the quality and type of the study. The Bifurcation Academic Research Consortium (Bif-ARC) recommends 6 classes of study type, based on the investigation. For every category of study, dedicated endpoints are provided and classified in 3 groups. The follow-up includes clinical, noninvasive, and invasive assessment.*

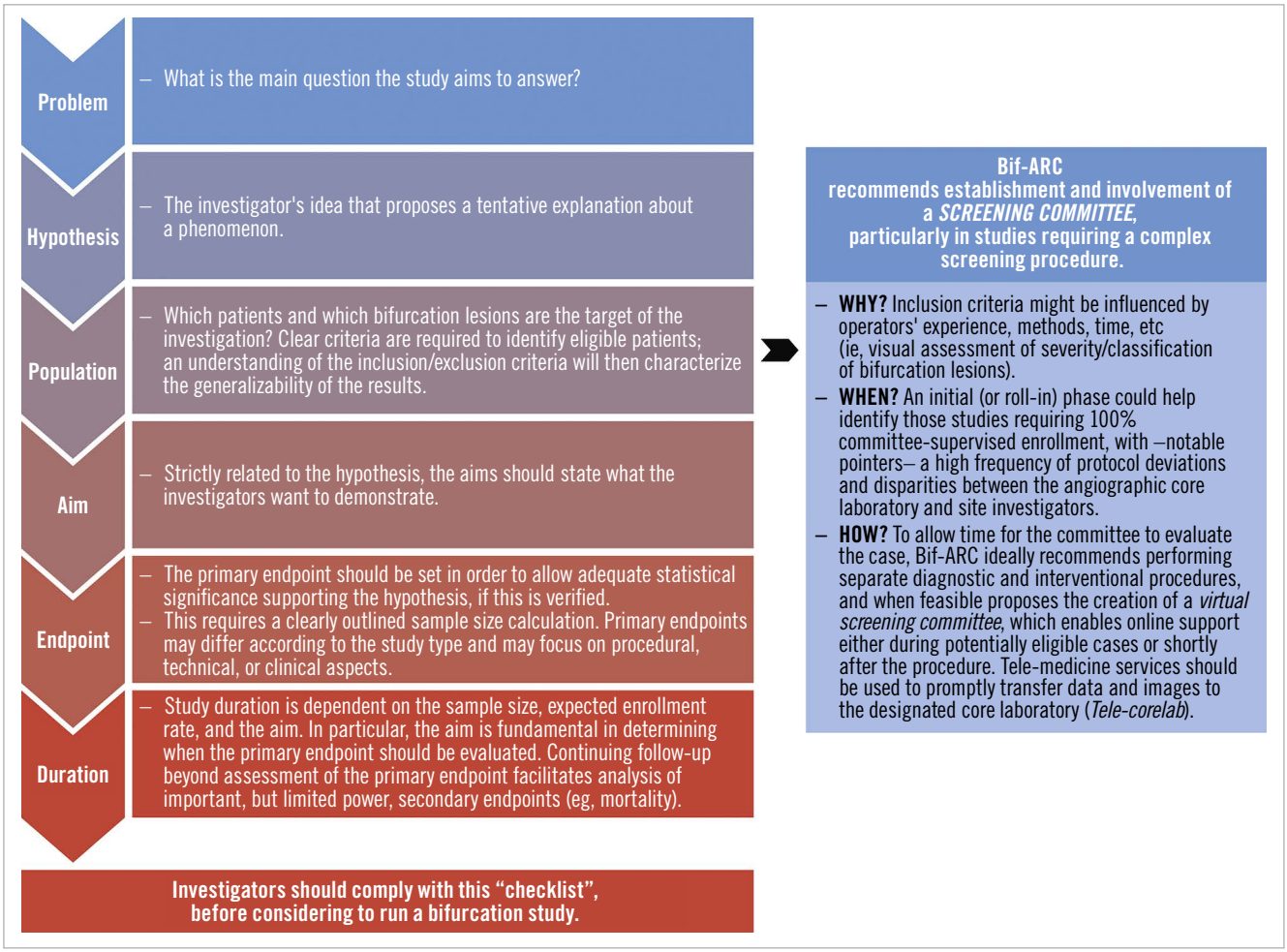

Figure 2. *General requirements for coronary bifurcation lesions studies. The investigators should comply with minimal requirements before running a bifurcation study. Bif-ARC: Bifurcation Academic Research Consortium.*

1.2. CLASSIFICATION

Bif-ARC recommends that dedicated bifurcation trials adopt the MEDINA classification, which has gained acceptance for being both simple and prognostically relevant.[3,4]

According to that, we can identify "true" bifurcation lesions, involving a significant (≥50%) diameter stenosis (%DS) both in the main vessel (MV) and SB (ie, MEDINA 1,1,1; 1,0,1; or 0,1,1), and "non-true" lesions in all other cases.[5]

In the presence of a trifurcation, Bif-ARC recommends using the adapted MEDINA classification **(Figure 4)**. The 4 numbers must be in order of diameters of the distal segments, corresponding, respectively, to the proximal MV (PMV), distal MV (DMV), SB1, and SB2. To avoid confusion, we suggest associating the MEDINA class to the abbreviated name of each segment (ie, MEDINA left main coronary artery [LM], left anterior descending coronary artery [LAD], left circumflex coronary artery, ramus: 0,1,1,0).[6]

Although site-reported MEDINA can be based on visual assessment alone (somewhat inaccurate[7]), dedicated bifurcation quantitative coronary analysis (QCA) software should be used either onsite or by core laboratory analysis. To improve onsite assessment, Bif-ARC suggests using intravascular imaging obtained with intravascular ultrasound (IVUS) or optical coherence tomography (OCT),[8] which have been reported to be more accurate in detecting atheroma compared with invasive angiography.[9-11] Notably, intracoronary imaging performed using motorized pullbacks at a set rate permits detailed analysis and is an important parameter of quality because this is the only way to accurately estimate lesion length.

According to the MEDINA classification, Bif-ARC also suggests a ranking of bifurcation lesions in order to evaluate and compare their severity (from highest to lowest severity):

1) 1,1,1; 2) 1,1,0; 3) 1,0,1; 4) 0,1,1; 5) 1,0,0; 6) 0,1,0; and 7) 0,0,1.

Moreover, Bif-ARC recommends classifying the bifurcation lesions in LM and non-LM bifurcations, in addition to SB size and atherosclerotic involvement. SBs with a diameter <2.75 mm are "minor" SBs, whereas those with a diameter ≥2.75 mm are "major" SBs. The length of a SB lesion influences the complexity of SB intervention; as such, a SB lesion ≥10 mm renders the treatment potentially more challenging.[12]

Table 1. Anatomical bifurcation and trifurcation lesion definitions.

	Definition
Coronary bifurcation[2,89]	A coronary region consisting of 3 major parts: 1) PMV; 2) DMV (both together forming the MV); and the 3) SB.[2] The longest and largest distal branch should be designated the DMV given the linear relationship between diameter, length, flow, and supplied myocardial mass.[90] Bifurcation carina is the tissue connecting DMV and SB. Within the bifurcation, we define the POB and the POC (Figure 3).[91] POB is the center of the largest circle that fits in the bifurcation and touches all 3 contours. The POB is the point where all 3 centerlines (ie, the lines through the middle of the vessel) from the PMV, DMV, and side branch meet (Figure 3). POC represents the smallest possible independent region that behaves differently from a single vessel segment. It is defined on the 2D radiographic image as the area or region that encompasses the start and the end of the bifurcation region. The intersections of the largest circle, touching all 3 contours of the bifurcation, with the centerlines of each vessel indicate the boundaries of the POC (Figure 3). Considering the limitation of 2D angiography, such entities should be identified in the optimal angiographic view for a given bifurcation, which requires no overlap of distal branches, minimal foreshortening, and displaying of the widest bifurcation angle.
Bifurcation lesion[2]	Angiographically, a bifurcation lesion is defined as a coronary stenosis adjacent to and/or involving an adequate-sized SB (≥2.0 mm in RefD).[6] The lesion is considered significant when its %DS is >50 and the MLD in at least 1 of the 3 segments is located ≤4 mm from the POB.[6,89]
Relevant side branch[92]	Relevance, according to the proposed algorithm (Figure 5), to be considered only if RefD ≥2.0 mm.
Coronary trifurcation[93]	Anatomically, we define a trifurcation as a division of an MV into 3 branches, each of which has a lumen diameter ≥2.0 mm. The DMV is defined as the longest and the largest branch, likely reflecting the largest perfusion territory. Between the SBs, the one with the larger diameter is defined as SB1, while the other is SB2.[93]
Trifurcation lesion[93]	Trifurcation lesions are defined by a %DS ≥50 within 4 mm from the POB involving either the MV (proximal and/or distal), with or without significant disease in either 1 or both SBs.

%DS: percentage diameter stenosis; DMV: distal main vessel; MLD: minimum lumen diameter; MV: main vessel; PMV: proximal main vessel; POB: point of bifurcation; POC: polygon of confluence; RefD: reference diameter; SB: side branch.

As per MEDINA classification, the SB size should be evaluated using bifurcation dedicated QCA, or in case of onsite assessment and unavailability of QCA, through intravascular imaging to improve its accuracy (cf. the Intravascular Imaging in Bifurcation Lesions section in the **Supplemental Appendix**).

1.3. DEDICATED BIFURCATION QCA

The diameters of the 3 segments of a bifurcation lesion follow the Murray's law (Finet's and Huo-Kassab formulas).[13-15] Single-vessel analysis overestimates the reference vessel diameter (RVD) at the ostia of the distal branches, thus overestimating the %DS. By contrast, when the PMV is used for the RVD, the %DS is underestimated. Therefore, the following dedicated 2-dimensional (2D) bifurcation QCA algorithms were developed by incorporating the principles of fractal geometry based on mass conservation (Mandelbrot Set, and fractal object self-similarity) to address the "step-down" reduction in diameter in the bifurcation branches: CAAS bifurcation software (Pie Medical Imaging) and QAngio XA bifurcation software (Medis Medical Imaging Systems) **(Figure 5)**. The accuracy and precision of these packages have been compared *in vitro* with bifurcation Plexiglas phantoms, and both have proved to be more accurate than single-vessel QCA; therefore Bif-ARC recommends sites and core laboratories use these software for dedicated bifurcation QCA measurements. For further information, see the Technical details and instructions on performing dedicated bifurcation QCA in the **Supplemental Appendix** and **Supplemental Figure 1**.

2. Target bifurcation lesions for bifurcation studies

2.1. INDICATIONS FOR BIFURCATION LESION REVASCULARIZATION

Both acute and chronic coronary syndromes (ACS and CCS) involving bifurcation lesions deemed suitable for revascularization can be included in bifurcation trials, as per the study design. In CCS with angiographically intermediate stenosis (%DS <70), documenting ischemia is recommended via noninvasive stress testing or invasive functional assessment (with SB assessment limited to MEDINA 0,0,1 lesions), with revascularization indicated in accordance with the latest European and American guidelines on coronary artery revascularization[16,17] **(Supplemental Table 4)**. In ACS cases, revascularization is guided by the detection of plaque disruption and/or thrombus at the site of the bifurcation, plus physiology.[17-19]

In the presence of multivessel coronary disease, the heart team evaluation should be emphasized by protocol. The selection of the target vessel, the method of revascularization, and the prediction of the patient's prognosis may be guided by the SYNTAX Score 2020,[20] taking into account functional evaluation in its calculation (functional SYNTAX Score), whereby the functional SYNTAX Score is calculated by counting only ischemia-provoking lesions.[21]

2.2. LESION ELIGIBILITY FOR BIFURCATION STUDIES ACCORDING TO SB PROGNOSTIC RELEVANCE

A significant coronary lesion has 3 potential consequences: 1) symptoms (neurogenic component, subjective[22]); 2) ischemia (subtended

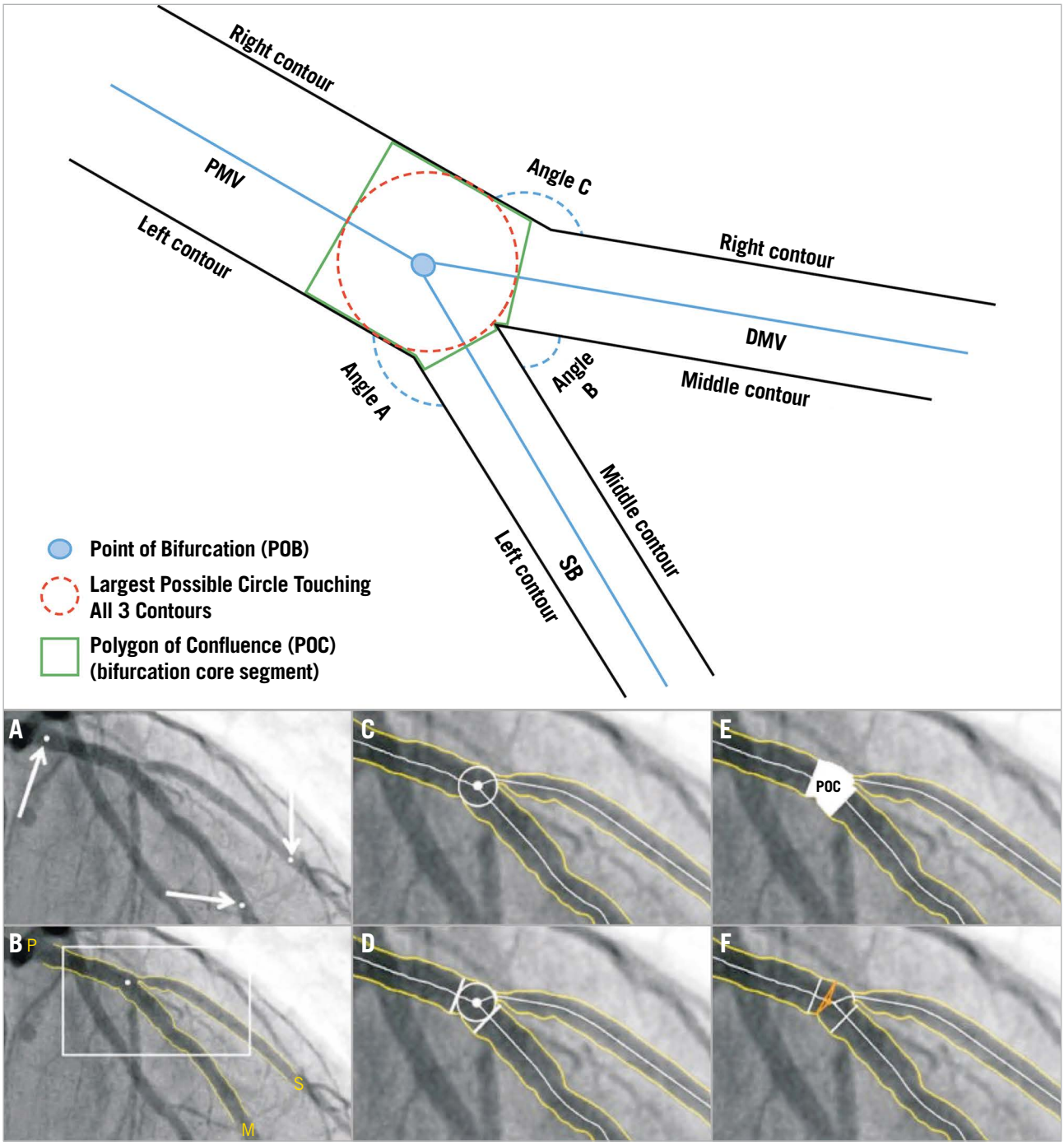

Figure 3. *Coronary bifurcation composition. (Top) Schematic representation of coronary bifurcation components. Angle A: access; Angle B: between; Angle C: PM-DM vessel angle. (A to F) Case example of coronary bifurcation on angiography analyzed with dedicated bifurcation quantitative coronary analysis. Arrows: identification of PMV, DMV, and SB by the analyst. DMV: distal main vessel; PMV: proximal main vessel; POB: point of bifurcation; POC: polygon of confluence; SB: side branch.*

ischemic myocardium, objective); and 3) prognosis (resulting from the amount of myocardium at ischemic or electrical risk).[23]

The relevance of the SB is fundamental to define the bifurcation lesion as such, and thereby eligibility for inclusion in a dedicated bifurcation study.

