PERCUTANEOUS CORONARY INTERVENTION
FOR BIFURCATION CORONARY LESIONS.

THE 15th CONSENSUS DOCUMENT FROM THE EUROPEAN BIFURCATION CLUB

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ABSTRACT

The 15th European Bifurcation Club (EBC) meeting was held in Barcelona in October 2019 and it facilitated a renewed consensus on coronary bifurcation lesions (CBL) and unprotected left main (LM) percutaneous interventions.

Bifurcation stenting techniques continue to be refined, developed and tested. It remains evident that the provisional approach with optional side-branch treatment utilising T, T and small protrusion (TAP) or culotte continue to provide flexible options for the majority of CBL patients. Debate persists regarding the optimal treatment of side branches, including assessment of clinical significance and thresholds for bail-out treatment. In more complex CBL, especially when involving the LM, adoption of dedicated 2-stent techniques should be considered. Operators using such techniques have to be fully familiar with their procedural steps and should acknowledge associated limitations and challenges. When using 2-stent techniques, failure to perform a final kissing inflation is regarded as a technical failure, since it may jeopardize clinical outcome.

The development of novel technical tools and drug regimens deserve attention. In particular, intracoronary imaging, bifurcation simulation, drug-eluting balloon technology and tailored anti-platelet therapy are identified as promising tools to enhance clinical outcomes.

In conclusion, an evolution of a broad spectrum of bifurcation PCI components have resulted from studies extending from bench testing to randomised controlled trials. However, further advances are still needed to achieve the ambitious goal of optimizing the clinical outcomes for every patient undergoing PCI on a CBL.
CLASSIFICATIONS
Bifurcation, Left Main, drug-eluting balloon, drug-eluting stent, optical coherence tomography

CONDENSED ABSTRACT
The paper reports the updated consensus statements regarding coronary bifurcation lesions and unprotected left main percutaneous interventions generated from the 15th European Bifurcation Club meeting held in Barcelona in October 2019.

ABBREVIATIONS
CABG: coronary-artery-bypass-graft
CBL: coronary bifurcation lesions
DAPT: dual-antiplatelet-therapy
DEB: Drug-eluting balloon
DK-crush: double-kissing crush
EBC: European Bifurcation Club
IVUS: intravascular ultrasound
LAD: left anterior descending
LCX: ostial left circumflex artery
LM: coronary bifurcation lesions
MV: main vessel
OCT: optical coherence tomography
PCI: percutaneous coronary intervention
POT: proximal optimization technique
SB: side-branch
TAP: T and small protrusion
INTRODUCTION

Since 2004, the European-Bifurcation-Club (EBC) has continuously promoted the improvement and standardization of percutaneous coronary intervention (PCI) for coronary bifurcation lesions (CBL) and coronary bifurcation lesions (LM). The annual meeting constitutes a unique opportunity for comprehensive overview of the available data and incorporates “pro et con” debates (that are followed by electronic voting sessions involving all attendants) to facilitate generation of consensus statements. The 15th EBC meeting was held in Barcelona on 18th-19th October 2019 and all presentations are freely accessible on the EBC website (https://bifurc.eu/). The present document reports the updated EBC consensus. Table 1 summarizes the (established and new as compared with the last documents, 1-3) recommendations.

IMAGING IN BIFURCATIONS: LATEST EFFORTS ARE GOING TO PROVIDE NOVEL INSIGHTS

Intracoronary imaging use represent an important and promising aspect of CBL PCI. EBC released documents on the specific issues related with intravascular ultrasound (IVUS) (4) and optical coherence tomography (OCT) (5) in such context.

Selection of a preferred imaging modality should reflect operator experience and the primary objective of assessment. It is acknowledged that many operators have greater IVUS experience and IVUS is favoured for ostial LM and large-vessels evaluation. However, the superior resolution of OCT provides major advantages for specific steps of bifurcation interventions, including visualisation of the site of guidewire crossing and stent optimisation tools. Finally, the recently released high-definition IVUS is an attractive evolution of IVUS technology that combines high resolution imaging with image depth: its usefulness in bifurcation stenting has still to be established.

