Recent Perspectives on Left Main Bifurcation Interventions

Debabrata Dash¹
Nanavati Superspeciality Hospital, Mumbai, India

¹Corresponding author: Debabrata Dash, Nanavati Superspeciality Hospital, Mumbai, India, Tel: 912266529666; E-mail: dr_dash2003@yahoo.com

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Abstract

For several decades, coronary bypass grafting has been considered as the gold standard treatment of unprotected left main (LM) disease. However, because of large vessel caliber and anatomic accessibility, percutaneous coronary intervention (PCI) for LM has been an attractive option for interventional cardiologists. PCI of LM bifurcation can be technically demanding, but warrants reinforcement of integrated approach combining advanced devices, tailored techniques, and adjunctive pharmacologic agents. The provisional one-stent approach has shown more favorable outcomes compared with two-stent technique, making the former the preferred strategy in most types of LM bifurcation lesions. In complex lesions, two-stent technique may be required and may yield superior results. Selecting the proper strategy using intravascular ultrasound for ostium of the side branch (SB) is critical for reducing the risk for SB occlusion and for improving patient's outcome. Even unnecessary complex interventions can be deferred by measuring fractional flow reserve in angiographic isolated SB. Importantly, final successful procedure is more than the type of stenting technique, emphasizing the greater importance of optimizing the selected technique rather than choice of method. Alongside the evolution of bifurcation techniques, there has been development of several dedicated bifurcation stents which are safe and effective in LM bifurcation PCI both at short and mid-term follow-up.

Keywords: Left main coronary artery; Percutaneous coronary interventions; Bifurcation lesions

Introduction

Significant unprotected LM disease constitutes approximately 5-10% of patients undergoing coronary angiography [1,2]. Randomized clinical trials (RCTs) have demonstrated a higher rate of repeat revascularization after percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG), but a lower incidence of cerebrovascular events; no differences were reported in overall major adverse cardiovascular events (MACEs) [3-8]. Although CABG has been the gold standard therapy for LM disease until recently, significant innovation in stent technology, revascularization techniques and antithrombotic therapies make PCI feasible [9]. Treatment of ostial and mid-shaft have shown excellent outcomes with minimal mortality and long-term complications compared with distal LM bifurcations [6]. Lack of RCTs addressing LM bifurcation has led to uncertainties regarding optimal stenting strategy. Although the provisional one-stent technique has been the default strategy based on non-randomized studies and extrapolations from results of non- LM bifurcation trials, two-stent techniques are selected more frequently for LM bifurcation than non-LM [10]. Issues related to bifurcation PCI are common in practice and strategies to overcome will continue to evolve. This review therefore discusses various stenting techniques to manage LM bifurcation lesions.

Anatomy and Physiology of LM

As the LM supplies approximately two-thirds of the blood to the heart and 100% to the left ventricle, severe LM disease would reduce flow to significant areas of the myocardium, placing the patient at high risk for life-threatening LV dysfunction and arrhythmias. It is a large artery and therefore tends to have a high plaque volume. It also is prone to calcification. Plaque shift and incomplete stent expansion are therefore important technical considerations in stenting of LM [11].

The distal LM, by definition always ends in a bifurcation, or even trifurcation, giving rise to the left anterior descending (LAD) and left circumflex (LCX) arteries, and probably an intermediate artery. Greater elastic tissue content of this artery explains elastic recoil and high restenosis following balloon angioplasty [11,12]. Seventy percent of significant LM lesions involve the bifurcation. Intimal atherosclerosis in this location is accelerated primarily in area of low shear stress along the lateral wall extending distally on the myocardial walls of the LAD and LCX arteries. Involvement of flow divider (carina) is minimal or absent. A long LM (≥10 mm) has more pressure drop and lower shear stress contributing to plaque formation [13]. The current trend to treat distal LM bifurcation by extending the main vessel stent into the proximal LAD is supported by continuous extension of plaque from LM to proximal LAD artery in 90% of cases [14]. The LM typically has a diameter ranging between 4.5-6 mm in a majority of cases while the LAD and LCX have diameters ranging from 3.5-4.5 mm and 3.0-4.5 mm respectively. The take-off angulation of LCX is greater than 90° in more than 70% of the patients. The size discrepancy and take-off angle of LCX have great implications for LM bifurcation stenting [15].