Previous clinical studies, mostly underpowered, suggest that RVD could be used as a surrogate marker for the extent of myocardial territory, thereby determining the clinical relevance of that SB.[24] However, most studies including only large branches failed to prove the benefit of aggressive intervention for SBs over conservative treatment, underlining the limitation of angiographic vessel size in defining the clinical significance of a branch, or our incorrect understanding of what really constitutes a significant SB.[25-27] Recent studies using computed tomography (CT) coronary angiography

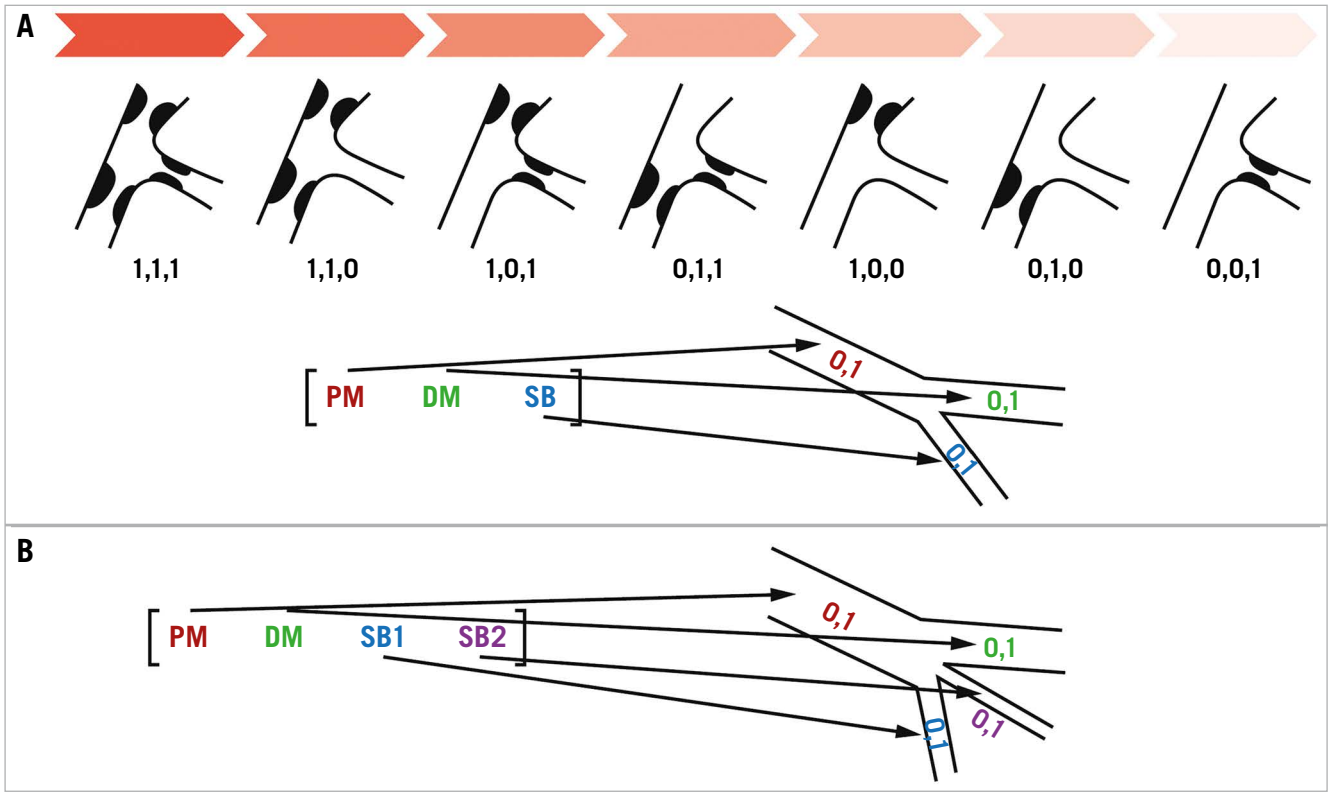

Figure 4. *MEDINA classification. Schematic representation of MEDINA classification for bifurcation lesions (A) showing the ranking of lesions severity (from highest to lowest severity), and adapted MEDINA classification for trifurcation lesions (B). Abbreviations as in Figure 3.*

demonstrate alternative methods to assess the myocardial territory subtended by a specific vessel.[28] Of note, one study reported that only about 20% of non-LM SBs supply a myocardial mass ≥10% of the left ventricular (LV) mass.[29,30] However, the supplied myocardial mass is always larger than the ischemic myocardial mass, and the 2 parameters are not interchangeable, nor can they accurately describe electrical and other adverse prognosis.

Previous studies indicate a 10% cutoff in ischemic myocardium is the minimum to justify revascularization over medical therapy (except for a chronic total occlusion), with respect to improved prognosis (cardiac death).[23] This cutoff represents an important benchmark combining the ischemic and prognostic implications of a coronary lesion. Although this evidence is not specifically focused on bifurcation lesions, any coronary stenosis causing such

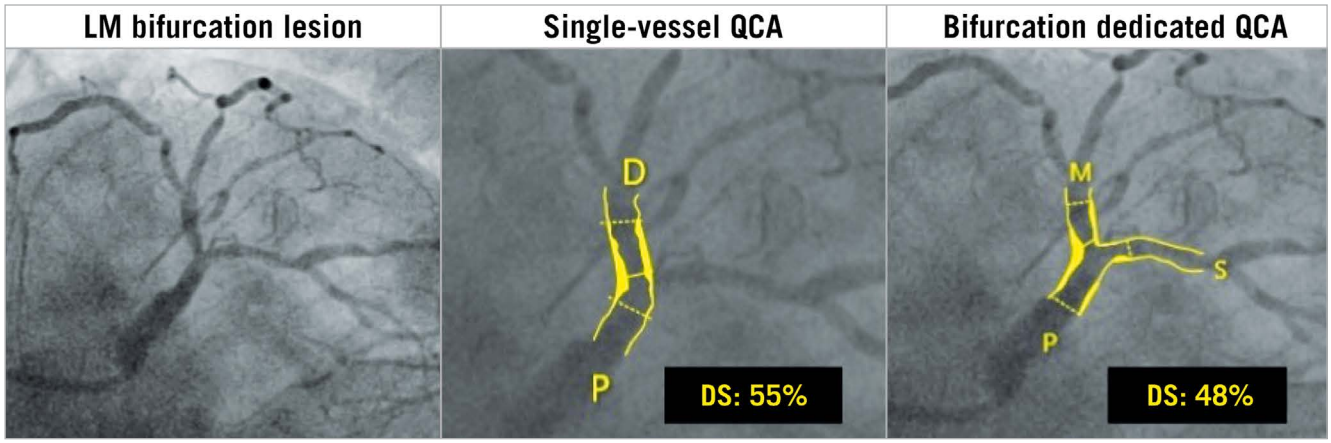

Figure 5. *Pseudo-Fractal Geometry and Dedicated QCA. Without implementation of dedicated bifurcation algorithms, taking into account the natural step-down phenomenon of the vessels in presence of bifurcations, the single-vessel QCA leads to erroneous estimation of the main vessel and side branch reference diameters, with over/underestimation of related stenosis. D: distal; DS: diameter stenosis; LM: left main coronary artery; M: main vessel; P: proximal; QCA: quantitative coronary analysis; S: side branch.*

a grade of ischemia should be considered relevant, regardless its location in the coronary tree. Therefore, we propose that criterion for identifying a significant SB. Defining SBs on the basis of symptoms (eg, angina) is a much more challenging prospect, whereas development of significant angina after SB compromise clearly indicates its relevance.

Therefore, we propose that a SB should be defined as "relevant" if symptoms are stemming from a large amount (>10%) of ischemic SB-related myocardium, impacting prognosis.

Assuming that SBs of LM bifurcations are always considered prognostically relevant, to specifically estimate or quantify the SB-related myocardium at risk of non-LM bifurcations, Bif-ARC proposes a standardized algorithm based on available diagnostic techniques to help classify bifurcation studies into different categories, which should be defined in the study protocol, before enrolment commences **(Figure 6)**. This strategy will require specific expertise from the centers involved; however, it will facilitate comparisons across studies of similar technical requirements.

The minimum requirement to assess the relevance of a SB is a baseline coronary angiogram in 2 orthogonal views (Category A), which allows indirect measurements (ie, SB length, anatomical scores) that are surrogates of SB-related myocardial mass, and despite their deficiencies, offer an estimation of its relevance. The minimum required criterion is an angiographic reference diameter

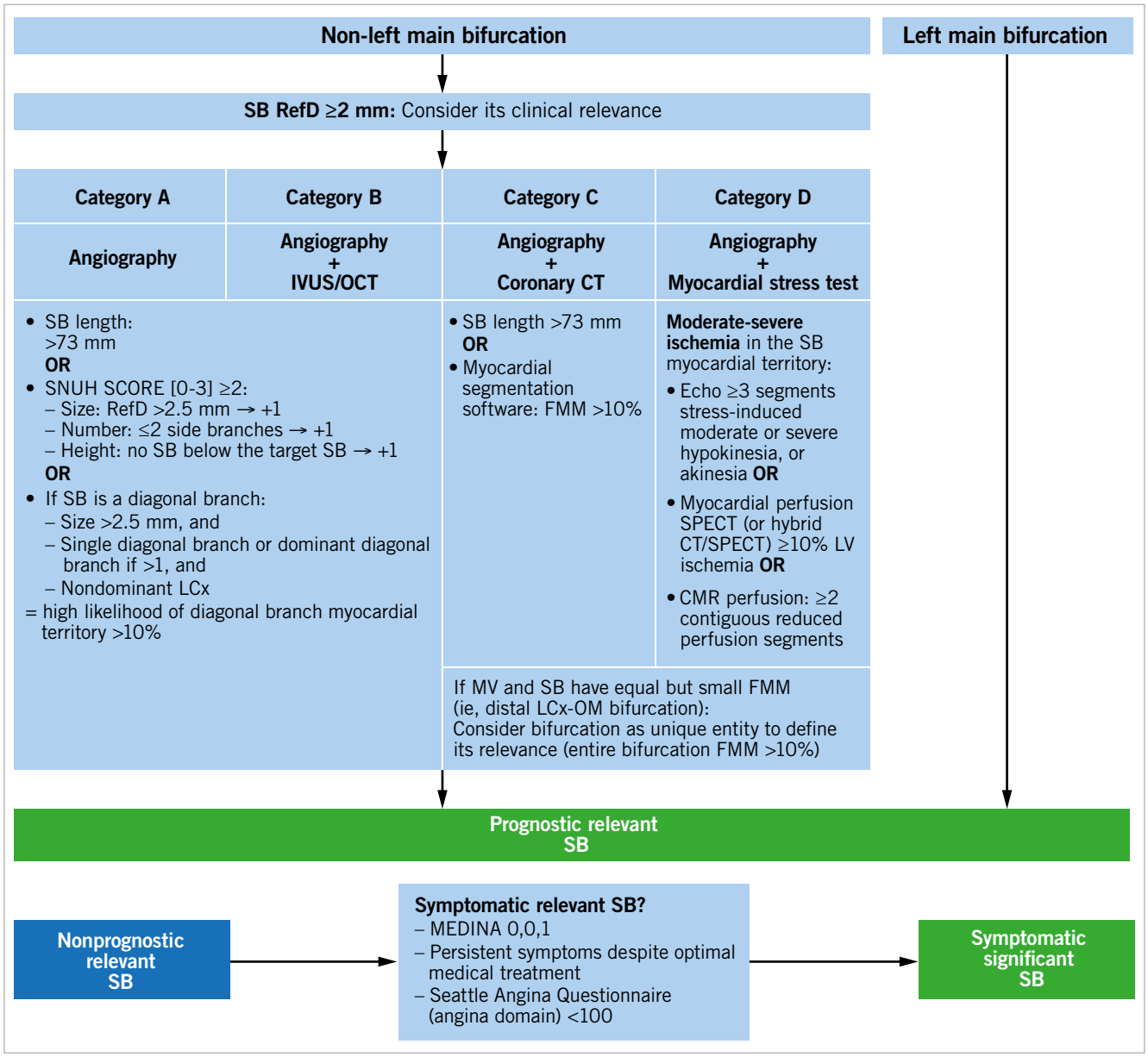

Figure 6. *Algorithm to determine the lesion eligibility according to the sb relevance. CMR: cardiac magnetic resonance; CT: computed tomography; FMM: fractional myocardial mass; IVUS: intravascular ultrasound; LCx: left circumflex coronary artery; MV: main vessel; OCT: optical coherence tomography; OM: obtuse marginal branch; RefD: reference diameter; SB: side branch; SPECT: single-photon emission computed tomography*

≥2 mm, plus additional criteria according to the diagnostic technique. The use of additional imaging (eg, intravascular imaging, CT angiography, nuclear imaging, etc), when available, is strongly recommended to increase the accuracy of the assessment and quality of the study (Categories B, C, and D), and in these cases, it should drive the definition of the SB relevance instead of the angiography.

Among them, we recommend:

- Intravascular imaging (Category B): increased accuracy of SB reference vessel dimension measurements;
- Coronary CT angiography (Category C): target SB length >73 mm,[31] or dedicated coronary CT software to calculate SB-related myocardium at risk >10%[28,31,32];
- Exercise or pharmacological stress echocardiography (Category D): ≥3 segments involving the SB territory showing stress-induced moderate or severe hypokinesia, or akinesia[16,33];
- Myocardial perfusion single-photon emission computed tomography (SPECT) (Category D): SB-related ≥10% LV ischemia[16,33];
- Cardiac magnetic resonance (CMR) perfusion (Category D): ≥2 contiguous reduced perfusion segments involving the SB territory[16,33];
- Hybrid cardiac imaging (Category D): SPECT/CT, positron emission tomography/CT,[34] or CMR/CT, to identify SBs subtending myocardium at risk >10%.

Retrospective analysis of these imaging techniques is also allowed if acquired in the previous 3 months, provided clinical status has remained the same.

In studies providing core lab analysis, the SB relevance, being a critical part of lesion eligibility, should also be evaluated by the core lab, whatever diagnostic test is used.

Angiography is the must-have test, and it is necessary when other techniques are unable to identify SB-related myocardial ischemia (healthy SB or MV/SB ischemic territories not identifiable). For diagonal SBs, we recommend using the SNuH (size, number, highest) score, which is a simple anatomical scoring system based on angiography to estimate the mass of myocardium at risk.[35] For further details, see the SB prognostic relevance according to the SNuH score section in the **Supplemental Appendix**.

Performing intravascular imaging is important considering that angiography can underestimate the exact size of the SB. Direct comparisons between angiography and intravascular imaging reveal a 5% underestimation of the RVD using QCA,[9] whereas the most accurate measurement is obtained using OCT.[10,36] Therefore, Bif-ARC suggests using intravascular imaging, and preferably OCT, to ascertain the reference diameter of the SB. Regardless of the adopted strategy, all image acquisition should be preceded by intracoronary nitroglycerin administration to maximize vessel size.

Integrated techniques involving coronary CT angiography and SPECT or positron emission tomography, by coregistration and fusion of either standalone or combined acquired images, offer incremental diagnostic value beyond that of either imaging modality alone, and in the context of a bifurcation lesion, the integration of dual imaging appears to improve the identification of the culprit vessel and the size of the subtended myocardium.[34]

2.3. LESION ELIGIBILITY FOR BIFURCATION STUDIES IN SYMPTOMATIC, BUT NONPROGNOSTICALLY RELEVANT SB LESIONS

Despite the absence of any of the aforementioned criteria of a prognostically relevant SB, the bifurcation lesion may still be considered eligible for a bifurcation study. SBs supplying <10% of the myocardium but still causing symptoms despite optimal medical therapy including aggressive therapy aimed at plaque regression, may require revascularization to maintain quality of life (QoL), even with uncertain prognostic benefit. Indeed, acute occlusion of even nonrelevant SBs can cause clinically evident myocardial infarctions.

Discrimination of SB-related angina symptoms in the presence of significant plaque involving the MV (either proximal or distal) is not possible. The only scenario in which angina symptoms can be unequivocally attributed to a SB is when the bifurcation disease has a MEDINA 0,0,1 pattern. In this case, a bifurcation with a nonrelevant SB can be considered for bifurcation studies if the symptoms are unremitting **(Figure 6)**.

In the absence of symptoms, there are also scenarios when a nonprognostically relevant SB could be considered eligible for a bifurcation study. In patients with poor LV function and chronic total occlusions – not amenable to recanalization – but collateralized by SBs stemming from bifurcation lesions, restoring patency of the SBs may assume an important perfusion role, regardless of size.

MEDINA 0,0,1 lesions without these characteristics do not meet the criteria for bifurcation studies.

2.4. COMPLEXITY OF BIFURCATION LESIONS

Overall, a number of clinical, anatomical, and procedural factors might contribute to the technical difficulties and risk of complications in an individual patient, therefore defining lesion complexity.[2]

Complex lesions are more likely to have characteristics (eg, long ostial SB lesions) that prompt operators to use longer or multiple stents, associated with higher long-term events,[37] however, we do not know whether this aggressive approach is the best way to manage complex lesions. It is therefore imperative to standardize the definition of lesion complexity and trial design in order to make future studies in the context of complex bifurcation lesions comparable.

Their definition can be based on different (or complementary) criteria, according to the method used for evaluation (eg, better calcium distribution evaluation with IVUS than angiography alone). In order to improve comparability between studies addressing complex lesions, Bif-ARC proposes different criteria to define complexity according to the method of evaluation **(Table 2)**.