Calcium, a key determinant of stent optimisation, is easily recognized by IVUS and OCT. Novel OCT criteria predicting stent under-expansion have been recognized: calcium circumferential (>180°) or longitudinal (>5mm) extension and calcium thickness (>0.5mm) (6). Algorithms to guide the selection of calcium modification tools have started to be developed (7) but deserve clinical validation. Of note, data regarding best management of calcification in the setting of CBL are lacking, so that calcium recognition and lesion preparation should not differ from non-CBL.
Advances in OCT imaging processing now facilitate real-time analysis of stent-vessel interactions and precise location of guidewire crossing through stent side cells into the side-branch (SB). In particular, a recent study documented that the position of “link” struts across SB ostia, a phenomenon that cannot be controlled by the operator during stent implantation, is associated with incomplete stent apposition after kissing (8). After stenting, the assessment of adequate stent expansion and “landing”, together with the recognition of edge dissections may guide further PCI optimization (5).

Two independent trials have been are assessing the impact of OCT guidance in bifurcation PCI. The ongoing OCTOBER is a large randomized trial aimed to assess clinical superiority (two-year major adverse cardiac events) of OCT guided stent implantation compared to standard angiographic guided implantation in bifurcation lesions (9). The OPTIMUM is a proof of concept randomized trial (end-point: malapposed struts) comparing on-line three-dimensional OCT guided PCI to angiography-guided PCI in bifurcation lesions treated by provisional with kissing inflation (10).

**IN-VITRO, EX-VIVO AND COMPUTATIONAL SIMULATIONS**

The last EBC meeting placed special emphasis on bifurcation stenting simulations and the use of advanced technologies, including artificial intelligence, machine and deep learning, and extended reality (virtual, augmented and mixed), to facilitate precision and planning of bifurcation interventions (11,12).

Three types of stent simulations were discussed: *in-vitro (bench)*, *ex-vivo* (Visible Heart® methodologies) and *computational*:

In-vitro simulations represent bench testing of bifurcation stenting using patient-specific silicone-based bifurcation anatomies coupled with experimental flow dynamics and imaging (micro CT) (13) There is potential to explore how flow changes in different coronary anatomies, and to explore how stent designs and deployment techniques may optimize flow.

Ex-vivo simulations represent experimental stenting of porcine or cadaveric human donor hearts (14) in a sophisticated perfusion circuit (Visible Heart® methodologies, [http://www.vhlab.umn.edu/](http://www.vhlab.umn.edu/)) eventually combined with invasive (OCT) or non-invasive (micro CT) imaging.
Computational simulations involve computational (virtual) stenting using patient-specific bifurcation anatomies, and realistic plaque, stent and balloon geometries and material properties coupled with computational fluid dynamics and solid mechanics (15) (example in Figure 1). Computational simulations run in computer clusters and they are feasible, widely applicable, accurate and time- and potentially cost-effective. Accordingly, patient-specific stenting simulations are anticipated to shift the future evolution of coronary bifurcation interventions and to offer valuable tools for education and training.

WHAT DEFINES A COMPLEX BIFURCATION LESIONS?

To date, no unique definition for a “complex” CBL lesion exists within the literature. The historical “Medina” bifurcation classification, endorsed by EBC, allows easy description of the angiographic plaque distribution and is known to influence the occurrence of procedural complications and adverse clinical events (16). Medina 1,1,1 and Medina 0,1,1 have been regarded as complex CBL subsets in some studies. Yet, SB lesion length (17), SB take-off angle and plaque composition (calcification, thrombus) are important modulator on CBL PCI complexity. In keeping with such perspective, the DEFINITION registry (18) generated a multi-parametric system where major criteria, and minor criteria have been combined to categorize simple and complex CBL. This classification has been recently used for patient selection in the DEDICATION II trial (19).

Overall, a series of clinical, anatomic and procedural factors might concur to determine the technical difficulties and complication risk in an individual patient (Figure 2).

MAJOR CONTROVERSIES REGARDING DECISION MAKING IN THE CONTEXT OF A ONE-STENT STRATEGY

Implantation of a MV stent (sized according to the distal MV diameter) across the SB ostium ("crossover” stenting) followed by the proximal optimization technique (POT) is the minimal recommendation for a one-stent strategy in CBL. Of note, bench tests demonstrated that superior results from POT are obtained when the balloon is positioned immediately proximal to the carina (20). Incorrect placement of the POT balloon too proximal or distal is associated with sub-optimal results, as shown in Figure 3. Details regarding the technical aspects of one-stent technique have
been provided elsewhere (21). During the last EBC meeting, the following key issues regarding one-stent strategy were debated.