Patient selection

Traditionally patients referred for LM PCI are those who have been turned down for CABG because of excessive surgical risk such as poor LV function, porcelain aorta, advanced age, poor distal targets and the presence of severe co-morbidities. Patients with ostial or mid-shaft disease have improved clinical outcomes compared with patients with LM bifurcation and trifurcation after PCI. Similarly, the extent and complexity of concomitant disease in other coronary arteries portends increased risk. Chronic total occlusion of right coronary artery has
higher risk of adverse outcomes compared to one without. When stratified by score, the 5-year incidence of major adverse cardiac or cerebrovascular events (MACCE) in patients with LM disease was similar between groups with low (<23) and intermediate (23–33) SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) scores, continuing the trend noted at 12 months within the LM disease cohort. Therefore, the SYNTAX score continues to be an important tool in the LM disease evaluation and suggests that patients with low or intermediate scores have similar long-term outcomes with PCI or CABG. In addition, the SYNTAX data demonstrate a significantly lower rate of stroke in the PCI group at 1 year and maintain a trend at 5 years [8,16]. Min et al found that a EuroScore ≥ 6 was an independent predictor of deaths in patients undergoing PCI or CABG for LM disease in MAIN-COMPARE (Revascularization for Unprotected Left main Coronary Artery Stenosis; Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry [17]. Combining the SYNTAX and the EuroSCORE (European system for cardiac operative risk evaluation) into a common risk model (Global Risk Classification) was correlated with a significant improvement in predicting cardiac mortality in patients undergoing LM PCI [18]. Another score, the NERS (New Risk Stratification Score) demonstrated a higher sensitivity and specificity to predict clinical outcome [19]. Similarly, fractional flow reserve (FFR) has been integrated in addition to SYNTAX score. Nam et al. [20], demonstrated ‘Functional SYNTAX Score’ (FSS) to be better predictive accuracy for MACE compared with the traditional SYNTAX score. The author feels that following are the group of patients with unprotected LM disease that are likely to have favourable clinical outcomes with PCI as that of CABG [9].

Ostial and/or mid-shaft LM disease

- Isolated LM disease
- LM disease plus single-vessel disease
- LM bifurcational disease treatable by single stent approach
- Low or intermediate Syntax score (Syntax score<33)

Choosing a LM Bifurcation Treatment

Distal LM lesions are mostly treated as true bifurcation. The exception to this is when one branch is small (usually the LCX), when one branch is chronically occluded or if protected by a patent graft. As LCX supplies large myocardial territory in many patients, the possibility of circulatory collapse after LM-LAD stenting should be kept in mind. Therefore, the presence or absence of significant disease in LCX ostium is considered as an important factor in selecting a stenting strategy. The provisional one-stent approach is preferred for LM bifurcations with insignificant LCX ostial stenosis or a non-dominant left coronary artery (LCA). In contrast, the elective two-stent approach may have to be employed in patients with significant stenosis of the ostium of the LCX with dominant LCA (Table 1) [21,22]. FFR evaluation for the side branch (SB) can be used to make correct choice of the treatment strategy [23]. If the LCX is either occluded, its diameter is less than 2.5 mm, it can be ignored and a stent can be placed between the LM and the LAD [24]. A guidewire kept in a small LCX may help to maintain flow after a single stent is placed across the ostium. For a non-diseased LCX ostium, if the angle of bifurcation is of T shape, it is the operator's choice to place a protective guidewire but it may not be necessary. However, if the bifurcation angle is of Y shape, a protective guidewire is recommended. For a significant and diseased LCX ostium, there are several techniques depending on the bifurcation angle. If it is of T shape, the T-stent, mini-crush, double kiss (DK) crush or T and protrusion (TAP) stent technique is recommended whereas if the angle is of Y shape, the culotte, mini-crush or DK crush technique is recommended, while T stenting is not (Figure 1) [9,11].