2.5. INVASIVE FUNCTIONAL ASSESSMENT OF BIFURCATION LESIONS

Either when clinically required to assess ischemia, or when mandated by the study protocol, functional investigation of a bifurcation lesion requires technical precautions, that are fundamental to

Table 2. Complexity definition of bifurcation lesions according to diagnostic technique.

Category		
A **Angiography**	**B** **Intravascular imaging**	**C** **Coronary CT**
1) True bifurcation lesions (MEDINA 1,1,1; 1,0,1; 0,1,1)[94] + 1 of the following: • SB disease length ≥10 mm[95-97] • Calcified lesion • Thrombotic lesion • Difficult SB access (higher risk if bifurcation angle A <90°) 2) RESOLVE score[98] Dedicated bifurcation QCA recommended	1) True bifurcation lesions (MEDINA 1,1,1; 1,0,1; 0,1,1)[94] +1 of the following: • SB disease length ≥10 mm[99-101] • Thrombotic lesion • Calcium arc >60° at the culprit lesion site[99] • Difficult SB access (higher risk if bifurcation angle A <90°)[a]	1) True bifurcation lesions (MEDINA 1,1,1; 1,0,1; 0,1,1)[94] +1 of the following: • SB disease length ≥10 mm[99-101] • Thrombotic lesion • Calcium arc >60° at the culprit lesion site[99] • Difficult SB access (higher risk if bifurcation angle A <90° [3D assessment]) • Plaque composition: presence of low attenuation plaque in the SB or spotty calcifications within the bifurcation lesion[100] • Abnormal CT-derived FFR in the SB, suggesting dedicated 2-stent strategy 2) CT bifurcation score >1[101]: • Ca-plaque in PMV (+1) • Low attenuation plaque in PMV/SB (+1) • SB lesion length >5 mm (+1) • MV area/SB area >4.3 (+1) 3) CT-derived RESOLVE SCORE[102]

[a]Angiography based. Ca: calcium; CT: computed tomography; FFR: fractional flow reserve; QCA: quantitative coronary analysis; other abbreviations as in Table 1.

avoid measurement errors. SB flow is, in normal conditions, less than the flow toward the MV. In the presence of a PMV lesion and additional MV downstream lesions, the flow toward the SB increases ("branch steal effect"), increasing the distal pressure value (Pd) measured by the pressure wire in the SB. As a result, the SB functional assessment may be underestimated.[38]

Accordingly, we recommend using invasive functional assessment as follows **(Supplemental Table 5)**:

– Before intervention: To evaluate the functional significance of a MV stenosis or pure SB stenosis (MEDINA 0,0,1) when ischemia has not been confirmed elsewhere;
– During intervention: To decide whether additional interventions are required in a jailed SB (ie, occurrence of tight ostial stenosis of SB after crossover stenting of the MV)[39-43];
– After intervention: To assess the functional significance of a jailed SB, or to assess procedural success in the MV and in the SB, if treated. In the first case, a jailed pressure wire was shown utilizable for the assessment.[44]

Similar considerations, except for a few caveats, are valid for LM bifurcation stenoses **(Supplemental Table 5)**.

Image-based functional assessment is a novel diagnostic modality for functional testing of coronary artery stenoses without using pressure wires and/or the induction of hyperemia.[45] Unfortunately, the accuracy of these methods is yet to be validated in bifurcation lesions; therefore, whereas this image-based methodology (possibly retrospective) allows a standardized physiological assessment of every lesion involved in a trial, for the time being, it should not replace standard invasive physiological assessment, which remains the gold standard.

Bif-ARC supports investigational use of image-based fractional flow reserve (FFR) analysis pre-treatment, posttreatment, and during follow-up, especially with algorithms using fractal laws (ie, Murray's law in quantitative flow ratio[46]). For further details, see the Image-based functional assessment of bifurcation lesions section in the **Supplemental Appendix**.

2.6. INTRAVASCULAR IMAGING

Angiography often limits a comprehensive evaluation of bifurcation disease, whereas intracoronary imaging offers better definition of plaque composition (eg, localizing and quantifying calcium and lipid) and better assessment of its extension. In addition, it provides crucial periprocedural information (eg, lesion coverage, wire positions, stent expansion, and strut apposition) to help optimize treatment. Its feasibility during trials, and routine practice, is well documented.[47-49] Therefore, Bif-ARC supports the use of intravascular imaging as an adjunctive technique in bifurcation trials.

Specific recommendations for optimal image acquisition and core lab analysis are reported in the Intravascular imaging in bifurcation lesions section of the **Supplemental Appendix**.

3. Types of clinical studies in coronary bifurcations

Any investigation relating to a bifurcation lesion, including new dedicated devices, pharmacological, and/or new surgical or percutaneous treatments, requires a specific study design with standardized endpoints.

As a primary classification, Bif-ARC suggests separate trials of LM and non-LM bifurcations in order to prevent including both types of bifurcation lesion in the same study. In particular cases where the investigators desire to include both types, their inclusion in the study should be stratified according to that variable, or a stratified randomization should be considered.

Beyond this, Bif-ARC proposes the following classification of studies **(Table 3)**:

1. First-in-human studies:

Any study introducing a new device for use in humans for the first time (ie, specifically designed and dedicated to treat bifurcation lesions). The comparison will be made between the new device and historical data, or predefined benchmarks (ie, TRYTON trial).[50] The key endpoints of this study type lie in the Objective Performance Criteria.[51] To date, multiple devices specifically developed for bifurcation treatment were tested, but often with unsuccessful results, limiting their application.

Unfortunately, most of these were tested in bifurcation lesions with limited clinical relevance, often of small caliber and providing significant interventional challenges. Future dedicated devices should be investigated preclinically and clinically in relevant bifurcation lesions. Therefore, in particular for these studies, Bif-ARC recommends the aforementioned stratification according to the nature of bifurcation: 1) LM bifurcations; and 2) non-LM bifurcations with major or minor SB (RefD $\geq$ or <2.75, cf. Section 1.2 Classification). To offer the possibility to assess the actual efficacy and safety of new devices, these studies should cover the range of SB sizes applicable by definition, as per device Instructions For Use.

A subgroup of this category consists of technical studies, which are aimed at investigating the feasibility of specific procedural maneuvers, the use of specific procedural tools, or a particular technique to impact on procedural results. Examples include comparing the damage of different types of jailed wire by electronic microscopy,[52] or the feasibility of jailing a pressure wire.[44]

2. Comparison of percutaneous procedural strategies:

Studies comparing different percutaneous techniques to treat a bifurcation lesion belong to this category (eg, DK-Crush [Double Kissing Crush versus Provisional Stenting for Left Main Distal Bifurcation Lesions] and EBC MAIN [The European Bifurcation Club Left Main Study] trials[53,54]). They will encompass different stent strategies (eg, provisional strategy, and the variety of 2-stent strategies including different ways to perform similar techniques [eg, Crush vs DK-Crush), but also any investigation regarding adjunctive mechanical treatment for the bifurcation lesion (eg, the use of plaque modification techniques such as rotational atherectomy, cutting balloons, intracoronary lithotripsy).

Every strategy must be declared prior to the procedure (categorized as intention-to-treat, according to the latest updated MADS (Main-Across-Distal-Side) classification (MADS-2)[55] **(Figure 7)**.

3. Device comparisons:

These studies investigate new or existing devices (both stents and balloons, either dedicated bifurcation or not). The POLBOS II (DES Versus BiOSS LIM) trial[56] is an example of this type of study, in which a new dedicated bifurcation stent (BiOSS LIM, Balton) was compared with conventional drug-eluting stents (DES). Of note, this includes both intracategory (ie, DES vs DES) and intercategory device comparisons (eg, DES vs bioresorbable vascular scaffold, DES vs DCB).

4. Diagnostic assessment of bifurcation lesions:

This category includes clinical trials aiming to compare different diagnostic techniques (both imaging and functional). These studies can compare different types of diagnostic imaging (ie, 2D angiography vs 3-dimensional [3D] coronary CT angiography) and different types of physiological assessment (either invasive or image-based). For instance, recent techniques based on 3D reconstruction of a patient's anatomy and developed to assess flow, shear, and radial stress of a bifurcation lesion, can be included in this group.[57]

5. Revascularization strategy:

These studies will compare percutaneous vs surgical revascularization treatments and is especially important for LM bifurcation lesions (eg, LM bifurcation subgroup of the SYNTAX [Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery] trial, EXCEL [Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization] trial, etc). The nature of these studies will associate with a greater complexity of disease, and the outcome of LM bifurcation treatment may by influenced by the presence and/or treatment of additional lesions. Any study comparing the 2 strategies in any relevant bifurcation lesion (including non-LM bifurcation) will be part of this group.

6. Pharmacological treatment after percutaneous coronary intervention:

The choice of appropriate antiplatelet regimen, combined or not with anticoagulation, after complex percutaneous coronary intervention (PCI) such as bifurcation PCI, is a particular challenge, with new evidence continuing to emerge.[58,59] Studies comparing different medical strategies after bifurcation PCI (single vs dual antiplatelet therapy [DAPT], short vs long DAPT, DAPT vs triple therapy, different targets of platelet inhibition, etc) will be included in this category.

Due to the recognized value of bench testing in bifurcation interventions, any novel technique or device should first be tested in bench studies before undertaking a clinical study. Similarly, preclinical studies in large animal models may also reveal important information.

4. Endpoint definitions

For every category of study, Bif-ARC proposes 3 levels of endpoints: procedural, imaging and functional, and clinical **(Table 3)**.

Procedural endpoints include procedure-related outcomes, particularly relevant for studies comparing different techniques or new devices. Additional endpoints regarding the complexity of the procedure (eg, procedural time, x-ray exposure, etc) and health-economic data are also included in this category.

Imaging and Functional endpoints include mechanistic endpoints based on angiographic, intravascular, noninvasive imaging or functional evaluation. These endpoints serve as reports of common angiographic complications, immediate imaging, and function-based results, and are preferably assessed by the core lab. They are applied both post-procedural and at follow-up.

Table 3. Coronary bifurcation study types and related endpoints.

Type of study	Description	Procedural endpoints	Imaging and functional endpoints	Clinical endpoints
Procedural strategies comparison	Comparison of provisional vs upfront 2-stent strategy or 2 different 2-stent strategies (as per ITT) eg, DK-Crush II trial: DK crush double stenting vs provisional stenting in coronary bifurcation[103]	1) Intended primary strategy success (eg, crossover rate: the placement of a second stent in the SB, as part of a declared provisional strategy in the preprocedural planning, is not considered a crossover to a 2-stent strategy in strategies comparison studies On the contrary, it is, in studies comparing 1- vs 2-stent procedures Procedural strategy reported as per MADS-2) 2) Procedural success: • Device success • Free from event during the index hospitalization (CV death, TBR, PMI, any stroke, BARC 3 or 5 bleeding) 3) Health-economic endpoints: • Procedural time (min) • Procedural cost • Fluoroscopy time (min) • Contrast medium amount (mL)	1) Acute endpoints: • Residual stenosis (bifurcation dedicated-QCA, IVUS, OCT) • Dissection • Perforation • SB temporary flow impairment or occlusion • SB loss • MV and SB TIMI flow • Postprocedural invasive functional assessment and/or image-based FFR ≤0.89[104] • IVUS/OCT: underexpansion, malapposition, accidental crush, double stent layers, stent edge dissection, tissue protrusion (see Supplemental Appendix) • Post-PCI systolic-diastolic bifurcation angle B range <10°[105] 2) Late endpoints: • Late lumen loss or gain (in all the bifurcation segments, using the same method as per postprocedural assessment) • Binary restenosis (in all the bifurcation segments, using the same method as per postprocedural assessment) • Functional deterioration or net gain (invasive or image-based FFR ≤0.89)	1) BOCE: • CV death • Target bifurcation-related MI • Target bifurcation-related ischemia • TBR 2) Efficacy endpoint: • Target vessel revascularization • Target bifurcation-related ischemia • TBR 3) Safety endpoint: • BARC 3 or 5 • Definite ST • Any stroke • Any MI • CV death • All-cause death
Device comparison	Comparison of different devices (DCB vs stent, ie, BABILON trial[106]: DCB in both branches + BMS in PMV vs DES in MV only; or new dedicated bifurcation devices vs conventional devices, eg, POLBOS II trial: BiOSS LIM bifurcation dedicated stent vs conventional DES[56]	1) Procedural success: • Device success • SB stenting necessity (if provisional strategy) • Free from event during the index hospitalizations (CV death, TBR, PMI, any stroke) 2) Health-economic endpoints: • Procedural time (min) • Procedural cost • Fluoroscopy time (min) • Contrast medium amount (mL)	1) Acute endpoints: • Residual stenosis (bifurcation dedicated-QCA, IVUS, OCT) • Dissection • Perforation • SB temporary flow impairment or occlusion • SB loss • MV and SB TIMI flow • Postprocedural invasive functional assessment and/or image-based FFR ≤0.89[104] • IVUS/OCT: underexpansion, malapposition, stent edge dissection, tissue protrusion (see Supplemental Appendix) • Post-PCI systolic-diastolic bifurcation angle B range <10°[105] 2) Late endpoints: • Late lumen loss or gain (in all the bifurcation segments, using the same method as per postprocedural assessment) • Binary restenosis (in all the bifurcation segments, using the same method as per postprocedural assessment) • Functional deterioration or net gain (invasive or image-based FFR ≤0.89)	1) DOCE: • CV death • Device failure-related MI • Device failure-related ischemia • TBR 2) Efficacy endpoint: • Target vessel revascularization • Target bifurcation-related ischemia • TBR 3) Safety endpoint: • BARC 3 or 5 • Definite ST • Any stroke • Any MI • CV death • All-cause death
Diagnostic assessment comparison	Comparison between different physiological evaluation (both invasive and noninvasive) (ie, FFR vs NHPR in bifurcation lesions)	1) Assessment feasibility of the intended bifurcation segment before the treatment 2) Safety: • Any complications related to the assessment 3) Health-economic endpoints: • Procedural time (min) • Procedural cost • Fluoroscopy time (min) • Contrast medium amount (mL)	1) Accuracy of the investigated evaluation method (at preprocedure, postprocedure, follow-up) 2) Reproducibility	1) BOCE: • CV death • Target bifurcation-related MI • Target bifurcation-related ischemia • TBR

Table 3 (cont'd). Coronary bifurcation study types and related endpoints.

Type of study	Description	Procedural endpoints	Imaging and functional endpoints	Clinical endpoints
First-in-human studies	Comparison between a new device and historical data or predefined benchmarks (ie, TRYTON trial)[107]	1) Procedural success: • Device success • Free from event during the index hospitalizations (CV death, TBR, PMI, any stroke)	1) Acute endpoints: • Residual stenosis (bifurcation dedicated-QCA, IVUS, OCT) • Dissection • Perforation • SB temporary flow impairment or occlusion • SB loss • MV and SB TIMI flow • Postprocedural invasive functional assessment and/or image-based FFR ≤0.89[104] • IVUS/OCT: underexpansion, malapposition, device fracture, stent edge dissection, tissue protrusion (see Supplemental Appendix) • Post-PCI systolic-diastolic bifurcation angle B range <10°[105] 2) Late endpoints: • Late lumen loss or gain (in all the bifurcation segments, using the same method as per postprocedural assessment) • Binary restenosis (in all the bifurcation segments, using the same method as per postprocedural assessment) • Functional deterioration or net gain (invasive or image-based FFR ≤0.89)	Objective performance criteria (vs historical data or predefined benchmarks)[51]: 1) Safety endpoint: • All-cause death CV death • Any MI • Definite ST 2) Efficacy endpoint: • Any coronary revascularization • Target vessel revascularization • TBR 3) Composite efficacy and safety: • CV death, target vessel-MI, and TBR (DOCE) • All-cause death, any MI, and any revascularization (POCE)
Postprocedural pharmacological comparison	Comparison between different antiplatelet strategies after PCI (DAPT vs SAPT; short DAPT vs long DAPT; ie, GLOBAL LEADERS bifurcation subgroup study)[108]	1) Final strategy adopted (ie, 1-stent vs 2-stent; procedural strategy reported as per MAD-2) 2) Procedural success: • Device success • Free from event during the index hospitalizations (CV death, TBR, PMI, any stroke, BARC 3 or 5 bleeding)	1) Acute endpoints: • Residual stenosis (bifurcation dedicated-QCA) • Dissection • Perforation • SB temporary flow impairment or occlusion • SB loss • MV and SB TIMI flow • Postprocedural invasive functional assessment and/or image-based FFR ≤0.89[104] • IVUS/OCT: underexpansion, malapposition, stent edge dissection, tissue protrusion (see Supplemental Appendix) • Post-PCI systolic-diastolic bifurcation angle B range <10°[105] 2) Late endpoints: • Late lumen loss or gain (in all the bifurcation segments, using the same method as per postprocedural assessment) • Binary restenosis (in all the bifurcation segments, using the same method as per postprocedural assessment) • Functional deterioration or net gain (invasive or image-based FFR ≤0.89)	1) Bleeding endpoint: • BARC 3 or 5 2) POCE: • All-cause death • Any stroke • Any MI • Any revascularization 3) NACE • Bleeding endpoint • POCE 4) Nonadherence classifications according to NARC[74] 5) PROMs (ie, SAQ)[81]

Table 3 (cont'd). Coronary bifurcation study types and related endpoints.