**What about diseased side-branch pre-dilation?**

When applying a provisional approach to CBL with extensive atherosclerosis involving both MV and SB take-off, the issue of optimal lesion preparation represents a major issue since the SB may occlude after MV stenting. A prospective randomized study on “true” CBL by Pan et al, documented that SB pre-dilation results in improved flow after MB stenting and less need to subsequently treat the SB (22).

The standard practice for CBL dilation in complex lesion is sequential dilation of MV and SB. However, simultaneous dilation (“pre-kissing“ technique) has the potential to avoid bifurcation carina displacement during pre-dilation at the risk of proximal MV overstretch and dissection. Undersized (to limit dissections) balloon pre-kissing technique was recently reported to be associated with lower incidence of SB-associated complications (23) in a small observational study. Yet, these findings are regarded as inconclusive.

**What is best treatment of ostial left anterior descending or circumflex artery lesions?**

The optimal management of ostial left anterior descending (LAD) or ostial left circumflex artery (LCX) lesions (also called Medina 0,1,0 and 0,0,1 LM bifurcations) represents an unresolved issue. Of note, angiography is known to underestimate LM bifurcation atherosclerosis extension (4,5), so that IVUS or OCT confirmation of isolated LAD/LCX stenosis is advisable before ostial stenting is considered.

A recent study compared treatment with one-stent positioned precisely at the LAD ostium with crossover stenting showing the feasibility of ostial stenting (24). Yet, higher restenosis as compared with crossover stenting (24) was documented. Thus, ostial stenting might be considered in order to avoid LM stenting when anatomy is particularly favourable (rectangular angle between LAD-LCX, perfect visualization of SB take-off, un-diseased LM). In all other situations, crossover stenting (covering the involved ostial LAD or ostial LCX and the diseased segment of LM) followed by POT and eventual kissing (according to either provisional or “inverted” provisional, 21) represents a valuable option.

**When to perform side-branch dilation during one-stent strategy for distal left main?**
Whether to perform SB dilation after crossover stenting in an unprotected LM is a daily-practice challenge. According to the “provisional” strategy, SB intervention is recommended anytime the result in the SB is considered sub-optimal. However, defining ‘sub-optimal’ result for the LCX ostium is difficult and not standardized (see Supplementary Table 1 for overview of sub-optimal SB result criteria adopted in recent studies).

Even in the absence of a sub-optimal SB result, the need to clear stent struts from SB ostium, facilitating access to the LCX, continues to be debated. Indeed, “floating” struts across the ostium may support the development of a LCX ostial “multiple-holes” restenosis (Figure 4). Contrary to this concern, a large registry of patients treated with crossover stenting from the LMCA to the LAD, has demonstrated that the cumulative 5-year incidence of target lesion revascularization was not significantly different between the kissing and non-kissing balloon groups (25).

**How and why to perform kissing?**

Over the years, it has clearly emerged that the efficacy of strut clearance from the SB by kissing balloon inflation is dependent on the location of the wire re-cross and that kissing balloon may induce a major oval distortion in the proximal MV. Thus, POT, distal SB rewiring followed by kissing balloon (eventually conducted with short non-compliant balloons) and repeat POT are recommended (21) in order to minimize proximal MV distortion and to restore the ideal bifurcation anatomy (Figure 5). To date, clinical data does not support the use of routine kissing balloon inflation (26). Yet, the results of a recent multi-centre registry on CBL, treated by ultra-thin stents, suggested that kissing inflation performed with short balloon overlap may reduce target lesion revascularizations (38).