As LM bifurcation disease is mostly diffuse and not focal, angiography may be inaccurate in assessing the disease severity of both branch ostia [25]. Thus angiography-guided PCI may lead to SB occlusion for a “true” bifurcation resulting in unnecessary complex intervention that may be preventable. Preprocedural intravascular ultrasound (IVUS) may be quite useful in selecting an appropriate and safe strategy for LM bifurcation PCI as it throws light on disease status of distal LM complex including the LCX ostium (Figure 2). Han et al demonstrated that IVUS reduced the rate of SB occlusion after MB stenting in bifurcation [21]. Moreover IVUS-guided LM PCI has been associated with reduced mortality [26,27]. IVUS-derived minimal lumen >3.7 mm² or plaque burden<56% in the LCX ostium could exclude functional SB compromise (FFR<0.80) after MB stenting in LM bifurcations [28].

Table 1: Recommendation for provisional one-stent or two-stent approach to LM bifurcation PCI.

### Preference for the provisional one-stent approach

<table>
<thead>
<tr>
<th>Situation</th>
<th>Strategy</th>
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<tbody>
<tr>
<td>Small LCX ≤2.5 mm in diameter</td>
<td>One-stent approach</td>
</tr>
<tr>
<td>No or insignificant LCX ostial disease</td>
<td>One-stent approach</td>
</tr>
<tr>
<td>Lesion in ostial LCX extending&lt;6 mm</td>
<td>One-stent approach</td>
</tr>
<tr>
<td>Diminutive LCX, right dominant coronary system</td>
<td>One-stent approach</td>
</tr>
<tr>
<td>Wide angle between LAD and LCX</td>
<td>One-stent approach</td>
</tr>
<tr>
<td>No significant ostial LCX disease by IVUS (MLA&lt;4 mm² and PB&lt;50%)</td>
<td>One-stent approach</td>
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</tbody>
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### Preference for two-stent technique

<table>
<thead>
<tr>
<th>Situation</th>
<th>Strategy</th>
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<tbody>
<tr>
<td>Significant and long (&gt;5 mm) lesion in ostial LCX</td>
<td>Two-stent approach</td>
</tr>
<tr>
<td>Complex lesion in LCX ostium</td>
<td>Two-stent approach</td>
</tr>
<tr>
<td>Large LCX ≥ 2.5 mm in diameter</td>
<td>Two-stent approach</td>
</tr>
<tr>
<td>Diseased left dominant coronary system</td>
<td>Two-stent approach</td>
</tr>
<tr>
<td>Narrow angle between LAD and LCX</td>
<td>Two-stent approach</td>
</tr>
<tr>
<td>Significant LCX ostial disease by IVUS (MLA&lt;4 mm² and PB&gt;50%)</td>
<td>Two-stent approach</td>
</tr>
<tr>
<td>Poor result after provisional stenting</td>
<td>Two-stent approach</td>
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and advanced to the LAD. Final kissing balloon inflation (FKBI) may be performed in significant ostial SB lesions (TIMI flow<3 or FFR<0.8). Predilatation of LCX in most cases probably not needed, but may be considered.

Figure 1: Algorithm for left main (LM) bifurcation percutaneous coronary intervention (PCI)* In general minimal lumen area>4 mm$^2$ or plaque burden<50% of LCX ostium is considered in significant stenosis. †Adequate stent apposition and expansion to avoid restenosis (MSA: 5 mm$^2$ LCX ostium, 6 mm$^2$ for proximal left anterior descending artery, 7 mm$^2$ for polygon of confluence, and 8 mm$^2$ for distal left main) without procedural complications. LM: Left Main; PCI: Percutaneous coronary Intervention; IVUS: Intravascular Ultrasound; LAD: Left Anterior Descending artery; LCX: Left Circumflex artery; MB: Main Branch; SB: Side Branch; TAP: T And Protrusion; DK crush: Double Kiss Crush.

The T and protrusion (TAP) stenting
This modification of T stenting technique can be used in majority of the bifurcation lesions especially when the bifurcation angle is less than 90°. It can provide good reconstruction of distal LM bifurcation with minimal stent overlap [9,11]. The LM-LAD is stented jailing the LCx guidewire. Kissing balloon inflation is performed after rewiring the LCX. After positioning the proximal edge of the LCX stent 1-2 mm inside the LAD stent, the LCX stent is deployed at high pressure with deflated balloon kept in the LAD stent. Then, the LCX balloon is slightly retrieved and aligned to the LAD balloon. Afterwards, a FKBI is performed in order to reconstruct the carina (Figure 3).