Type of study	Description	Procedural endpoints	Imaging and functional endpoints	Clinical endpoints
Revascularization type comparison (percutaneous vs surgical)	Comparison between the 2 revascularization strategies (eg, bifurcation LM subgroups of SYNTAX, EXCEL trials[109])	PCI arm 1) Procedural success: • Device success • Free from event during the index hospitalizations (CV death, TBR, PMI, any stroke, BARC 3 or 5 bleeding) CABG arm 1) Procedural success: • Successful performance of the intended coronary revascularization surgical strategy • Free from event during the index hospitalizations (CV death, TBR, PMI, any stroke, BARC 3-5 bleeding)	1) Acute endpoints: PCI arm • Residual stenosis (bifurcation dedicated- QCA, IVUS, OCT) • Dissection • Perforation • SB temporary flow impairment or occlusion • SB loss • MV and SB TIMI flow • Postprocedural invasive functional assessment and/or image-based FFR ≤0.89[104] • IVUS/OCT: underexpansion, malapposition, stent edge dissection, tissue protrusion (see Supplemental Appendix) • Post-PCI systolic-diastolic bifurcation angle B range <10°[105] • Residual SYNTAX score 2) Late endpoints: • Functional deterioration or net gain (invasive or image-based FFR ≤0.89) PCI arm • Late lumen loss or gain (in all the bifurcation segments, using the same method as per postprocedural assessment) • Binary restenosis (in all the bifurcation segments, using the same method as per postprocedural assessment) CABG arm • Graft stenosis >70% or graft occlusion	1) POCE: • All-cause death • Any stroke • Any repeat revascularization • Any MI 2) Bleeding endpoint: PCI arm: BARC 3 or 5 CABG arm: BARC 3, 4, or 5 3) NACE • Bleeding endpoint • POCE 4) PROMs (eg, SAQ)

BARC: Bleeding Academic Research Consortium; BMS: bare-metal stent; BOCE: bifurcation oriented composite endpoint; CABG: coronary artery bypass graft; CV: cardiovascular; DAPT: double antiplatelet therapy; DCB: drug coated balloon; DES: drug eluting stent; DK-Crush: Double Kissing Crush versus Provisional Stenting for Left Main Distal Bifurcation Lesions; DOCE: device oriented composite endpoint; EXCEL: Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; ITT: intention-to-treat; IVUS: intravascular ultrasound; MADS: Main-Across-Distal-Side; MI: myocardial infarction; MV: main vessel; NACE: net adverse clinical events; NARC: Non-adherence Academic Research Consortium; NHPR: nonhyperemic pressure ratio; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; PMI: periprocedural myocardial infarction; POCE: patient oriented composite endpoint; POLBOS: POLish Bifurcation Optimal Stenting; PROMs: patient reported outcome measures; SAPT: single antiplatelet therapy; SAQ: Seattle Angina Questionnaire; SB: side branch; ST: stent thrombosis; SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TBR: target bifurcation revascularization; TIMI: Thrombolysis In Myocardial Infarction; other abbreviations as in Tables 1 and 2

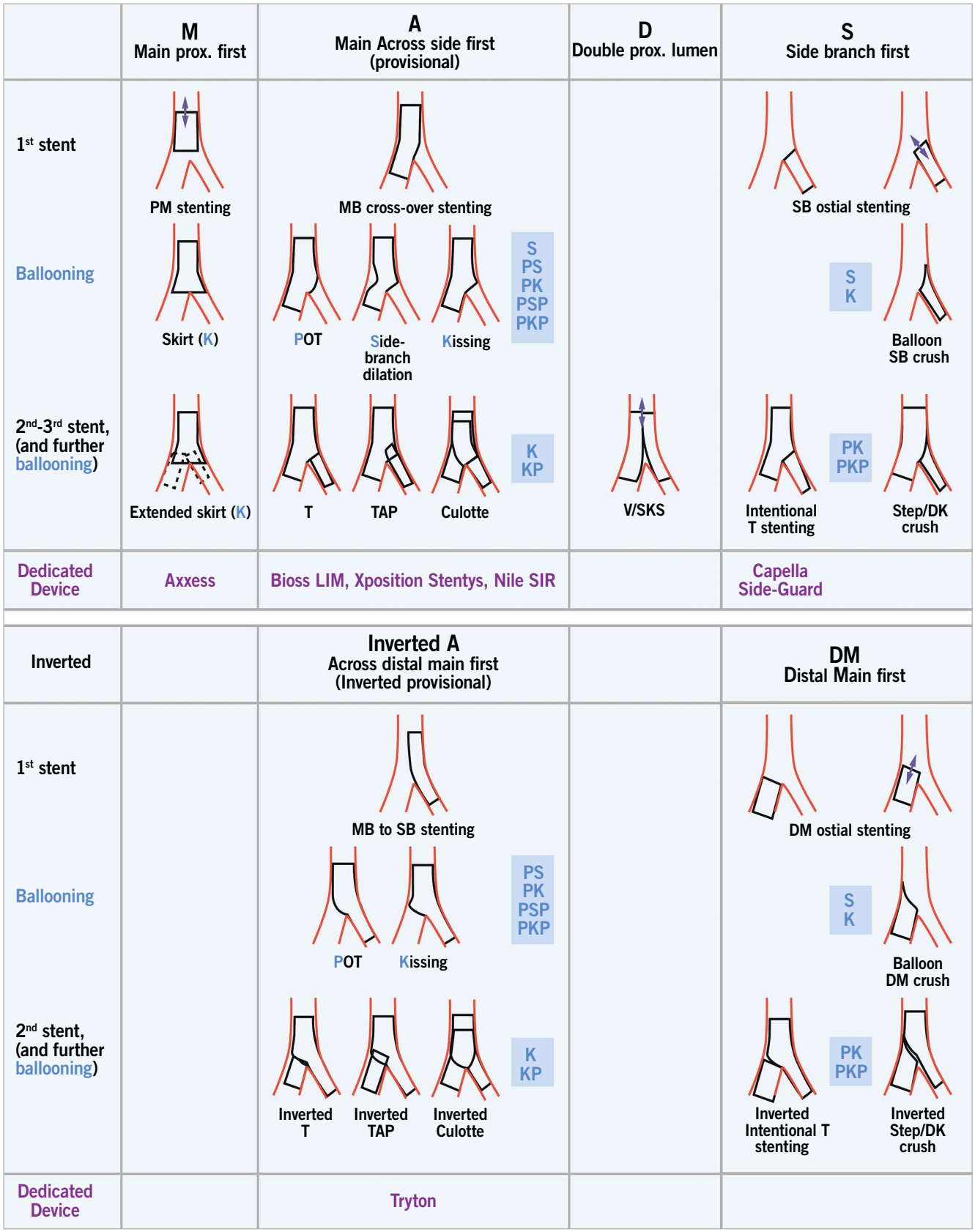

Figure 7. *MADS-2 classification of bifurcation stenting techniques. The upper panel shows the standard techniques, whereas the lower panel shows the "inverted" techniques. Blue capital letters refer to the standard ballooning techniques, whereas the lower panel shows the "inverted" techniques. Common combinations of ballooning techniques are described as the sequential blue capital letters. Reproduced from Burzotta et al.[55] DK: double kissing; MB: main branch; other abbreviations as in Figure 3*

Clinical endpoints encompass efficacy and safety endpoints, and depending on the study, patient or device-related endpoints should be included.

On the basis of the specific study category the consensus defines specific and different composite endpoints. The itemized components, however, should be reported individually. Events should be adjudicated by an independent Clinical Events Committee based on redacted source documents, eventually supported by core lab assessment.

TRIALS AIMING AT PROCEDURAL SUCCESS

With respect to first-in-human studies (category 1), the endpoints are evaluated by comparison with Objective Performance Criteria,[51] in particular for those concerning efficacy and safety outcomes. Such studies are not necessarily statistically powered, but stopping rules may be used as criteria of success or failure (ie, ASET [Acetyl Salicylic Elimination Trial] pilot study[60]). The supervision of the trial by an independent data safety monitoring board, with a consultative role in advising continuation or discontinuation of the trial, is mandatory.

In trials comparing procedural strategies, devices, and in diagnostic assessment studies (categories 2 to 5) procedural and imaging, and functional endpoints have a particular relevance and should be defined as primary endpoints.

Imaging and functional endpoints are required for postprocedural evaluation and at mid-term follow-up (cf. section 6. Follow-Up Methods).

Analysis by an independent core laboratory using standardized operational procedures with predefined analytical plans is strongly recommended. For those studies, where core lab analysis is not available, we recommend following the aforementioned Bif-ARC indications for angiography and intravascular imaging analysis.

Clinical endpoints play a secondary role in these studies, and are suggested to be set as secondary endpoints.

TRIALS INVESTIGATING CLINICAL BENEFIT

In trials focusing on pharmacological regimens, or comparing different types of revascularization strategy (eg, surgical vs percutaneous, categories 6 and 7), clinical composites should be set as primary endpoints, which should include safety (eg, bleeding events) and ischemic endpoints. Net adverse clinical events that incorporate safety-related events and patient-reported outcomes should also be reported.

4.1. INDIVIDUAL ENDPOINTS

All individual endpoints definitions are reported in **Table 4** and are outlined in the following text when requiring a bifurcation-specific description.

DEVICE AND PROCEDURAL SUCCESS

Device success is defined as the composite of successful delivery of the first assigned device at the intended target bifurcation, successful withdrawal of its delivery system, and a final in-stent/scaffold %DS <20 in each stented segment of the bifurcation by visual assessment or <30% by bifurcation QCA[61] (<50% in case of balloon angioplasty alone[62]). When use of intravascular imaging is mandated by the study protocol, device success is defined by a final minimum stent area >80% of the reference vessel area in each stented segment of the bifurcation. The use of bail-out devices (as allocated by randomization) due to edge dissections or geographic miss is not regarded as a device failure but rather as a clinical issue.

Procedural success herein defined as the composite of device success plus additional criteria related to clinical outcomes of the procedure, regardless of whether the protocol-assigned device is used **(Table 4)**.

MYOCARDIAL INFARCTION

Periprocedural myocardial infarction

Myocardial infarction (MI) may occur in the periprocedural period, or long after the procedure because of spontaneous events or late complications related to the investigated device/strategy. The definition of MI, and in particular periprocedural MI (PMI), varies across trials and cardiac societies, and may require different criteria according to study type in order to effectively use the sensitive biomarkers of subtle myocardial injury, and balance them against clearly adverse clinical outcomes.[63] Unfortunately, evidence regarding this is scarce; however, it has been shown that PMIs defined by the Society for Cardiovascular Angiography and Interventions (SCAI) criteria, as opposed to the 4th Universal Definition of Myocardial Infarction (UDMI) or the SYNTAX definition, have the best correlation to adverse outcomes after stenting true bifurcations.[64]

Furthermore, there are still debates about the most accurate cardiac biomarker to use, although in recent times the cardiology community has seen the extinction of creatine kinase-myocardial band (CK-MB) in favor of high-sensitivity cardiac troponin (hs-cTn). Nevertheless, the correlation among the many available type I hs-cTn assays is unclear and leaves room for potential differences between studies or incorrect endpoint definitions.

Considering this, Bif-ARC proposes a modified version of the ARC-2 PMI criteria, incorporating type T hs-cTn,[65] currently measured with a single assay. Accordingly, in bifurcation studies, a PMI is defined by either an absolute rise ≥35 upper limit of normal (ULN) threshold for type T hs-cTn plus clinical evidence of MI or an absolute cTn rise ≥70 ULN as a stand-alone criterion within 48 hours of the PCI or coronary artery bypass graft (CABG) **(Table 4)**.

Such criteria reflect the SCAI definition, except for the use of hs-cTn instead of CK-MB, given concerns related to its unavailability. However, the proposed thresholds for hs-cTn have been calculated based on the SCAI CK-MB cutoff values (≥5 ULN and ≥10 ULN, respectively).[66]

In cases where different cardiac enzymes are measured (ie, cTn and CK-MB), Bif-ARC suggests recording the rate of availability of the different enzymes within the study (ie, % of patients having CK-MB reported).

Given the complexity of the definition of PMI and numerous related issues raised in previous studies, ARC is working to release a PMI-dedicated document in 2022, and this consensus will be updated accordingly.

Table 4. Single endpoints definitions.

Endpoints definitions	Description
Device success	All of: • Successful delivery, balloon expansion, and deployment of the first assigned device, at the intended target lesion/bifurcation. When deployment of >1 assigned device is planned in advance for a single bifurcation lesion (eg, a 2-stent technique), all assigned devices are assessed and reported as 1 device. In that case, only when all assigned devices are successfully implanted at the intended target lesion is this classified as device success. (Multiple attempts using the same instrument are allowed; for example, success at a second attempt with the same [first] investigational device after rewiring the vessel, use of a support catheter, or additional ballooning, vessel preparation, etc). • Successful withdrawal of the device delivery system. • Attainment of a final in-stent or in-scaffold residual stenosis of <30% (or <50% in case of balloon angioplasty alone) with final data reported by core laboratory QCA using dedicated bifurcation software (preferred methodology when no intravascular imaging is provided wsee Supplemental Appendix])
Cardiovascular death	1. Death caused by acute MI 2. Sudden cardiac, including unwitnessed, death 3. Death resulting from heart failure 4. Death caused by stroke 5. Death caused by cardiovascular procedures 6. Death resulting from cardiovascular hemorrhage (hemorrhage deriving from cardiac and/or vascular disease/injuries)
Periprocedural MI	Evaluation <48 h: • hs-cTn T rise ≥35 URL AND ≥1 of the following criteria: • "Flow-limiting" angiographic complications in a major epicardial vessel (RefD ≥2. 0 mm evaluated by core-lab QCA), at the end of the procedure • New significant Q waves (or equivalent) in 2 contiguous leads, after the procedure • A new wall motion abnormality on echocardiography, after the procedure OR • hs-cTn T rise ≥70 URL (All events should be adjudicated, ideally after core-lab analysis, by an independent CEC)
Cardiac biomarkers rise[67]	Any CK-MB and/or hs-cTn T rise >6 h after the procedure Type 1: due to SB occlusion a) Intraprocedural, after lesion predilation b) Intraprocedural, after device (stent, scaffold) implantation c) Final result at the end of the procedure Type 2: due to other angiographic complications a) Intraprocedural occlusion of the main branch b) Intraprocedural distal embolization c) Intraprocedural coronary perforation d) Intraprocedural dissection (after predilation, after device implantation) e) Residual dissection at the end of the procedure f) Intraprocedural thrombus g) Residual thrombus at the end of the procedure Type 3: No angiography identifiable causes
Stroke	Neuro-ARC definitions (according to ARC-2 criteria)
Bleeding	BARC definitions (according to ARC-2 criteria)
Target bifurcation-related ischemia	The target bifurcation ischemia is defined in presence of ischemic myocardium supplied by the bifurcation coronary segments treated during the initial procedure. Identification and localization of ischemia requires the use of the same ischemic test, utilized during the inclusion in the study.
Target bifurcation revascularization	The target bifurcation lesion is commonly considered as the treated coronary segment during the index procedure plus 5 mm distance from the stent edges or the balloon angioplasty site, applied both for MV and SB in case of bifurcation lesions. When an SB does not undergo either balloon angioplasty or stent placement at the time of the index procedure, but at the time of angiographic follow-up (either mandated or clinically indicated) has developed a stenosis (%DS ≥50 according to bifurcation QCA) Bif-ARC considers that the region extending up to a 5 mm distance from the ostium of the SB should be included within the target bifurcation definition. Target bifurcation revascularization is defined as a repeat percutaneous intervention of the target bifurcation or bypass surgery of the target vessel performed for restenosis or other complication of the target bifurcation. MEDINA classification of the newly diseased bifurcation segments and the repeat revascularized segments is recommended.
Target vessel revascularization	The target vessel is defined as the entire major intervened coronary vessel, including side branches. In case of LM-LAD/Circ bifurcation treatment, LM-LAD lesion without significant stenosis in LCx / target vessel: LM-LAD only; otherwise LM, LAD, LCx Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target bifurcation.
Target vessel nontarget bifurcation revascularization	Target vessel nontarget bifurcation revascularization is defined as any repeat percutaneous intervention or surgical bypass of the target vessel for pre-existing disease, disease progression, or other reasons unrelated to the target lesion as defined above.

Table 4 (cont'd). Single endpoints definitions.