**What about POT-Side-POT strategy?**

The sequential application of single balloon dilation in the proximal MV, SB and proximal MV (POT-side-POT) is appealing due to its simplicity and efficacy in bench tests. Of note, recent data documented that this technique is probably less simple than theorized. In particular, SB ballooning induces a distortion in the MV stent deserving appropriate correction and it is able to remove SB stent’s struts only when done after distal re-wiring (similarly to kissing). Furthermore, the position of the final (re)POT balloon (a factor that can be challenging to control in clinical practice) significantly impacts on final SB obstruction (28).
NOVELTIES IN ELECTIVE TWO-STENT STRATEGY

CBL with extensive atherosclerosis involving large and significantly diseased SB may benefit from an elective 2-stent bifurcation technique. Different technical options are available and should be selected according to the specific lesion anatomy and operator's experience. T, T and small protrusion (TAP), culotte and double-kissing (DK) crush, represent the most popular 2-stent techniques and their recommended steps have been previously summarized (21). In all 2-stent techniques, repeated POT manoeuvres (21) before any branch rewiring are pivotal since malapposed stent struts in the proximal MV or around the carina may easily be displaced during devices (balloon/stent) advancement, finally causing metallic struts accumulations. Observational data on patients treated by 2-stent techniques are continuing to report better clinical outcomes with final kissing balloon inflation (27) so that its performance can be regarded as a measure of procedural success.

The culotte technique represents a very “flexible” technique offering the opportunity to liberally select the first treated branch between distal MV and SB. Among possible technical improvements, the minimization of stent overlap in the MV and the addition of a further kissing balloon inflation after first stent implantation are notable. These modifications add technical complexity during the practice, but the resulting “DK-mini-culotte” has the potential for outstanding stent configuration (29).

Regarding the DK-crush technique, a further increase in its popularity is expected after the outstanding results recently reported in the DK-CRUSH V trial (30) and the DEFINITION II trial (19). Yet, the complexity of the technique continues to pose specific challenges, and the different high-volume DK-crush operators are still looking for technique's refinements and this may imply the addition of further steps. Among these, the immediate high-pressure post-dilation of SB stent ("proximal SB optimization") proposed by Lavarra (31) has been recognized by EBC as useful (21). Other operators are suggesting that the selection of ultra-thin strut biodegradable polymer-coated stents may minimize stent overlap thickness and enhance healing after stent crushing (32).

DRUG-ELUTING BALLOON FOR BIFURCATION: WHERE ARE WE?

Drug-eluting balloon (DEB) technology represents devices with known heterogeneity (no class effect) and potential interest in the setting of bifurcation PCI.
In de-novo CBL, DEB use in the SB is an attractive approach. The PEPCAD BIF trial showed that SB lesions without both major dissections and significant early vessel recoil have a very acceptable late lumen loss (33). A meta-analysis including 349 patients compared the SB result using standard balloon vs DEB angioplasty (34). At 9-month, DEB use was associated with lower SB late lumen loss compared with balloon angioplasty but SB binary restenosis was not significantly reduced. Overall, the data are inconclusive, with many unanswered questions including the optimal SB selection, technique (DEB with or without final kissing ballooning or repeat POT) and the actual impact on meaningful clinical end-points.

DEB usage in restenosis has been more extensively tested and clearly provides an advantage of minimising multiple stent layers in patients presenting with CBL restenosis, especially where index PCI involved 2-stent techniques (35).

**CERTAINTIES AND EMERGING DOUBTS ON UNPROTECTED LM PCI EFFICACY**

Within the last year, long-term clinical follow-up results have been published from important landmark studies comparing PCI and coronary surgery (CABG) for patients with unprotected LM.

In the extended 10-year follow-up of mortality within the SYNTAX trial (36), all-cause death was not significantly different between PCI and CABG. Of note, CABG provided a significant survival benefit in patients with three-vessel disease, but not in those with LM disease.

The recently published 5 year results from the EXCEL and NOBLE trials (37,38) have generated vigorous debate regarding contemporary PCI vs CABG in the treatment of LM disease. Repeat revascularization was higher in the PCI arm in both trials. Total mortality differed significantly in EXCEL but not in the NOBLE trial.

A very recent meta-analysis (39) of 5 randomized trials (including NOBLE and EXCEL) on a total of 4612 unprotected LM patients with a weighted mean follow-up duration of 67 months allowed derivation of the data summarized in **Supplementary Table 2**.

These novel data reinforce the need for tailored patient selections and PCI improvements. The role of a multi-disciplinary Heart Team in the treatment decision for stable or stabilised patients with unprotected LM disease is emphasized. The key issues (anatomy assessment, team organization)
that might be critical for successful LM PCI programs were extensively reviewed in the previous EBC consensus documents (2,3).