The culotte stenting
This technique is suitable for lesions where the angulation between LAD and LCX is <60° and two vessel are of similar diameter. The more angulated branch usually the LM-LCX is stented. The LAD is rewired through the stent struts and dilated. A second stent is advanced through the struts of the first into the LAD. The LM-LAD stent is then deployed. Each limb of the culotte is dilated at high pressure using non-compliant balloon followed by FKBI at medium pressure. In contemporary culotte stenting, POT is recommended after first and second stent deployment, as well as a final POT after kissing balloon inflation. It is advisable to avoid a long overlap of stents in the proximal MB whenever possible (mini-culotte). This technique ensures near-perfect coverage of the carina and the LCX ostium. The main disadvantage of the technique is that rewiring both branches through stent struts can be technically demanding, and time-consuming. Open-cell stents are preferred for this technique.

The classical T stenting
This technique is performed when the angle between the two vessels is close to 90°.
Integrated use of intravascular ultrasound (IVUS) and fractional flow reserve (FFR) in LM bifurcation PCI

After placing the wires in both the LAD and LCX, a stent is deployed in LCX, making sure to cover the ostium with minimal protrusion into the LAD. The LM-LAD lesion is then stented. The LCX is rewired and dilated followed by FKBI [9,11]. This technique is associated with the risk of leaving a small gap between the branches leading to restenosis at the LCX ostium. For this reason, this technique has largely been replaced by the modified T stenting technique.

The modified T stenting

The modified T stenting is performed by simultaneously positioning stents at LCX and LAD with the LCX stent minimally protruding into the LAD, when the angulations between the branches approach 90°. The LCX stent is deployed first, and then after guidewire and balloon removal from this branch, the LAD stent is deployed. The procedure is completed with FKBI [9,11].

The mini-crush stenting

The mini-crush technique is suitable for LM bifurcation when LAD diameter exceeds that of LCX and the angle between them is less than 60°. The immediate patency of both branches is assured making this technique useful in conditions of instability or complex anatomy. This technique provides excellent coverage of the LCX ostium. The mini-crush technique can be used in almost all true bifurcation lesions except in wide angled bifurcations. The main disadvantage is that in order to perform FKBI, there is need to re-cross multiple struts with wire and a balloon [9,11]. The SB stent is positioned in the LCX, followed by advancement of the LAD stent. The LCX stent is pulled back into the LAD about 1-2 mm and is deployed. The deployment of LAD stent crushes the proximal LCX stent against the LM wall. The LCX is rewired through the stent struts of both LAD and crushed LCX stent to perform FKBI.

The double kiss (DK) crush stenting

A stent is placed into the LCX and a balloon placed in LM-LAD. 1-2 mm of the LCX stent is positioned in the LM. The LCX stent is deployed and then the guidewire and balloon from the LCX are removed. The prepositioned balloon in LM-LAD is inflated to crush the protruding segment of the LCX stent against the LM wall.
The balloon is removed and a stent is deployed in the LM-LAD segment. The wire is then recrossed into the LCX and FKBI is applied to finish the procedure (Figure 4). As a result, the DK crush technique consists of five steps: side branch-stenting, balloon-crush, first-kissing, second-crush, and FKBI. This technique results in less stent distortion, improved stent apposition, and facilitate FKBI. It may be superior to classic crushing optimizing acute procedural results and possibly improves clinical outcomes by facilitating FKBI [11,30]. DK-CRUSH II is the only randomized trial to suggest that double stenting may be superior to provisional stenting and associated with a lower rate of restenosis and repeat revascularization [11,31]. DK-CRUSH III study demonstrated that among patients with bifurcation angle ≥ 70°, NERS score ≥ 20, and SYNTAX score ≥ 23, the 1-year MACE rate in the DK group was significantly less compared to the Culotte group [32].

The V and the simultaneous kissing stent (SKS)

The V stenting is performed by placing and deploying two stents together in narrow angled bifurcation [11,33]. Guidewires are placed in both the LAD and LCX and, with or without predilatation, the two stents are placed into LM and the respective branches and deployed by simultaneous inflation (Figure 5). The author is not a proponent of SKS that allows a variable amount of protrusion creating rather long double barrel. V stenting is relatively easy and fast and thus an ideal in emergencies. It is indicated in patients with a short LM free disease and critical disease of both the LAD and LCX ostia [11].