Endpoints definitions	Description
Target bifurcation-related MI	Any MI with angiographic confirmation of culprit lesion corresponding to the target bifurcation previously treated Nonconfirmed bifurcation related MI should be considered as target vessel MI
Definite stent thrombosis	Angiographic confirmation: the presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent or in the side branch originating from the stented segment and the presence of at least 1 of the following criteria: 1) Acute onset of ischemic symptoms at rest 2) New electrocardiographic changes suggestive of acute ischemia 3) Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction) OR Pathological confirmation: 1) Evidence of recent thrombus within the stent determined at autopsy 2) Examination of tissue retrieved following thrombectomy (visual/histology) Early acute: 0-24 h; early subacute: 1 d-30 d; late: 30 d-1 y; very late: >1 y
Probable stent thrombosis	Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause Early acute: 0-24 h; early subacute: 1 d-30 d; late: 30 d-1 y; very late: >1 y
SB occlusion	SB flow impairment: SB TIMI flow less than main vessel TIMI flow after procedure SB occlusion: loss of angiographic visualization of SB PMV TIMI flow 0-1: SB flow not assessable
MV occlusion	PMV or DMV: 1) When TIMI flow grade 3 or 2 at baseline; TIMI flow grade 0 or 1 after the procedure 2) When TIMI flow grade 1 at baseline; TIMI flow grade 0 after the procedure 3) When TIMI flow grade 0 at baseline and vessel patency (TIMI flow grade 2 or 3) established during procedure; TIMI flow grade 0 after procedure
Major dissection (angiographic)	Dissection in the target vessel greater than Type b from National Heart, Lung, and Blood Institute classification[110]
Perforation	Type 1) extraluminal crater without jet extravasation Type 2) pericardial or myocardial blushing without jet extravasation Type 3) active jet extravasation exit jet >1 mm Type 4) leaking into another cardiovascular cavity Type 5) distal perforation
Late lumen loss or gain	Difference between the MLD immediately after the procedure and the MLD at follow-up
Binary stenosis	>50 %DS at follow-up

ARC: Academic Research Consortium; Bif-ARC: Bifurcation Academic Research Consortium; CEC: clinical event committee; CK-MB: creatine kinase-MB; DMV: distal main vessel; hs-cTn: high- sensitivity cardiac troponin; LCx: left circumflex artery; LAD: left anterior descending artery; LM: left main; PMV: proximal main vessel; URL: upper reference limit; other abbreviations as in Tables 1 to 3.

Spontaneous MI

Bif-ARC endorses the definition of spontaneous MI as per the 4th UDMI (Type 1, 2, 3, 4b, or 4c). Of note, in the 4th UDMI, "prior or silent/unrecognized MI" is defined as abnormal Q waves with or without symptoms in the absence of nonischemic causes, imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology, or pathoanatomical findings of a prior MI. Bif-ARC suggests that MI as a component of the primary endpoint does not include "prior or silent/ unrecognized MI" because there is no evidence of cardiac biomarker elevation.

In the setting of bifurcation treatments, Bif-ARC defines target bifurcation-related MI as any MI with angiographic confirmation that the culprit lesion corresponds to the previously treated target bifurcation. Any MI not clearly attributed to a nontarget bifurcation lesion should be considered a target bifurcation-related MI.

The reporting of target bifurcation-related MI is of particular relevance for device-related endpoints.

POSTPROCEDURAL CARDIAC BIOMARKERS RISE

Even when not meeting the criteria for a PMI, Bif-ARC suggests reporting any postprocedural rise in cardiac biomarkers after a minimum of 6 hours from the end of the procedure.[67] In the context of investigating a new device, even events of little clinical relevance may be important for the safety profile of the new device. In this setting, when available, CK-MB represents a better biomarker to detect the subsequent fall, given its shorter elimination kinetics.

The enzymatic rise should be classified according to the angiographic findings, as proposed in **Table 4** (eg, SB occlusion). The proposed classification discriminates between angiographic complications occurring during the procedure (eg, intraprocedural stent thrombosis or transient SB occlusion) and those complications persisting at the end of the procedure. The record of intraprocedural complications, which may be transient, is relevant considering solid evidence whereby intraprocedural (transient)

stent thrombosis has been associated with adverse short-term ischemic outcomes in patients undergoing PCI.[68]

BLEEDING

Bleeding events should be classified and reported according to the Bleeding Academic Research Consortium criteria.[69]

International guidelines encourage weighing bleeding risk before selecting a treatment regimen in patients at high risk of bleeding and/or undergoing complex PCI procedures, such as bifurcation revascularization.

Bif-ARC categorizes patients into 2 groups, according to the need for anticoagulant therapy:

1. For patients not requiring anticoagulants, Bif-ARC recommends the recent algorithm proposed by the European Bifurcation Club that bases the decision of DAPT duration on clinical presentation (ACS vs CCS), bleeding risk (high vs low), and use of intravascular imaging.[70]
2. For patients on anticoagulants (eg, atrial fibrillation), several different antiplatelet/anticoagulant regimens have recently been proposed specifically for patients with atrial fibrillation undergoing PCI, considering the different weight of their bleeding and thrombotic risk.[71,72]

Overall, Bif-ARC supports the use of the ARC-HBR (Academic Research Consortium High Bleeding Risk) tool to evaluate patients' bleeding risk and in particular their ischemia/bleeding tradeoff, although further validation in the specific context such as bifurcation PCI is needed.[73]

In addition, for studies investigating pharmacological treatment after bifurcation revascularization, Bif-ARC suggests the collection and analysis of medication adherence according to the 4 classes (Type 0, 1, 2, and 3) proposed by the Nonadherence Academic Research Consortium. The adoption of such classification will afford robustness and consistency in the comparative safety and effectiveness evaluation of investigational pharmacological regimens,[74] and frequently requires a per-protocol analysis (cf. section 7. Statistical Consideration).

REPEAT REVASCULARIZATIONS

Nomenclature

Repeat revascularization will be defined according to the vessel/lesion treated, identifying them as target or nontarget, based on the initial site of revascularization.

A target bifurcation revascularization (TBR) is defined as a repeat revascularization of the target bifurcation by PCI or bypass surgery of the target vessel(s), performed for restenosis or another complication of the target bifurcation.

Because some revascularization techniques lead to iterative restenosis–retreatment, Bif-ARC recommends collecting the number of additional repeat revascularizations that can be considered with dedicated statistical approaches (win ratio analysis, Cox-based models for recurrent events, and weighted composite endpoint [WCE] analysis, cf. section 7.2 Statistical Analysis Including Repeated Events and Sample Size Calculation), whereas the first recurrence occurring after the initial treatment is classically included in the time-to-first event analysis.

The target bifurcation is commonly considered as the bifurcation coronary segment treated during the index procedure plus 5 mm from the stent edges or the site of balloon angioplasty, applied to both the MV and SB. When a SB that did not undergo either balloon angioplasty or stent placement at the time of the index procedure, but at the time of angiographic follow-up (either mandated or clinically indicated) has developed a stenosis (%DS ≥50, according to bifurcation QCA), Bif-ARC considers that the region extending up to 5 mm from the ostium of the SB should be included within the target bifurcation definition.

Bif-ARC proposes a new nomenclature, according to which any TBR should be accompanied by the identification of the diseased bifurcation segments using the MEDINA classification (MEDINArestenosis), based on the core lab–dedicated bifurcation QCA[75] **(Supplemental Table 6)**.

In trials comparing CABG and PCI, in the CABG arm, the ascertainment of TBR should consider the patency (stenosis or occlusion) of the graft either on the DMV, SB or both branches as a surrogate for restenosis in the native vessels. In such cases, to define the diseased segments, Bif-ARC proposes a modified version of the MEDINA classification consisting of 2 binary values (0 or 1) referring to the grafts towards the DMV and the SB, respectively, preceded by an "x" (representing the PMV = not applicable in case of grafts) **(Supplemental Table 7)**.

Once repeat revascularization is performed, the operators should report the type of revascularization and nomenclature of revascularized segments using the MEDINA classification as shown in **Supplemental Table 8** ($MEDINA_{revasc\text{-}CABG}$ or $MEDINA_{revasc\text{-}PCI}$).

Target vessel non-TBR is defined as any repeat percutaneous intervention or surgical bypass of the target vessel for pre-existing disease, disease progression, or other reasons unrelated to the target bifurcation lesion as defined in the preceding text.

Adjudication criteria for TBR

Adjudication of repeat revascularization requires clinical, angiographic, and functional criteria.[76]

A core lab using dedicated QCA bifurcation software is recommended, especially when functional evaluation is not available or provided. Bif-ARC underscores the importance of functional assessment in order to justify the need for repeat revascularization procedures. When the functional test is negative (ie, FFR >0.80) despite the presence of angina pectoris, Bif-ARC suggests investigating the presence of microvasculature dysfunction, from functional or structural origin.[77] **Supplemental Table 9** reports the hierarchical order of functional and angiographic criteria recommended for event adjudication of clinically indicated repeat revascularizations. The functional assessment of a bifurcation lesion requires precautions as outlined in section 2.5 and in the **Supplemental Appendix**.

Whenever the functional evaluation of the target lesion is not possible or reliable, and in the presence of a bifurcation QCA %DS ≥50, we recommend categorizing the revascularization as clinically driven, based on either recurrent symptoms or a positive

noninvasive ischemia test. A bifurcation QCA %DS ≥70 in the absence of such criteria may also be considered as a clinically indicated revascularization. Of note, any planned staged procedure is not considered a TBR, at least within the protocol-defined timeframe allocated for staged procedures.

5. Procedural, technical, and clinical information to collect

5.1. PROCEDURAL AND TECHNICAL DATA

Procedural and technical data before and after the procedure, and at follow-up should be collected according to the study type. A list of the essential variables that Bif-ARC recommends to be recorded in the case report form are presented in **Supplemental Table 10**.

Specifically for LM bifurcation studies, given the importance of operators' experience for clinical outcomes, Bif-ARC recommends reporting the volume of LM bifurcation PCI/year of the center.[16,53,78]

5.2. CLINICAL DATA

Similarly, clinical variables should be collected at baseline, during the hospital stay, and at the various follow-up visits, according to the type of study. Some differences in data collection are expected for CABG arms in revascularization type comparison trials. The list of essential data to be reported in the case report form recommended by Bif-ARC is detailed in **Supplemental Table 11**.

6. Follow-up methods

Bif-ARC recommends carrying out follow-up on a 3-level basis:

1. Clinical and patient level (eg, clinical and patient-reported endpoints);
2. Noninvasive testing (eg, ischemia tests, coronary CT);
3. Invasive testing (eg, coronary angiography).

6.1. CLINICAL AND PATIENT-BASED FOLLOW-UP

Bif-ARC recommends the use of composite clinical endpoints at every follow-up visit, as defined for every study in **Table 3**.

Timing for their evaluation is according to the study protocol, but as a minimum we recommend 12-month clinical follow-up when no angiographic follow-up is required. In order to avoid interference by confounding angiographic findings (eg, restenosis leading to repeat intervention, not clinically indicated), when angiography is mandated by the protocol, clinical endpoints should be collected before invasive follow-up takes place.

In studies comparing surgical vs percutaneous revascularizations, Bif-ARC recommends extending clinical follow-up to 10 years.

The final goal of coronary revascularization, however, is not only to prevent hard cardiac events, but also to improve symptoms, functional status, and the patient's QoL. From a broad perspective, quality adjusted life-years is the ultimate endpoint for the trialists and the patient, because it represents the combination of survival and QoL gain.

Therefore, Bif-ARC recommends analyzing patient-related outcome measures during follow-up.[79,80] In the context of bifurcation studies, patient-related outcome measures play a key role in particular in studies investigating the clinical benefit derived from different revascularization treatments (PCI vs CABG) and different pharmacological regimens, when the 2 competing strategies might lead to significant differences in health status as perceived by the patient.

On the contrary, studies investigating bifurcation percutaneous strategies (eg, provisional vs upfront 2-stent strategy) or dedicated bifurcation devices (eg, bifurcated stents vs standard stents), are less likely to produce measurable differences in patients' perception.

As an assessment tool, it is important to choose the one that best quantifies the domain of health most likely affected by the treatment under investigation. For instance, studies comparing surgical vs percutaneous treatment should use an angina status questionnaire (eg, Seattle Angina Questionnaire)[81,82] or health status questionnaires addressing in a wider way the impact of the 2 different clinical interventions (eg, Short Form 36 Health Survey Questionnaire).[83] Nevertheless, any tool selected by the investigators should have psychometric properties (validity, reliability, responsiveness, and interpretability) proven to measure the intended domain (eg, Seattle Angina Questionnaire, Short Form 36 Health Survey Questionnaire).[81,83]

6.2. NONINVASIVE FOLLOW-UP

Noninvasive testing should be undertaken whenever a clinical suspicion of recurrent ischemia exists, or if mandated by the study protocol. In first-in-human studies, or in the presence of clear ongoing ischemia (eg, unstable angina), however, invasive assessment should be performed first.

The test type is left to trial designers' discretion (eg, cycle ergometer stress testing, echocardiography stress test, nuclear imaging test, stress CMR, et al).

6.3. INVASIVE FOLLOW-UP

Invasive follow-up consists of a coronary angiogram either as protocol mandated or secondary to adverse events requiring invasive diagnosis/intervention.

It is vital for all studies investigating new devices (first-in-human or through comparison with existing devices) to define their mechanical efficacy, and it is also of relevant benefit in studies comparing percutaneous strategies.

In cases of invasive follow-up, core lab analysis is recommended. In regard to QCA, the same segmental analysis used at the time of postintervention should be considered at this stage. This should include dimensional analysis of residual stenosis and the precise location of treatment failure or restenosis at follow-up (cf. Repeat Revascularization in Section 5.1).

Functional assessment of the target bifurcation is advised to measure its "functional deterioration," defined as a reduction in the functional values compared with the postprocedural values.

Depending on study design and the interrogated device or strategy, angiography may require intravascular imaging. When required by the study protocol or for clinical reasons, IVUS or

OCT can be used according to the aforementioned indications/criteria.

7. Statistical consideration

The general recommendation of Bif-ARC is to design separate dedicated bifurcation studies for LM and non-LM bifurcations; however, there may be cases when investigators include both in the same study. In this scenario, Bif-ARC recommends stratifying the analysis accordingly and, when randomization is required, mandating a stratification randomization variable.

7.1. INTENTION-TO-TREAT VS PER-PROTOCOL VS AS-TREATED

In bifurcation studies comparing interventional treatments, the rate of cross-over is expected to be higher than others studies, given the complexity of the intervention and the difficulties in predicting results, particularly in the SB. Hence, a clear definition of the operator's strategy upfront is mandatory, as well as the exact report of the actual strategy/technique used. Primary analysis should be based on the intention-to-treat principle, but Bif-ARC also recommends performing statistical analyses according to the per-protocol and as-treated principles **(Supplemental Table 12)**.

7.2. STATISTICAL ANALYSIS INCLUDING REPEATED EVENTS AND SAMPLE SIZE CALCULATION

The time-to-first-event analysis, which treats all components of the composite endpoint as having equal severity, is the standard method and should be used in the primary analysis.[84] On the other hand, this analysis only considers the first endpoint encountered in time. Thus, nonfatal events that occurred earlier have more impact than more serious events such as stroke or death that occur later. Bifurcation lesion revascularization is one of the most complex coronary interventions, and some clinical events, such as MI and repeat revascularization, often occur repeatedly. Several methods have been proposed to overcome these limitations. These methods consider all events occurring during follow-up and/or incorporate the severity of clinical events. They include win ratio analysis, Cox-based models for recurrent events, and WCE analysis (further details in **Supplemental Table 13** and in the Statistical analysis including repeated events section in the **Supplemental Appendix**).

Although all methods have strengths and weaknesses, they may enhance our understanding when components of composite endpoints vary substantially in severity and timing.

Therefore, Bif-ARC recommends their use as pre-specified secondary analyses, according to patient type, devices and strategies used, and events.

For every prospective study, a statistical plan and sample size calculation are mandatory.

In the statistical analysis plan, the method of counting repeated events (Cox-based models for recurrent events and WCE analyses) and the ranking and/or weighting of cardiovascular events (win ratio and WCE analyses) should be prespecified to avoid any uncertainty.[85]

The sample size calculation should be based on the primary analysis; to date, the time-to-first-event analysis is recommended. When analyses considering recurrent events and/or event severity are used, simulation techniques and dedicated codes are required for sample size calculations.[86-88]

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The scientific value of the Bif-ARC consensus document has been affirmed by the Society for Cardiovascular Angiography and Interventions.

Impact on daily practice

There is a paucity of standardization and comparability across studies involving coronary bifurcation lesions. This document provides standardized definitions and criteria for use in studies of such lesions, from diagnosis through follow-up. Implementation of these recommendations in clinical trials will improve their relevance and improve the quality of care for patients with bifurcation coronary artery disease.

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Supplementary data

Supplemental Appendix. Methods section.

Supplemental Table 1. Historical bifurcation lesions treatment techniques.

Supplemental Table 2. Examples of bifurcation lesions dedicated devices investigated so far.

Supplemental Table 3. Historical limitations of heterogeneous definitions in bifurcation studies.

Supplemental Table 4. Indication to bifurcation lesion revascularization in stable angina or silent ischemia patients.