**DUAL ANTIPLATELET THERAPY IN BIFURCATION LESION PCI PATIENTS**

The ESC guidelines highlight coronary bifurcation as a risk factor for coronary ischemic events, suggesting that a longer duration (≥12 months) of dual-antiplatelet-therapy (DAPT) may be considered (40). This recommendation is mainly based on a meta-analysis (41) comprising 9,577 patients showing that 2-stent bifurcation stenting was the strongest risk factor of adverse events.

In the recent EBC registry (41) including 5,036 patients underwent bifurcation PCI, the risk of adverse events was significantly increased among patients who discontinued DAPT prematurely (<6 months in stable CAD, <12 months in ACS). Also, as compared with 1-stent, 2-stent techniques were associated with significantly increased major adverse events.

Given the trade-off between ischemic and bleeding risks for any DAPT duration, a careful patient risk stratification seems of utmost relevance and an EBC-promoted study group has recently revised available DAPT selection (42).

**CONCLUSIONS**

Devices, techniques and imaging modalities are evolving at an incredible pace and their use in bifurcated lesion and unprotected left main needs to be updated. Bifurcation stenting techniques, intra-coronary imaging, bifurcation simulation, drug-eluting balloon technology and tailored anti-platelet therapy are identified as pivotal to enhance clinical outcomes.
REFERENCES


FIGURE LEGENDS

Figure 1. Example of In-vitro and computational stenting simulations using a patient-specific coronary bifurcation anatomy.

A. In-vitro stenting of a patient-specific coronary artery bifurcation (TAP with a long neocarina denoted by the white arrow); B. Computational simulation of the same stenting technique in the same bifurcation anatomy; C. Virtual fly-through view of the neo-carina; D. Computational fluid dynamics of the stented bifurcation; and E. Von-Mises stress distribution.

Figure 2. Main determinants of bifurcation PCI complexity

Figure 3. Possible consequences of incorrect balloon position during POT.

Figure 4. “Multiple-holes” restenosis after crossover stenting.

A. Pre-PCI angiography. B. Result after stent implantation into the LM-LAD followed by POT; C. 36-month follow-up with short restenosis at LCX ostium; D. three-dimensional OCT assessment showing neointima growth over the stent struts splitting the LCX ostium in three different, small, orifices; E. fractional flow reserve assessment documenting the haemodynamic significance of the multi-hole restenosis. (Case presented at EBC 2019 by Dr Rony Mathew Kadavil).

Figure 5. Efficacy of provisional technique in modifying the stent platform allowing to achieve good result in a patient with complex bifurcation lesion.

A. Pre-PCI angiography. B. Result after LAD stent implantation followed by POT, distal rewiring, kissing balloon inflation with short balloon overlap and re-POT; C and D. Three-dimensional OCT reconstructions of the final result achieved.
TABLE 1. OVERVIEW ON EBC RECOMMENDATIONS