Dedicated bifurcation stents (DBS)

Several DBS have been adopted recently for LM disease [34]. These devices offer common advantages over conventional DES to cover LM bifurcation segment. Their design confirms to natural anatomy of the bifurcation and can facilitate more effective SB ostial scaffolding. Furthermore, DBS provides easier and quicker access to MB and SB thereby lowering the risk of SB closure. Stenting of LM with these devices is safe and effective both at short and mid-term follow up [35-38]. As the anatomy of LM bifurcation varies considerably, further studies are required to define their role in this subset of patients.

Drug-eluting balloon (DEB)

The risk of restenosis is significantly reduced with DEB technology by delivering cytostatic drug to reduce neo-intimal hyperplasia. There is no significant advantage of DEB over DES in bifurcation lesions; thus DEB may be considered in patients not eligible for CABG and with the need for shorter dual antiplatelet therapy (DAPT). There is a case report of kissing DEB successfully treating LM bifurcation DES stent restenosis [39].
**The pot technique**

The absolute difference between the reference vessel diameter of proximal MB and distal MB is relatively large with LM bifurcation. In this regard, the POT technique is useful in this subset of PCI. It is performed by inflating a short bigger balloon just proximal to the origin of the LCX (carina). This technique ensures adequate stent apposition in the LM stem, helps to avoid abluminal rewiring by a second wire, and facilitate rewiring the SB through distal strut which is important for complete SB ostial scaffolding. The stent diameter should be based on distal MB reference diameter to minimize carina shifting [40,41].

**Final kissing balloon inflation (FKBI)**

Theoretical advantages of FKBI after provisional single-stent include restoration of anatomy, expansion of the proximal MB, apposition of jailing struts and balloon treatment of ostial SB lesions. However, routine FKBI may not provide better long-term clinical outcome and may be unnecessary. It may be employed when an angiographically significant (>75% DS or TIMI flow<3) ostial SB remains after MB stenting. Distal recrossing promotes better ostial SB scaffolding and apposition. The optimal inflation sequence is uncertain, but there should be simultaneous deflation of the NC balloons to avoid distorting MB stent. FKBI is mandatory in two-stent technique for carina reconstruction. Final proximal MB high pressure inflation using NC balloon may be considered to reduce malapposition of multiple strut layers and correct proximal distortion. In mini-crush or DK crush technique, it is advisable to avoid distal recrossing and aim for proximal to middle position. In vitro study it has been demonstrated that in culotte technique, proximal SB recrossing as opposed to distal, resulted in a lot more struts unapposed at the ostium, neo stent-strut carina formation, and reduced strut-free ostial area [42].

**Bvs in LM bifurcation**

There are certain limitations of BVS implantation in LM subsets. The manufacturer provides the dilatation limits of BVS to avoid the potential for scaffold disruption. The largest BVS available is 3.5 mm which has dilatation limit of 4.0 mm and too small for many LM bifurcations. Dilatation of struts into SB, in this case the LCX, with >2.5 mm balloon may result in scaffold disruption.
When the LCX is larger than 2.5 mm and needs treatment at the ostium, BVS on the LM may not be ideal. The author feels that a possible compromise is to expand 3.5 mm BVS to 4.0 and avoid malapposition. One should focus on the maximal lumen diameter rather than vessel diameter to avoid incomplete apposition of scaffolds, and reconsider whether BVS is suitable for the LM. The current recommendation is to use provisional stenting in the majority of cases, with sequential noncompliant balloon inflations in the SB and then MB, reserving mini FKBI (snuggle balloon dilatation) only for cases in which it is necessary [43]. POT is recommended with 0.5 mm larger MB, reserving mini FKBI (snuggle balloon dilatation) only for cases in which it is necessary [43]. POT is recommended with 0.5 mm larger NC balloon. If SB is compromised, an undersized NC balloon (≤2.5 mm) is used to open a cell and POT is performed with larger balloon in proximal MB to correct scaffold malapposition (the sequential strategy: POT+SB opening+final POT) [44,45]. A final OCT pullback in the MB should be done to assure adequate strut apposition in the distal and proximal segment. T or TAP stenting with a metal DES in the SB is preferable in case of crossover. Unlike the crush or culotte technique, V-stenting does not deform the BVS struts and is feasible in Medina 0, 1, 1 LM bifurcation [46]. Before a firm recommendation on clinical application can be made, all two-stent techniques would require further evaluation in clinical trials.