Supplemental Table 5. FFR/NHPR indications for bifurcation interventions when ischemia was not confirmed.

Supplemental Table 6. Nomenclature for restenosis segments after initial bifurcation PCI, based on MEDINA classification.

Supplemental Table 7. Nomenclature for restenosis segments after initial bifurcation CABG, based on modified MEDINA classification.

Supplemental Table 8. MEDINA-based nomenclature for each diagnostic and treatment stage of bifurcation lesions.

Supplemental Table 9. Functional and anatomical analysis for event adjudication of clinically indicated repeat revascularizations.

Supplemental Table 10. Procedural and technical data to collect.

Supplemental Table 11. Clinical data to collect.

Supplemental Table 12. Different analysis approach description.

Supplemental Table 13. Advantages and limitations of each statistic method for composite endpoints comparison.

Supplemental Table 14. Example of Machine Learning application in bifurcation studies.

Supplemental Figure 1. Bifurcation segment models.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-E-22-00018

DEFINITIONS AND STANDARIZED ENDPOINTS FOR TREATMENT OF CORONARY BIFURCATION:

A consensus document of Bifurcation Academic Research Consortium and European Bifurcation Club

Supplementary files

1. Technical details and instructions to perform dedicated bifurcation QCA

The analysis is initiated by the user defining some reference points of the bifurcation, which enables the software to model the bifurcation contours, which can be corrected, if necessary, by the analyst. The software then uses different anatomical points to define the components of the bifurcation and their measurements. The CAAS bifurcation QCA software, uses the point of bifurcation (POB) and the polygons of confluence (POC) to calculate the diameter in each component of the bifurcation (implementing different algorithms for inside and outside the POC). The QAngio XA software on the other hand uses the carina point on the middle contour as the cornerstone to define four "building blocks" of the bifurcation analysis model (proximal main vessel [PM], bifurcation core, distal main vessel [DM] and side branch [SB]).

Regardless of which software is used, in order to obtain standardized reporting of QCA analyses the operators, appointed core laboratory or site analysts should abide by the following[1]:

1) Two angiographic projections orthogonal to the bifurcation plane should be acquired for optimal visualization of the lesion. These projections should be separated by at least 30° to facilitate dedicated QCA bifurcation analysis. The quantitative analysis should be performed in two views with no vessel overlap, minimal foreshortening and displaying the widest bifurcation angle.
2) A qualitative assessment of the bifurcation lesion, such as calcification, the presence of thrombus etc, should be reported in each of the three segments.
3) Bifurcation angles should be reported pre-intervention, post-intervention and at follow-up. We suggest that the angle between the PMV and the SB be called Angle A (Access). This angle influences the accessibility of the SB, which is frequently the reason for initially stenting it. Angle B (Between) is the angle between the two distal branches (representing one of the risks for SB occlusion during MB stenting), while Angle C is

the angle between the PMV and the DM[2] (**Figure 2**). Importantly, vessel angulation/tortuosity may limit the ability to obtain the projections above.

4) The assessment of the bifurcation lesion dimensions, its severity and extension should be performed using a segmental analysis (**Supplemental Figure 1**), with minimum lumen diameter (MLD), reference vessel diameter (RVD) and percent diameter stenosis (%DS) reported for each coronary segment (PMV, DMV and SB).

   For post-procedural and follow-up analyses, we recommend reporting these three measurements in each component of the six-segment model (BSM6): PMV= segment 2; DMV= segment 3; SB = segment 5; 5 mm segment beyond the treated PMV segment = segment 1; 5 mm segment beyond the treated DMV segment = segment 4; and 5 mm segment beyond the treated SB segment = segment 6. The segments 2, 3, and 5 are divided by the POB.

   Additionally, a 11-segment model (BSM11) analysis could be reported: POC = segment 7; 3 mm ostial segment of the SB = segment 8; and of the DMV= segment 11; the entire main vessel = segment 9 (segments 1+2+3+4); and the entire SB = segment 10 (segments 5+6).

   BSM11 better defines specific bifurcation portions such as the SB ostium, but it requires longer analysis time and given its higher complexity is prone to more analysis-dependent errors.

5) The same segmental analysis used at the time of post-intervention should be used for follow-up analyses. This segmental analysis will provide a detailed analysis of the location of any residual stenosis post intervention and the precise location of treatment failure or restenosis at follow-up.

6) The size of the SB should be defined as the RVD at the ostium of the SB (3 mm segment from the POC contour and before any secondary bifurcation, corresponding to the 3 mm proximal portion of segment 5 in the BSM6 and to segment 8 in the BSM11).
7) The highest %DS and the MLD should be reported as one metric for the entire bifurcation lesion.

To overcome potential limitations associated with 2D QCA of bifurcation lesions (i.e., vessel overlap, tortuosity and foreshortening), the dedicated 3D QCA software packages CAAS QCA 3D system (Pie Medical Imaging, Maastricht, the Netherlands) and QAngio XA 3D (Medis medical imaging systems, Leiden, the Netherlands) have been developed [3,4]. In these packages, a 3D image is reconstructed from two 2D images data sets, and dedicated QCA algorithms for bifurcation lesions are applied to automate calculation [5,6]. The use of 3D QCA analysis improved the predictive ability in determining a positive fractional flow reserve (FFR), compared with analysis using single-vessel QCA[6]. Furthermore, a 3D reconstruction of the bifurcation allows more accurate measurement of the bifurcation angle than 2D QCA, as the bifurcation is a 3D structure, and therefore its maximal opening can only be accurately appreciated in 3D [3], as confirmed by a phantom study [7].

The importance of accurately measuring bifurcation angles comes from previous studies investigating their association with clinical outcomes, although evidence remains contradictory. Colombo et al[8] demonstrated that a large pre-stenting systolic-diastolic distal left main (LM) bifurcation angle (Angle B) range (>7.2°) leads to 5x higher risk of target lesion failure at 3-years. In contrast, in the SYNTAX trial, the pre-procedural diastolic angle did not impact outcome, while a restricted post-procedural systolic-diastolic Angle B range (<10°), suggestive of bifurcation stiffening and altered shear stress, resulted in higher five-year adverse event rates after LM bifurcation PCI[9]. Data on the risk of SB occlusion based on Angle B are

also contradictory, with some studies suggesting an acute Angle B a predictor of SB impairment [10], whilst others demonstrate the opposite[11].

2. SB prognostic relevance according to the SNuH score

The SNuH score incorporates the size, number and distribution of SBs [12]. The total score is calculated as the sum of each factor (0 absent or 1 present), and ranges from 0 to 3, with a SNuH score ≥2 a predictor of ST-segment elevation during a 1 minute balloon occlusion of the diagonal [12]. Notably, recent evidence demonstrates that only a minority of diagonal branches sub-tend >10% of myocardium at risk, with specific anatomical characteristics an RVD>2.5 mm, and a single or dominant diagonal branch in conjunction with a non-dominant left circumflex artery [13,14].

3. Image-based functional assessment of bifurcation lesions.

Image-based functional assessment is based on computation of standard acquired coronary angiograms, with different algorithms used by the currently available software packages from vFFR (Pie Medical Imaging), FFR_{angio} (CathWorks), QFR (quantitative flow ratio, Medis Medical Imaging Systems), and caFFR (Rainmed Ltd).

For analytical purposes, baseline angiography for angiography-based FFR assessment requires the following acquisition criteria:

- 2 angiographic views showing the minimum DV-SB overlap, separated by a minimum angle of 25° in the position of the X-Ray gantry, which has to rotate orthogonally around the axis of the vessel.
- Nitro-glycerine administration before the acquisition.
- Minimum acquisition frame rate of 15 images/sec.

At the end of the revascularization procedure, acquisition of 2 angiographic views is usually recommended to enable calculation of a post-procedural angiography-based FFR.

New angio-based technologies are in development, aiming to derive functional assessment from a single projection through use of bifurcation fractal laws that permit vessel modelling from a single view[15], thus eliminating the needs of orthogonal views, and increasing the feasibility of routine use of computational FFR, and potentially increasing the utility to assess other aspects of bifurcation lesions. Similarly, CT-derived FFR has also been developed in recent years, avoiding the need for invasive catheterization altogether [16], and whenever this is available, Bif-ARC suggests its use prior to invasive procedures with experimental purposes. The same threshold as for hyperaemic invasive assessment, 0.80, has been validated for a functionally significant lesion during image-based FFR.

These tools potentially allow the individual hemodynamic effect of each lesion to be measured, Δ-FFR [17,18], thereby detecting which part of the bifurcation lesion (MB and/or SB) is functionally significant and therefore requires revascularization. However, similar to FFR, image-based FFR is also influenced by cross-talk.

Large Δ-FFR values have been associated with high-risk plaques and have been found to be predictors of acute events during follow-up, underlining the prognostic importance of such an index.

Recent evidence has reported a high correlation between a post-stenting residual QFR ≤0.89 and a vessel-oriented combined endpoint at 2-year follow up[19]. These findings suggest that any single lesion/segment generating a Δ-FFR ≥0.11 should be treated to minimize future related adverse events.

4. Intravascular imaging in bifurcation lesions

Compared to IVUS, OCT provides superior resolution with clearer delineation of lumen contours, quantification of calcific burden (arc, thickness and longitudinal extent), pre-dilation results, stent positions, wire positions and the SB ostium from both MB and SB pullbacks.

OCT may increase contrast use and in some cases limit aorto-ostial assessment, however this can be mitigated by using expedients of 50:50 contrast:saline flush or guide extension catheters. IVUS allows better characterization of plaque burden and does not require vessel flushing during acquisition[20].

Despite strong evidence in favor of IVUS-guided PCI vs angiography alone, there is still an evidence gap in the real clinical benefit of OCT[21-23]. Dedicated studies, such as ILUMIEN IV[24] (OPtical Coherence Tomography Guided Coronary Stent IMplantation Compared to Angiography: a Multicenter Randomized TriaL in PCI), OCTOBER[25] (European randomized Optical Coherence Tomography Optimized Bifurcation Event Reduction Trial) and DOCTORS-LM (NCT04391413) (Does OCT Optimise Results of Stenting on the Left Main Stem) will elucidate this.

General consideration for appropriate intravascular imaging use:

1) Use a motorized pullback device
2) Imaging run should start > 20 mm distal to the lesion and end at the ostium of the coronary vessel to include the longest vessel segment possible. Using OCT, a survey mode with long high-speed pullback is thus preferable for pre-PCI imaging and saves contrast.
3) Before treatment, in cases where the lesion cannot be crossed with the imaging catheter pre-dilatation is recommended.
4) Co-registration with angiography may facilitate angiography-guided actions and should be recommended by protocol.
5) IVUS and OCT allow assessment of the reference lumen and reference vessel dimensions (as delineated by the external elastic membrane [EEM]) proximal and distal to the lesion, in non-diseased reference sites; IVUS can also assess the vessel dimensions (delineated by the EEM) at the site of the MLD whereas this is not possible

with OCT in lipid laden lesions. EEM describes the interface between media and adventitia. The SB size is defined according to the reference vessel dimensions (i.e., EEM-to-EEM) and should be performed at the SB ostium (segment 8). Measurements based on EEM than lumen avoid discrepancies between minimum and maximum diameters in presence of eccentric plaques. The average of minimum and maximum diameters should be chosen as RefD of the vessel. Of note, also in presence of SB ostial lesions, IVUS allows vessel sizing according to EEM.

6) For the most accurate assessment of this area, imaging pullback should be obtained from both MV and SB. If safety concerns prevent SB pullback, then ostial measurements are estimated from MV pullback alone. In this case, the most straightforward method (recommended in absence of core laboratory analysis) consists of selecting a cross-section where the SB at the carina point is visualized best and measuring the area and diameters in both cross-sectional and longitudinal views. In the core-lab setting, the use of the Cut-plane technology is recommended for ostial SB evaluation.

7) Unlike IVUS, OCT can penetrate calcium allowing a better quantification. A combined three-dimensional assessment of calcific burden in a given lesion (longitudinal extent, angle and depth) provides prediction of stent under-expansion[26]. Target lesion OCT calcium assessment should consider the single largest deposit of calcium detectable within the lesion when more than one calcium deposit is present. Individual deposits are separated by at least 1 mm of non-calcified plaque and must have an angle ≥30°, with the largest deposit defined as the one with largest maximum calcium angle. Its maximum angle, thickness and length are representative of the lesion. When calcium is extremely thick and borders are not clear due to attenuation, the maximum visible thickness is reported. Calcium length is the total number of calcium-containing slices

multiplied by the frame interval[26]. A derived OCT-calcium score (+2 points if angle >180°, +1 point if thickness >0.5 mm, +1 point if length >5mm) of 4 predicts stent under-expansion. Evidence of calcium fractures following lesion preparation is associated with improved stent expansion and hence a pullback after plaque preparation may be mandated for applicable hypotheses. Criteria for lesion preparation should be outlined in the protocol. E.g. further intervention in cases of large (>180°) calcium pools and the absence of calcium fractures following initial lesion preparation.

Calcium evaluation is also relevant to define lesion complexity, with a calcium angle >60° in the culprit lesion, and the presence of calcium deposits within the SB lesion defining a complex bifurcation lesion.

4.1 Criteria for pre-procedural, post-procedural and follow-up assessment [27-29].

Pre procedural assessment

When used, intravascular imaging should guide the classification and characterization of the bifurcation lesion. Accordingly, the following measurement should be reported:

1) MEDINA class: the lesion significance at each segment of the bifurcation is defined according to the MLA (<6.0 mm^2 for LM segments; <4.0 mm^2 in the remaining cases).
2) Lesion length at the MV and SB.
3) Reference vessel and lumen dimension (area and minimum, maximum diameters) at each bifurcation segment (PMV, bifurcation core segment, DMV, SB) and at the site of MLD. The bifurcation core segment is defined as the segment where the SB branches from the MV (evaluated by longitudinal view) in the recording with the longest branch segment, and is defined to be at least 2 mm long from the carina point. When the SB RefD is > 2 mm, the bifurcation core segment length will be equal to the SB RefD.
4) Maximum calcium length, angle and thickness within the lesion.

Post procedural assessment

Both techniques can be used in this context, but OCT has proven to be superior in the detection of malapposition, stent edge dissections and thrombus. The post procedural assessment should report:

1) Stent expansion quantification: the minimum stent cross-sectional area (MSA) at the PMV, DMV and SB (when applicable). MSA should be >80% of the vessel reference area at the PMV, DMV and SB respectively. Absolute MSA > 5.5 mm^2 by IVUS and > 4.5 mm^2 by OCT are alternative methods and preferred in small vessels, except for LM bifurcations.

   For LM bifurcation lesions, specific absolute thresholds have previously been proposed. From a study involving Korean patients, Kang et al. have found that a residual post-procedural MSA < 5.0 mm^2 (ostial LCX), 6.3 mm^2 (ostial LAD), 7.2 mm^2 (POC), and 8.2 mm^2 (distal LM) predicted intra-stent restenosis on a segmental basis, associated with 2-year coronary events[30]. Similarly, in the EXCEL IVUS sub-study, the investigators found a LM MSA threshold of 9.9 mm^2 to predict 3-year MACE-free survival[31].

   The discrepancy between these LM MSAs may stem from differences in the body size of the involved population, however, there are no specific details about the reference diameters of the LMs reported in the two studies, making this assumption hard to prove. So far, most of the studies have based the procedural success on the same relative MSA (>80% of the vessel reference area)[22,32,33], but reporting different absolute values (e.g. IDEAL LM study[34]: MSA >8.5 mm^2 (distal LM), MSA >5.5 mm^2 (ostial LAD and LCX); LEMON study[32]: MSA >5.0 mm^2 (ostial LCX), 6.3 mm^2 (ostial LAD), 7.2 mm^2 (POC), and 8.2 mm^2 (distal LM)). Considering this, for LM bifurcation, Bif-ARC recommends measuring the stent expansion using relative MSA values.

2) Presence of malapposition (OCT preferable): Axial distance between stent struts and vessel wall >0.35 mm, associated with a length >1.0 mm. (Given the differences in stent geometry and bifurcation anatomy, malapposition is almost always expected in the Bifurcation core segment and the bifurcation carina; however, data on its consequences/treatment are lacking).
3) Presence and length of metallic carina.
4) Presence and length of multiple stent layers, in each bifurcation component (PMV, DMV, SB, bifurcation core).
5) Presence of stent edge dissection: > 60° of lateral expansion and > 2 mm in length; site (proximal and/or distal).
6) Presence of tissue protrusion (OCT preferable): tissue extrusion from inside the stent area in each bifurcation component.

Follow-up assessment

Follow-up assessment by intracoronary imaging may be mandated by the study protocol, however if not, it is strongly recommended to understand the mechanisms of stent failure (stent restenosis or thrombosis), with OCT preferred. The following should be reported:

1) Presence of intra stent restenosis and its identifiable cause (intima hyperplasia, under-expansion, stent fracture, neoatherosclerosis).