<table>
<thead>
<tr>
<th>TOPIC</th>
<th>PREVIOUSLY ESTABLISHED (AND CONFIRMED) RECOMMENDATIONS</th>
<th>NEW RECOMMENDATIONS</th>
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</table>
| **BIFURCATION LESION DEFINITION**          | - A bifurcation lesion is “a coronary artery narrowing occurring adjacent to, and/or involving, the origin of a significant SB”.  
  - A significant SB is a branch that the operator does not want to lose in the global context of a particular patient. |                                                                                     |
| **BIFURCATION ANATOMY DESCRIPTION**        | - Coronary bifurcation anatomy should be regarded as a complex vessel/function structure where 3 different vessel segments (proximal MV, distal MV and SB) are imbricated  
  - mathematical relationships regulate the size and flow at the level of three bifurcation segments  
  - the flow-divider (also called bifurcation carina) is a very important anatomic-functional structure |                                                                                     |
| **IN VIVO, IN VITRO AND COMPUTATIONAL SIMULATIONS** | - bench tests have pivotal importance in the understanding of devices performance in bifurcated lesions  
  - due to improvement in computational modeling, biomechanical and fluid-dynamic studies have started providing novel insights | - in-vitro (bench testing), ex-vivo (Visible Heart® methodologies) and computational simulations have an increasingly recognized relevance to improve the knowledge in the field of bifurcation interventions and to facilitate education and training on bifurcation techniques.  
  - patient-specific stenting simulations have the potential to optimize procedural planning, develop optimization of stenting techniques, guide device refinement, and provide the foundation for virtual (in-silico) clinical trials in bifurcations. |
| **DEFINING COMPLEXITY IN BIFURCATION PCI**  |                                                                                     | - the complexity of PCI on bifurcation lesion in clinical practice is a multifactorial phenomenon including clinical, angiographic and procedural aspects. |
| **GENERAL APPROACH TO BIFURCATION STENTING**| - PCI on bifurcation stenting should adhere to a KISS (keep it simple and safe) principle  
  - systematically wire both branches  
  - try to limit the number of stents  
  - aim for well apposed and well expanded stents with limited overlaps  
  - stenting technique reporting may be |                                                                                     |
| **ONE-STENT STRATEGY**  
**General issues.**  
Details regarding one-stent strategy reported in a specific techniques consensus paper (21) | - One stent strategy is recommended for the vast majority of bifurcated lesions and is based on a "provisional SB stenting philosophy" (stent implantation in the MV eventually followed by SB intervention and stenting if needed)  
- MV pre-dilation should be liberally performed  
- stent implantation in the MV (selected 1:1 according to the distal MV size) followed by systematic POT (post-dilation of the stent at the level of proximal MV with a balloon diameter sized 1:1 according to the proximal MV) is the recommended way to perform one-stent strategy  
- when SB intervention is required, the following steps are advised:  
  1. pullback rewiring technique to aim at "distal re-wiring"  
  2. kissing balloon inflation using short balloons (and MV balloon sized 1:1 according to the distal MV diameter, consider non-compliant balloons).  
  3. final POT (also called repeat POT or re-POT).  
- when "bail-out" SB stenting is needed, T / TAP and culotte are valuable options  
- in selected anatomic conditions, the provisional 1-stent technique may be practiced according to the "inverted provisional" approach (stent implanted in SB-proximal MV, across distal MV).  
  | - When treating complex bifurcations with tight SB ostial stenosis, SB dilation may be considered before MV stenting.  
- POT efficacy is dependent on correct balloon placement (best position: just proximal to the carina and reaching up to the proximal edge of the MV stent)  
- kissing balloon effect is highly dependent on SB wire re-cross site and balloon selection (distal re-cross and short balloon overlaps are strongly recommended).  
- POT-side-POT may simplify the procedure (no need to advance 2 balloons together) but its efficacy is strongly dependent on perfect position of POT balloon during each step.  
- the definition of optimal SB result has yet to be established |
| **TWO-STENT STRATEGY**  
**General issues.**  
Details regarding two-stent strategy reported in a specific techniques consensus paper (21) | - An intentional (up-front) two-stent approach represents optimal practice in selected patients with complex lesions involving large and diseased SB (especially in LM location)  
- meticulous lesion preparation recommended  
- when there is no concern about SB occlusion/re-access, techniques based on MV stenting first can be used (T, TAP and culotte stenting)  
- when there is major concern regarding SB occlusion/re-access, SB stenting first techniques have to be selected. Among these, best options are Inverted T / TAP, Inverted culotte or DK-crush.  
- final kissing inflation (sequential high pressure inflation followed by simultaneous inflation) mandatory | - the use of a 2-stent technique should be selected according to bifurcation anatomy and the operator’s experience.  
- extensive understanding of the 2-stent technical steps is pivotal since adherence to best practice (sequences of ballooning etc..) impacts the efficacy of all 2-stent techniques.  
- the use of POT (one, two or even three times) is part of an optimal two stent technique.  
- in 2-stent techniques, final kissing might be regarded as a measure of procedure quality since failure in its performance continues to be strongly associated with |
- repeat POT recommended (being careful not to reach neocarina in the case of TAP) adverse late clinical outcome.

**DRUG-ELUTING BALLOON**

- studies exploring DEB efficacy in de-novo bifurcation lesions had major limitations and to date have provided no conclusive evidence.
- DEB in bifurcation restenosis (especially after 2-stent techniques) is feasible and may minimize metal within the bifurcation.