Intracoronary image guided optimization

IVUS is considered to be a useful modality in selecting treatment strategy, and helpful in optimally expanding the stent, with or without post-stent balloon dilatation, to avoid under- or overstretch of the stent diameter, and might contribute to better long-term outcomes as compared with conventional angiography guidance [26]. Stent under-expansion is the most important cause of DES failure. A minimal stent area (MSA) less than 5.0-5.5 mm2 is the best predictor of first generation DES restenosis and early thrombosis [47,48]. The optimal IVUS-MSA criteria for in-stent restenosis (ISR) were assessed in 403 patients undergoing DES implantation for LM PCI. The cut-off values for MSA predicting angiographic restenosis on a segmental basis were 5.0 mm2 for LCX ostium, 6.3 mm2 for LAD ostium, 7.2 mm2 for polygon of confluence (POC), and 8.2 mm2 for the proximal LM above POC [49]. Underexpansion was more significantly frequent in the two-stent technique, the LCX ostium being the most common site of under-expansion. A smaller IVUS-MSA predicted angiographic ISR 9 months after DES implantation to treat LM disease, and post PCI under-expansion was an independent predictor of 2 year major adverse cardiac events, especially repeat revascularization [49]. A subgroup analysis from the MAIN-COMPARE registry demonstrates reduced mortality with IVUS as compared to angiography guidance [26] Another recent IVUS study demonstrated that the incidence of the composite of cardiac death, myocardial infarction, and target lesion revascularization and stent thrombosis are lower in IVUS-guided group [27].

Frequency domain OCT offers superior resolution and can identify stent malapposition, edge dissections, tissue protrusion, and thrombus more clearly than IVUS [50]. It has been demonstrated that OCT-guided optimization of LM PCI is feasible and safe [51,52]. As blood must be adequately replaced by the contrast for clear image, assessment of LM ostium or a relatively large LM is problematic. Furthermore, since there is no standardized OCT criteria for stent optimization, this modality may not be useful to guide LM bifurcation PCI. Nevertheless, with accumulating experience and data, it is expected that OCT will be an important adjunctive tool for LM PCI.

Application of FFR

It may be reasonable to defer LMCA PCI in patients with an FFR>0.80. In presence of concomitant lesions in both the LAD and LCx without repairing the downstream lesions, the FFR may underestimate the true significance of the LM lesion [9]. There may be a discrepancy stenting. One study reports that the need for PCI of the ostial LCX after LM-LAD crossover stenting may be reduced, if guided by FFR [53]. Given the nearly identical one-year MACE rates with both approaches in DKCRUSH-VI trial, either the angiography-guided or FFR-guided technique may be recommended for provisional side branch stenting of true bifurcation lesions [54]. However, further studies are needed to evaluate the efficacy of this strategy.
Conclusion

CABG remains the optimal treatment for majority of LM lesions. However, there have been emerging indications and growing trend in favor of PCI in the past few years. This has been supported by current evidences from clinical trials and large off-label experience updating current guideline. LM bifurcational lesions continue to pose considerable challenges and require expertise and performance of unique approaches for optimal results. Future randomized studies such as EXCEL, Evaluation of XIENCE PRIME or XIENCE V Everolimus-Eluting Stent System Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) (NCT01205776) and NOBLE (Nordic-Baltic British Left Main Revascularization) (NCT01496651) are awaited to definitely assess the long-term outcomes of PCI as compared to CABG. The single LM-LAD stent with provisional LCX stenting strategy should be the first-line treatment. Incorporation of FFR-guided PCI strategy may help avoid unnecessary SB interventions. In certain situations or important large LCX lesions, complex two-stent strategy may be necessary. Meticulous evaluation of LM bifurcations with intracoronary imaging is critical in choosing the proper stenting technique and in achieving optimized stent result. There are on-going researches and innovative technologies that would further define role of BVS in LM bifurcation PCI.

References