   In bifurcation lesions, the bifurcation core segment and ostium of the SB (segments 7 and 8) are particularly prone to in-stent restenosis. We recommend attempting full OCT assessment of the bifurcation in stent failure. In cases where only a MB pullback can be obtained (e.g., severe SB ostial stenosis or obstruction of the SB ostium by stent struts), important information on the SB ostium may be obtained from just the MB pullback and in the SB after predilatation.

Assessment should report lumen dimensions, predominant plaque type, and the portion of scaffolded SB ostium with struts, the presence of stent struts in front of the SB ostium, extent of dual strut layers, stent expansion (MSA) and apposition.

2) Presence of stent thrombosis: compared to IVUS, OCT can more easily identify thrombus, together with its underlining cause. In the presence of red thrombus, however, the ability of OCT to assess the underlying stent/plaque dramatically decreases. Thrombectomy might facilitate OCT evaluation.

   We recommend reporting the presence of potential 5 mechanisms related to the bifurcation treatment: 1) Presence of stent struts at the core bifurcation segment. Permanent metallic struts or bioresorbable struts can present as: a) jailing struts, b) a metal neocarina where struts proximally extend the native bifurcation carina, or c) non-apposed struts where struts have been manipulated and pushed into any other lumen position in the bifurcation core segment. 2) Compromised stented SB. This usually occurs due to under-expansion at the ostium of the SB, or because of an accumulation with different layers of stent struts leading to a delayed healing process leaving struts uncovered making them more prone to thrombus accumulation (e.g. double kissing balloon outside the SB stent due to incorrect rewiring resulting in crushing of the SB stent). 3) Compromise of the non-stented SB, usually due to plaque shift, carina shift or plaque overgrowth (neoatherosclerosis). 4) Problems remote from the core bifurcation segment, but related to the specific character of bifurcation PCI, e.g., problems due to double or triple layers of struts in the PMV or problems due to more extensive manipulation of stents in bifurcation PCI, such as damage to the polymer or mechanical integrity of the stent (e.g. longitudinal stent distortion during left main bifurcation provisional strategy stenting); 5) Problems not related to the bifurcation per se (e.g. edge dissection).

In absence of such complications, mandated intravascular imaging follow up should include the assessment of the following:

1) Absolute and relative values of MSA or minimum lumen area at each bifurcation segment (according to the segmentation model used for QCA).
2) Presence of malapposition at each bifurcation segment.
3) Presence and length of neocarina at the bifurcation carina site.
4) Stent edge dissections.

5. Statistical analysis including repeated events

Win ratio analysis was introduced by Pocock et al in 2012 and is a rank-based method[35]. It gives more importance to the most clinically relevant component of the composite endpoints. Given its nature, it is valuable when the components of the composite endpoint vary in their clinical severity and importance (e.g., composite endpoint of death, stroke, MI, and revascularization). However, this method has several limitations as the subjective ranking of adverse events is debatable and without universal consensus.

Cox-based models for recurrent events have also been developed (Andersen-Gill model, Lin, Wei, Yang and Ying model, Wei-Lin-Weissfeld model, etc). The *Andersen-Gill* model is a modified version of the standard Cox model and has been widely used for the assessment of recurrent events[36,37]. It considers the risk of an event as independent of previous events. Accordingly, the clock is reset after an event and the patient is considered at risk for the new event. The main limitation of Cox-based models for recurrent events lies in the lack of weighting of event severity.

Lastly, the *WCE* analysis, aims at combining the previous methods, in order to weigh each adverse event while including all of them in the analysis[38]. This method enables analysis of composite endpoints with different individual components of varying importance in high-

risk populations for repeat events. It is highly influenced by the assigned weight to the different events, however it requires large sample sizes since it usually reduces statistical power.

6. Machine Learning and patient-specific Computational Simulations of Bifurcation Stenting

The key-concept of machine learning (ML) function is that in contrast to rule-based algorithms, ML algorithms learn rules and patterns from the data, rather than being dictated by pre-programmed rules. This potentially facilitates data pattern discovery, providing insights and possible solutions for cardiology problems, beyond current human capability[39,40]. Bifurcation disease and treatment provide the perfect platform for ML implementation (**Supplemental Table 14**).

While many applications are possible, they should first aim at having a high clinical impact. Hence, ML should be implemented to beat the current standard of care or to create novel models to diagnose and treat (i.e., dedicated algorithm to define the SB relevance of a bifurcation lesion).

Computational simulations of bifurcation stenting have the potential to test a wide spectrum of "what if" scenarios using real patient data and generate important new knowledge applicable to clinical practice[41]. The input of computational stent simulations includes: (i) Patient-specific anatomical information derived from invasive (angiography, IVUS, OCT) or non-invasive imaging (coronary CT), (ii) Imaging-derived plaque stiffness, and (iii) Realistic stent and balloon designs and material properties[42,43]. Then, the simulation process is based on the finite element method. Finally, the output of stent simulations consists of: (i) Morphometric parameters (e.g. stent expansion, SB jailing), and (ii) Biomechanical parameters derived from computational fluid dynamics (e.g. shear stress, oscillatory shear index, relative residence time) and solid mechanics (e.g. von Misses stresses)[43]. Notably, both morphometric and

biomechanical parameters are highly predictive of clinical outcomes[44,45], and this provides the rationale for using computational stent simulations as a clinical, research and educational tool in bifurcation interventions. From the clinical standpoint, patient-specific computational simulations can facilitate pre-procedural planning and clinical decision making in terms of the optimal bifurcation stenting strategy (e.g. lesion preparation, stent technique, stent sizing, stent positioning). Research-wise, computational stent simulations can be used in virtual clinical trials generating important new knowledge, thereby leading to more focused and scientifically impactful actual clinical trials.

Supplemental Table 1. Historical bifurcation lesions treatment techniques.

TREATMENT STRATEGIES	DESCRIPTION	RESULTS
PROVISIONAL STENTING[45]	Provisional strategy (or inverted provisional strategy) - Double wiring (MV + SB) - MV stenting according to distal MB size - P When does jailed SB deserve attention? - SB treatment is indicated if the ostium is pinched or the flow is limited after P. - If SB treatment is required, rewire and dilate the SB and finalize with K and P. - SB stenting is indicated if the SB is occluded, dissected, or has limited flow despite K (T, TAP, Culotte stenting) -	- 1 stent + P/PSP/PK/PKP [46] - 2 stents
DOUBLE STENTING[45]	Elective use of two stents is indicated in very complex lesions with calcified SB and/or ostial disease extending >5 mm from the carina and in bifurcations with a major SB whose access is particularly challenging: - T stenting - TAP stenting - Culotte stenting - DKC stenting	- 2 stents (upfront SB + MV)

DKC: Double-Kissing-Crush; K: Kissing; MV: main vessel; P: POT (proximal optimization technique); S: Side; SB: side branch; TAP: T and protrusion

Supplemental Table 2. Examples of bifurcation lesions dedicated devices investigated so far.

BIFURCATION DEVICES	DESCRIPTION	
DRUG ELUTING DEVICES	Drug eluting balloon (small vessels)	
BIFURCATION DEDICATED DEVICES	Non bifurcated	Bifurcated
	Balloon expandable stents: - Tryton (SB) - Pathfinder (MV) - Twin Reil (MV) - Nile Pax (MV) - Petal (MV) - Antares (MV) - BiOSS LIM C stent (MV) - MultiLink Frontier (MV) Self expandable stents - Capella (SB) - Stentys (MV) - Axxess (MV) - Sideguard (MV)	Balloon expandable stents - Medtronic Y stent
ADDITIONAL DEVICES	Intracoronary lithotripsy for coronary calcification (i.e., Shockwave) Scoring balloons (i.e., AngioSculpt) Cutting balloons (i.e., Wolverine) Rotational atherecthomy (i.e., Rotablator)	

MV: main vessel; SB: side branch

Supplemental Table 3. Historical limitations of heterogeneous definitions in bifurcation studies.

	HETEROGENOUS DEFINITIONS	LIMITATION
BIFURCATION TREATMENT TECHNIQUES	- Planned stenting technique (i.e., provisional vs double stenting) - Actual stenting technique (i.e., 1-stent vs 2-stent)	Outcomes deriving from studies which report the planned strategy only (i.e., provisional vs double-stenting) can not be compared with those deriving from studies reporting only the final implemented stenting technique
DEFINITION OF RELVANT SIDE BRANCHES	- SB-related angina - SB-related ischemia - SB-related mortality - SB reference diameter size	Studies including SBs of different clinical relevance are not comparable.
BIFURCATION ANATOMICAL CLASSIFICATION	- MEDINA classification - Duke - Sanborn - Safian - Lefevre	Lesions with the same distribution of plaque burden are not comparable across studies using different anatomical classification.
QUANTITATIVE ANALYSIS OF BIFURCATION LESIONS	- Visual - Single vessel QCA - Bifurcation dedicated QCA - 3D-QCA - Intravascular assessment - Non-invasive imaging	Potential errors in eligibility assessment derive from different ways to evaluate the severity and distribution of a bifurcation lesion (e.g. visual assessment vs QCA)
FIRST IN HUMAN STUDIES	- New bifurcation-dedicated devices tested in non significant bifurcations (small SBs) - New bifurcation-dedicated devices tested in large bifurcations	First in human investigations in non significant bifurcation branches may result in worse outcome than expected

SB: side branch

Supplemental Table 4. Indication to bifurcation lesion revascularization in stable angina or silent ischemia patients.

	CRITERIA	ADDITIONAL CRITERIA
STABLE ANGINA OR SILENT ISCHEMIA[47]	- Left main disease with stenosis >50% - Proximal LAD stenosis >50%. - Two- or three-vessel disease with stenosis >50% with impaired LV function (LVEF ≤35%) - Single remaining patent coronary artery with stenosis >50% - Hemodynamically significant coronary stenosis in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapy.	With documented ischemia or a hemodynamically relevant lesion defined by FFR ≤0.80 or NHPR ≤0.89**, or >90% stenosis in a major coronary vessel. ** For MV lesion or to evaluate SB lesion in MEDINA 0,0,1 bifurcation lesion
	- Large area of ischemia detected by functional testing* (>10% LV) or abnormal invasive FFR *CMR, stress echocardiography, nuclear imaging	Based on FFR <0.75** indicating a prognostically relevant lesion ** For MV lesion or to evaluate SB lesion in MEDINA 0,0,1 bifurcation lesion

CMR: cardiac magnetic resonance; FFR: fractional flow reserve; LAD: left anterior descending; LV: left ventricle; LVEF: LV ejection fraction; MV: main vessel; NHPR: non-hyperemic pressure ratio; SB: side branch

Supplemental Table 5. FFR/NHPR indications for bifurcation interventions when ischemia was not confirmed

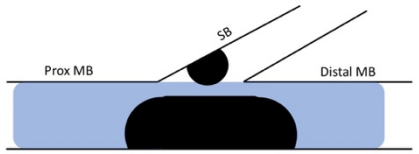
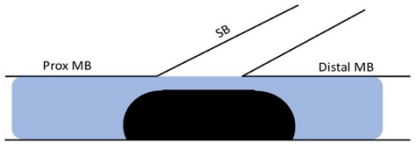
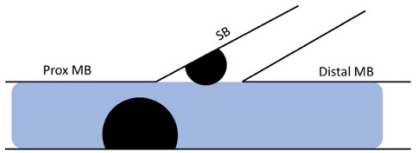
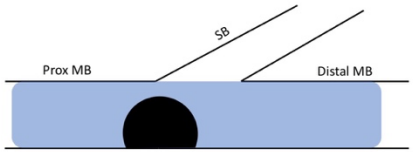
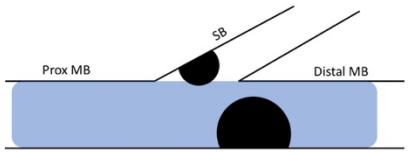
	WHEN FFR IS USEFUL	WHEN FFR IS NOT USEFUL
BEFORE INTERVENTION [48]	- To evaluate MV lesion - To evaluate SB lesion in MEDINA 0,0,1 and 0,1,1	- To evaluate SB lesion in presence of significant MB lesions (1,0,1 or 1,1,1) - Small SB size
DURING INTERVENTION [48]	- After MV stenting to evaluate the functional significance of a jailed SB (through jailed pressure wire)	- When the jailed SB is small, or present diffuse disease, or severely calcified - when residual slow flow
AFTER INTERVENTION [48]	- After MV stenting to evaluate residual ischemia - After SB treatment (balloon or stent) to evaluate residual ischemia	- To predict procedural outcome after complex 2-stent technique

FFR/NHPR INDICATIONS FOR LEFT MAIN BIFURCATION INTERVENTIONS *(adapted from Modi et al.* [49]**)**

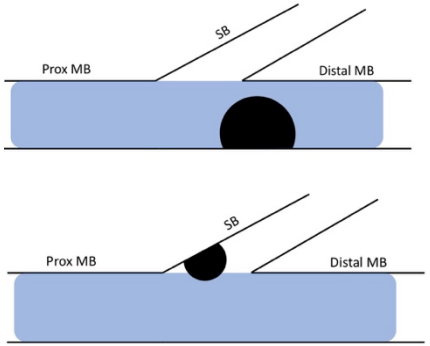
LM BIFURCATION SCENARIOS	FFR/NHPR INDICATIONS
ISOLATED LM STENOSIS (MEDINA 1,0,0) OR ISOLATED BRANCH STENOSIS (MEDINA 0,1,0; 0,0,1)	- Measure FFR/NHPR in either branch for left main stenosis - Measure FFR/NHPR in the diseased branch otherwise
LEFT MAIN STENOSIS + ONE BRANCH STENOSIS (MEDINA 1,1,0; 1,0,1)	- Measure FFR/NHPR by using the disease-free daughter vessel - In specific cases this is not reliable, however, as FFR value may be significantly overestimated (underestimating the LM stenosis functional significance) when the LAD stenosis is proximal and severe (FFR<0.50), due to the "coronary branch steal" effect (increased blood flow in non-stenosed vessel resulting in higher Pd value). In these cases, the use of NHPR with a pressure pullback tracing can be helpful. -
BOTH BRANCHES STENOSIS (MEDINA 1,1,1; 0,1,1)	- Measure FFR/NHPR in both branches - Perform pull-back FFR/NHPR

FFR: fractional flow reserve; LAD: left anterior descending; MV: main vessel; NHPR: non-hyperemic pressure ratio; SB: side branch

Supplemental Table 6. Nomenclature for restenosis segments after initial bifurcation PCI, based on MEDINA classification.

NEW LESIONS LOCATION			MEDINA$_{RESTENOSIS}$	
PM	**DM**	**SB**		
YES	YES	YES	1,1,1	
YES	YES	NO	1,1,0	
YES	NO	YES	1,0,1	
YES	NO	NO	1,0,0	
NO	YES	YES	0,1,1	

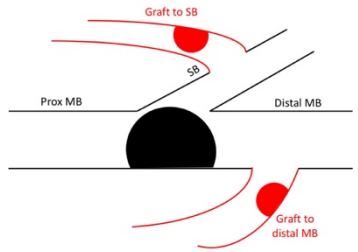
NO	YES	NO	0,1,0
NO	NO	YES	0,0,1

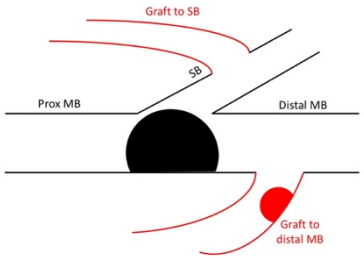


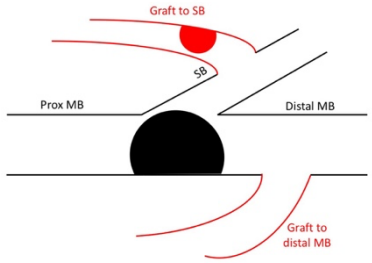
DMV: distal main vessel; PMV: proximal main vessel; SB: side branch.

Supplemental Table 7. Nomenclature for restenosis segments after initial bifurcation CABG, based on modified MEDINA classification.

GRAFT NEW LESIONS LOCATION			$MEDINA_{RESTENOSIS}$
PM	**GRAFT TO DM**	**GRAFT TO SB**	
-	YES	YES	x,1,1
-	YES	NO or not done	x,1,0
-	NO or not done	YES	x,0,1







DMV: distal main vessel; PMV: proximal main vessel; SB: side branch.

Supplemental Table 8. MEDINA-based nomenclature for each diagnostic and treatment stage of bifurcation lesions.
Two case examples are shown: left) a MEDINA 1,1,0 lesion initially treated with PCI in all 3 segments ($MEDINA_{treatment}$ 1,1,1), presenting restenosis of distal MB and SB at follow up ($MEDINA_{restenosis}$ 0,1,1), underwent a repeat revascularization through CABG with 2 grafts (to distal MB and SB, $MEDINA_{revasc\text{-}CABG}$ x,1,1). Right) the same lesion initially treated with single CABG to distal MB ($MEDINA_{treatment}$ x,1,0), presenting restenosis of the graft at follow up ($MEDINA_{restenosis}$ x,1,0), underwent repeat revascularization by means of PCI to the graft ($MEDINA_{revasc\text{-}PCI}$ x,1,0).