**QUANTITATIVE CORONARY ANALYSIS**

- QCA is an important standard analysis in scientific reporting and for regulatory assessment.
- contemporary 3D QCA systems further provide the optimal projection angle in bifurcations and in some systems form the backbone for co-registration to OCT and IVUS.

**INTRACORONARY IMAGING**

- intracoronary imaging is a valuable tool in PCI on bifurcation lesion and LM since it facilitates technical planning and optimization of the final result.
- selection of a preferred imaging modality should reflect operator experience and the primary objective of assessment.
- IVUS gold standard for LM
- OCT feasible for distal LM lesions
- OCT provides superior evaluation of stent and wire positions
- pullbacks in both MV & SB recommended in 2-stent procedures
- OCT combined with angio co-registration and sophisticated real-time analysis software provides real advantages for a step-wise bifurcation approach, especially 3D reconstruction to facilitate guidewire recrossing towards the SB
- intracoronary imaging should be available in the cath lab and it is recommended that it is used when faced with procedural complications or unexpected technical challenges.

**FRACTIONAL FLOW RESERVE**

- FFR should be used in MV before treatment when ischaemia was not confirmed.
- SB FFR reflects proximal main vessel and SB disease/plaque burden.
- pressurewires should not be routinely jailed in SB
- after MV stenting, FFR in the SB is feasible (but some risk of SB dissection during wiring does exist) and more accurate than angiographic pinching to establish SB ostial lesion severity.

**PCI FOR UNPROTECTED LEFT MAIN**

- Registries, trials and meta-analyses suggest that PCI (performed in experienced centers) represents a valuable option for myocardial revascularization in selected
- LM PCI efficacy and limitations have been highlighted in the recent extended follow-up of randomized trials. Thus, patient-tailored, collegial (heart-team) decisions for
### General issues.
Details regarding in the LM PCI consensus (15)

- PCI results are influenced by LM disease pattern (bifurcation involvement) and overall coronary atherosclerotic burden (other diseased vessels, SYNTAX score)
- non-emergent PCI in patients with LM should be performed by an experienced and appropriately equipped PCI team.
- DES should be selected and post-dilated (POT) in order to reach adequate matching with the individual patient’s anatomy.
- Provisional strategy preferred for majority of patients
- intracoronary imaging and functional assessment may improve the decision-making process in the course of LM PCI
- the use of intracoronary imaging during LM PCI is recommended whenever unexpected difficulties are encountered or the achievement of an optimal result is uncertain.

### ANTIPLATELET THERAPY

General issues.

Details regarding DAPT issues reported in a dedicated review paper (42)

- contemporary studies highlight bifurcation lesions, especially when treated by 2-stent techniques, as risk factors for thrombotic events.
- trials on antiplatelet drug-regimens focused on patients treated by PCI for bifurcation lesions are lacking.

SB: side-branch; MV: main-vessel or main-branch; LM: unprotected left main; POT: proximal optimization technique; DEB: drug-eluting balloon; FFR: fractional flow reserve; QCA: quantitative coronary analysis
**FIGURE 2:**

**DETERMINANTS OF BIFURCATION PCI COMPLEXITY**

- **CLINICAL SETTING & ANATOMIC RELEVANCE OF THE TWO BRANCHES**
  (sizes, length, supplied territory, viability, collaterals etc.)

- **DISEASE EXTENT IN THE TWO BRANCHES & PLAQUE MORPHOLOGY**
  (thrombus, calcium etc.)

- **EASE OF ACCESS TO THE TWO BRANCHES**
  (guidewires, balloons, stents etc.)
FIGURE 3:

POT WITH BALLOON Sized 1:1 ACCORDING TO PROXIMAL MV

- Imperfect balloon position (too distal): Proximal stent malapposition (bottle-neck shape)
- Perfect balloon position (immediately proximal to carina and reaching the proximal stent edge): Carina shift (SB ostium lumen reduction)
- Imperfect balloon position (too proximal): Incomplete expansion at the SB ostium (no favorable deformation of the stent's side cell for eventual rewiring and dilation)

Provisional with crossover stenting (stent size selected according to distal MV)
## SUPPLEMENTARY TABLE 1. DEFINITIONS OF SUB-OPTIMAL SIDE-BRANCH RESULT DURING PROVISIONAL STENTING APPROACH IN RECENT STUDY PROTOCOLS:

<table>
<thead>
<tr>
<th>ASSESSMENT METHODOLOGY</th>
<th>SUB-OPTIMAL SIDE-BRANCH RESULT DEFINITION</th>
<th>REFERENCE (DOI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual angiography</td>
<td>TIMI flow &lt; 3</td>
<td>10.1161/CIRCULATINOHA.106.664920</td>
</tr>
<tr>
<td></td>
<td>TIMI flow &lt;3 or DS&gt; 75%</td>
<td>10.1136/openhrt-2018-000947</td>
</tr>
<tr>
<td></td>
<td>TIMI flow &lt;3 or DS&gt;70% or threatened SB closure, or dissection type &gt;A</td>
<td>10.1161/CIRCULATINOHA.109.888297</td>
</tr>
<tr>
<td></td>
<td>decreased TIMI flow or DS &gt;50%, or dissection type &gt;B</td>
<td>10.1016/j.jacc.2010.10.023</td>
</tr>
<tr>
<td></td>
<td>TIMI&lt; 3 (non-LM bifurcations)</td>
<td>10.1016/j.jcin.2015.1.037</td>
</tr>
<tr>
<td></td>
<td>DS &gt;75% (non-LM bifurcations)</td>
<td>10.1016/j.jcin.2015.1.037</td>
</tr>
<tr>
<td></td>
<td>DS &gt;75% (LM bifurcations)</td>
<td>10.1016/j.jcin.2015.1.037</td>
</tr>
<tr>
<td></td>
<td>DS&gt;50% (LM bifurcations)</td>
<td>10.1016/j.jcin.2015.1.037</td>
</tr>
<tr>
<td></td>
<td>TIMI &lt;3, DS &gt;70%, or dissection type &gt;A</td>
<td>10.1016/j.jcin.2014.1.2.221</td>
</tr>
<tr>
<td></td>
<td>TIMI flow &lt;3 or DS&gt;90% or threatened SB closure, or dissection type &gt;A (LM bifurcations)</td>
<td>10.4244/EIJV1211A8 10.1161/CIRCINTERVENTIONS.115.003643</td>
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<tr>
<td></td>
<td>TIMI flow &lt;3 or DS &gt;75% or dissection type &gt;B</td>
<td>10.1016/j.jacc.2017.09.1066</td>
</tr>
<tr>
<td>3D-quantitative coronary analysis</td>
<td>SB lumen area &lt;50 % of SB reference area</td>
<td>10.1002/ccd.23218</td>
</tr>
<tr>
<td>Fractional flow reserve (FFR)</td>
<td>FFR &lt;0.75</td>
<td>10.1093/eurheartj/ehn045</td>
</tr>
<tr>
<td></td>
<td>FFR &lt;0.80</td>
<td>10.1016/j.jcin.2014.1.2.221 10.1016/j.jcin.2019.02.037</td>
</tr>
<tr>
<td><strong>Instantaneous wave-free ratio (iFR)</strong></td>
<td>iFR ≤ 0.89</td>
<td>10.1016/j.ihj.2018.01.028</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>Optical Coherence Tomography</strong></td>
<td>SB minimal diameter &lt; 50 % of SB reference diameter</td>
<td>10.1016/j.ahj.2018.08.003</td>
</tr>
<tr>
<td><strong>Intracoronary ECG</strong></td>
<td>ST-segment elevation &gt;1 mm</td>
<td>10.4244/EIJ-D-17-00189</td>
</tr>
</tbody>
</table>
SUPPLEMENTARY TABLE 2. ADVERSE EVENTS COMPARISON AT THE LONGEST AVAILABLE FOLLOW-UP IN TRIALS COMPARING PCI AND CABG IN PATIENTS WITH UNPROTECTED LEFT MAIN DISEASE (Data extracted from meta-analysis by Ahmad et al, Eur Heart J 2020, reference #39).

<table>
<thead>
<tr>
<th>END-POINT</th>
<th>PCI vs. CABG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Total Mortality</td>
<td>1.03 (0.82-1.30)</td>
<td>0.779</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>1.03 (0.79-1.34)</td>
<td>0.817</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.74 (0.36-1.50)</td>
<td>0.400</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.22 (0.96-1.56)</td>
<td>0.110</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>1.73 (1.49-2.02)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: confidence intervals