	PM	DM	SB	REVASCULARIZATION TYPE	PM	DM	SB	REVASCULARIZATION TYPE
INITIAL (MEDINA)	1	1	0	-	1	1	0	-
REVASCULARIZATION ($MEDINA_{TREATMENT}$)	1	1	1	PCI	x	1	0	CABG
RESTENOSIS ($MEDINA_{RESTENOSIS}$)	0	1	1	-	x	1	0	-
REPEAT REVASCULARIZATION ($MEDINA_{REVASC\text{-}CABG}$ OR $MEDINA_{REVASC\text{-}PCI}$)	x	1	1	CABG	x	1	0	PCI

CABG: coronary artery bypass graft; DMV: distal main vessel; PCI: percutaneous coronary intervention; PMV: proximal main vessel; SB: side branch.

Supplemental Table 9. Functional and anatomical analysis for event adjudication of clinically indicated repeat revascularizations.

HIERARCHICALLY
1. Core laboratory reported FFR ≤0.80 or NHPR ≤0.89[50]
2. Site reported FFR ≤0.80 or NHPR ≤0.89
3. Image based-FFR (e.g.QFR) *(not validated)*
4. Bifurcation-dedicated QCA diameter stenosis >50% (based on the average of multiple views) with either recurrent symptoms or positive non-invasive functional test
5. Bifurcation-dedicated QCA diameter stenosis >70% (based on the average of multiple views) regardless of other criteria

FFR: fractional flow reserve; QCA: quantitative coronary analysis; QFR: quantitative flow ratio.

Supplemental Table 10. Procedural and technical data to collect.

STUDY TYPE	BEFORE PROCEDURE	AFTER PROCEDURE	FOLLOW UP
• **PROCEDURAL STRATEGIES COMPARISON** • **DEVICE COMPARISON** • **FIRST IN MAN STUDIES** • **DIAGNOSTIC ASSESSMENT** • **PHARMACOLOGICAL TREATMENT AFTER PCI**	- Planned strategy according to MADS-2 classification[46] - Syntax Score I, II and 2020 - Visual DS% of bifurcation lesion segments - TIMI flow MV and SB - Bifurcation dedicated-QCA analysis - Invasive functional assessment (FFR/NHPR) in the MV and SB - Non-invasive functional assessment (image-based FFR) in each branch - IVUS/OCT measurements - Access - Planned use of debulking techniques (Rotablation atherectomy, intravascular lithotripsy) - Volume of LM bifurcation PCI/year of the center (LM bifurcations studies)	- Actual strategy used according to MADS-2 classification[46] - Delivery of the intended device - Complete revascularization - Residual anatomical Syntax Score (I) - Visual residual DS% - TIMI flow MV and SB - Bifurcation dedicated-QCA analysis - Residual FFR/NHPR in the MV and SB. - Residual non-invasive functional assessment in each branch. - Dissection (segment, type, treatment) - Perforation (segment, type, treatment) - IVUS/OCT measurements - Use of debulking techniques - Use of inotropic agents - Use of mechanical circulatory support - Procedural, fluoroscopy time - Contrast medium	*Angiographic follow up:* - Visual residual DS% - TIMI flow MV and SB - Bifurcation dedicated-QCA analysis - Invasive functional assessment in the MV and SB - Image-based-FFR in each branch - Residual SYNTAX score
• **REVASCULARIZATION TYPE COMPARISON**	- SYNTAX SCORE I, II and 2020 - Visual DS% of bifurcation lesion segments - TIMI flow MV and SB	*PCI arm:* - Actual strategy used according to MADS-2 classification - Delivery of the intended device - Complete revascularization	*Angiographic follow-up:* - Visual residual DS% - TIMI flow MB and SB - Bifurcation dedicated-QCA analysis

- Bifurcation dedicated-QCA analysis
- Invasive functional assessment (FFR/NHPR) in the MV and SB
- Non-invasive functional assessment (image-based FFR) in each branch
- IVUS/OCT measurements

PCI arm:

- Planned strategy according to MADS-2 classification
- Access
- Planned use of debulking techniques (Rotablation atherectomy, intravascular lithotripsy)
- Volume of LM bifurcation PCI/year of the center (LM bifurcations studies)

CABG arm:

- Planned intervention technique

- Residual anatomical Syntax SCORE
- Visual residual DS%
- TIMI flow MV and SB
- Bifurcation dedicated-QCA analysis
- Residual FFR/NHPR in the MV and SB.
- Residual non-invasive functional assessment in each branch.
- Dissection (segment, type, treatment)
- Perforation (segment, type, treatment)
- IVUS/OCT measurements
- Use of debulking techniques
- Use of inotropic agents
- Use of mechanical circulatory support
- Procedural, fluoroscopy time
- Contrast medium

CABG arm:

- Grafts number
- Grafts type
- Anastomosis type
- Procedural time
- Off pump CABG
- Intermittent cross clamp
- Bypass time
- Ventricular assist device
- IABP use
- Use of inotropic agents
- Complete revascularization

- Invasive functional assessment in the MB and SB
- Image-based/CT-FFR in each branch/graft
- Residual Syntax or CABG Syntax score
- Graft stenosis/occlusion (CABG arm)

		- Residual CABG SYNTAX score	

%DS: percentage diameter stenosis; CABG: coronary artery bypass graft;FFR: fractional flow reserve; IABP: intra-aortic balloon pump;IVUS: intravascular ultrasound; MV: main vessel; NHPR: non-hyperemic pressure ratio;OCT: optical coherence tomography;PCI: percutaneous coronary intervention; QCA: quantitative coronary analysis; SB: side branch; TIMI: thrombolysis in myocardial infarction.

Supplemental Table 11. Clinical data to collect.

STUDY TYPE	BASELINE	IN HOSPITAL	FOLLOW UP
• **PROCEDURAL STRATEGIES COMPARISON** • **DEVICE COMPARISON** • **FIRST IN MAN STUDIES** • **DIAGNOSTIC ASSESSMENT** • **PHARMACOLOGICAL TREATMENT AFTER PCI**	- Baseline demographics and comorbidities - Echocardiography assessment (LVEF) - Other non invasive ischemic test performed (details) - Silent ischemia - Stable angina - Unstable Angina - ACS (NSTEMI, STEMI) - NYHA class - EuroSCORE II - STS score - Complete laboratory tests - Bleeding risk scores - Seattle Angina Questionnaire	- Death - Cardiovascular death - TBR - TB-MI - PMI - TVR - Non-TVR - Any stroke, - BARC 3 or 5 bleeding - Contrast induced AKI - LVEF, pericardial effusion - Angina status - NYHA class - Troponin - CK-MB - Complete laboratory tests - UFH use, dose - ABCiximab use - Aspirin dose - P2Y12 inhibitors dose, type - Anticoagulant use, dose, type - Diuretics, dose, type - Statin, dose, type - Betablockers, dose, type - CCa, dose, type	- Death - Cardiovascular death - TBR - TB-MI - Non TB-MI - TVR - Non TVR - Any stroke, - BARC 3 or 5 bleeding - HF recurrence - Any rehospitalization - LVEF - Angina status - NYHA class - Aspirin dose - P2Y12 inhibitors dose, type - Anticoagulant use, dose, type - Diuretics, dose, type - Statin, dose, type - Betablockers, dose, type - CCa, dose, type - Nitrates, dose, type - ACEi/ARBs, dose, type

		- Nitrates, dose, type - ACEi/ARBs, dose, type - Other anti-angina drugs, dose, type	- Other anti-angina drugs, dose, type - Complete laboratory tests - Seattle Angina Questionnaire
• **REVASCULARIZATION TYPE COMPARISON**	- Baseline demographics and comorbidities - Echocardiography assessment (LVEF) - Other non invasive ischemic test performed (details) - Silent ischemia - Stable angina - Unstable Angina - ACS (NSTEMI, STEMI) - EuroSCORE II - STS score - Heart Team discussions - Complete laboratory tests - Bleeding risk scores - Seattle Angina Questionnaire	- Death - Cardiovascular death, - TBR - TB-MI - PMI - TVR - Non-TVR - Any stroke, - BARC 3, 4 or 5 bleeding - Contrast induced AKI - Arrhythmias - Hospital stay length - CCU stay length - RBCs transfusions - Infections - LVEF, valves, pericardial effusion - NYHA class - Angina status - Troponin - CKMB - Complete lab tests - UFH use, dose - ABCiximab use - Aspirin dose - P2Y12 inhibitors dose, type - Anticoagulant use, dose, type - Diuretics, dose, type - Statin, dose, type	- Death - Cardiovascular death, - TBR - TB-MI - Non TB-MI - TVR - Non TVR - Any stroke, - Any bleeding - HF recurrence - Any rehospitalization (details) - LVEF, valves, pericardial effusion - NYHA class - Angina status - Ischemic testing - Aspirin dose - P2Y12 inhibitors dose, type - Anticoagulant use, dose, type - Diuretics, dose, type - Statin, dose, type - Betablockers, dose, type - CCa, dose, type - Nitrates, dose, type - ACEi/ARBs, dose, type

		- Betablockers, dose, type - CCa, dose, type - Nitrates, dose, type - ACEi/ARBs, dose, type - Other anti-angina drugs, dose, type	- Other anti-angina drugs, dose, type - Complete laboratory tests - Seattle Angina Questionnaire

ACE: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome: AKI: acute kidney injury; ARB: angiotensin receptor blocker; CCa: calcium channel antagonist;CKMB: creatine kinase MB; HF: heart failure; LVEF: left ventricle ejection fraction; NSTEMI: non ST elevation myocardial infarction; NYHA: new york heart association; PMI: periprocedural myocardial infarction; STEMI: ST elevation myocardial infarction; TB-MI: target bifurcation myocardial infarction; TBR: target bifurcation revascularization; TVR: target vessel revascularization; UFH: unfractioned heparin.

Supplemental Table 12. Different analysis approach description.

METHODS	EXPLANATION
INTENTION-TO-TREAT	Analysis by randomization, ignoring treatment actually received
PER-PROTOCOL	Analysis by randomization, excluding patients/bifurcations that do not follow protocol
AS-TREATED	Analysis by treatment actually received, ignoring randomization (For example, if patient was randomized to group "A" but was actually treated with Group "B", this patient is categorized in Group "B")

Supplemental Table 13. Advantages and limitations of each statistic method for composite endpoints comparison.

	TIME-TO-FIRST-EVENT	WIN RATIO	COX-BASED MODELS FOR RECURRENT EVENTS*	WCE
USES FIRST EVENT	Yes	No	Yes	Yes
USES ALL EVENTS	No	No	Yes	Yes
DEATH AS MOST IMPORTANT	No	Yes	No	Yes
USES TIME TO EVENT	Yes	No	Yes	Yes
DISTRIBUTE WEIGHT	No	No	No	Yes
STATISTICAL EFFICACY	→	→ or ↑	↑	↓
INDICATIONS	Reference method	Individual components of composite endpoints vary a lot in severity	High risk of repeat events	High risk of repeat events and different single events severity.

* Andersen-Gill model, Lin, Wei, Yang and Ying model, Wei-Lin-Weissfeld model, etc. are included.

Supplemental Table 14. Example of Machine Learning application in bifurcation studies.

IMAGE ENHANCEMENT	**ML HAS BEEN APPLIED TO THE CLINICAL PROBLEM OF IMAGE POST-PROCESSING AND DE-NOISING. ITS USE CAN IMPROVE ANGIOGRAPHY IMAGE QUALITY AND THE DETECTION OF BIFURCATION SEGMENT FEATURES, WHICH ARE OTHERWISE INVISIBLE**
EXTRACTION AND REPRESENTATION OF FEATURES	ML can translate different type of data (text, images, etc.) into simpler, more compact and uniform formats, allowing standardization and easier comparisons
IMPROVEMENT OF PREDICTION SCORES AND ALGORITHMS	ML is being used to improve existing risk scores, using available registry data. In the context of bifurcations, the re-analysis of registries or images, can detect specific characteristics, missed by the human eye, or simply not consistently collected, that may better predict the complexity of a bifurcation lesion treatment, or its outcome

Supplemental Tables References

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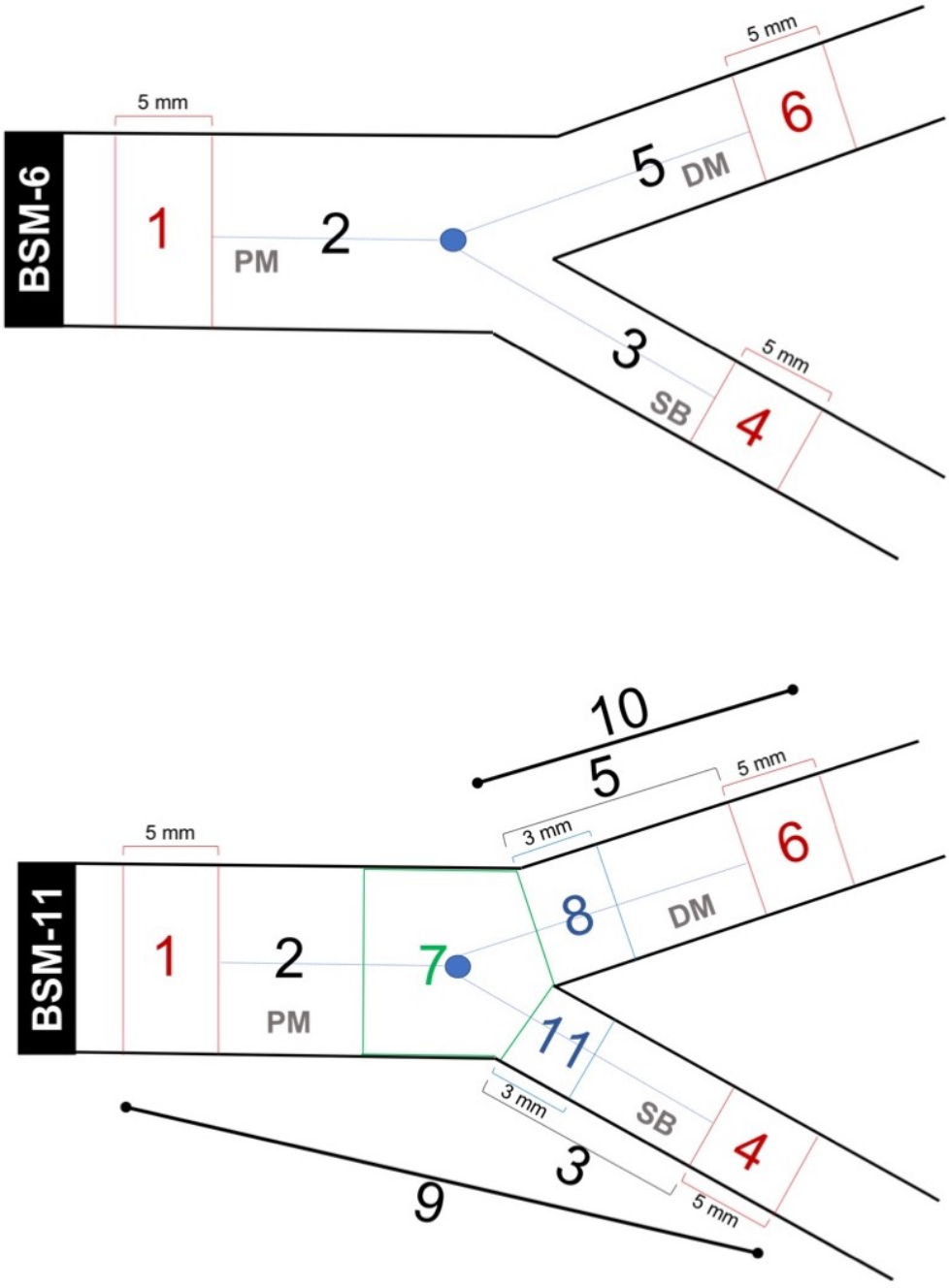

Supplemental Figure 1. **Bifurcation segment models.**
A composite of segments 2, 3, and 5 in the bifurcation six-segment model (BSM6) corresponds to the "treated segment," where the stents were implanted or balloons were dilated, including the proximal main vessel (PMV), distal main vessel (DMV) and side branch (SB). The segments 2, 3, and 5 are divided by the point of bifurcation (POB), defined as the point where all the centre lines meet and the mid-point of the largest circle/sphere that can reach all three contours in bifurcation. Segments 1, 4, and 6 correspond to 5 mm segments beyond the treated segment (TOP). In the 11-segment model (BSM11) the following additional segments are defined: polygon of confluence (POC) = segment 7; 3 mm ostial segment of the SB = segment 8; and of the DMV= segment 11; the entire main vessel = segment 9 (segments 1+2+3+4); and the entire SB = segment 10 (segments 5+6) (BOTTOM).