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Left main stenting: is it a different animal?

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Abstract

For several decades, coronary-artery bypass grafting (CABG) has been regarded as the treatment of choice for patients with unprotected left main coronary artery (LMCA) disease. However, because of marked advancements in techniques of percutaneous coronary intervention (PCI) with stenting and CABG, as well as adjunctive pharmacologic therapy, a new evaluation and review of current indications for optimal revascularisation therapy for LMCA disease may be required to determine the standard of care for these patients.

The available current evidence suggests that the composite outcome of death, myocardial infarction and stroke is similar in patients with LMCA disease who are treated with PCI with stenting or CABG, the only difference was the rate of repeat revascularisation. Although PCI can be performed successfully in most LMCA lesions, "high-risk" anatomic subsets, especially involving distal LMCA bifurcation lesions, continue to present unique technical challenges to interventional cardiologists, and, therefore, an integrated approach combing advanced devices, tailored techniques, adjunctive support of physiologic and morphologic evaluation, and adjunctive pharmacologic agents should be reinforced to improve clinical outcomes.

Introduction

The standard of revascularisation choice for unprotected left main coronary artery (LMCA) disease is coronary-artery bypass surgery (CABG), this is based on documented efficacy and survival advantages of CABG in reference to medical therapy since the 1970s.[1,2] However, because of anatomically easy accessibility and relatively large vessel calibre of the left main, percutaneous coronary intervention (PCI) for LMCA disease have been an attractive choice for the interventional cardiologist. Marked technical advances in PCI and stent technology have emboldened the physician to test the feasibility of LMCA intervention and, coupled with the widespread availability of drug-eluting stents (DES), has led to a re-evaluation of the role of PCI as a viable alternative treatment for unprotected LMCA disease.[3]

Recent data suggest clinical equipoise between PCI with DES and CABG surgery in LMCA disease including ostial or mid-shaft left main CAD.[3] These benefits notwithstanding, certain lesion subsets, especially distal LMCA bifurcation lesions, present unique challenges to the interventional cardiologist and are still associated with high rates of restenosis, technical difficulty, procedural complications and long-term safety concerns. As PCI procedures evolve for distal LMCA bifurcation lesions, there are many unresolved issues to optimally treat this complex lesion:

1. Are increased rates of repeat revascularisation at bifurcations vs. shaft/ostial lesions due to anatomical or technical factors or both?
2. Should single stent or complex stent techniques be used routinely for bifurcation lesions?
3. When two stents are necessary, which stenting technique should be preferred?
4. Should intravascular ultrasound (IVUS) be routinely used for PCI procedure?
5. How long should dual antiplatelet therapy be given for patients receiving distal LMCA stenting?

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With the above in mind, we reviewed the current evidence supporting PCI with stenting for LMCA disease as compared with standard CABG, and discuss contemporary interventional techniques, approaches, difficulties, as well as adjunctive treatment utilised for PCI of LMCA disease, especially focused on distal LMCA bifurcation lesions.

Current evidence of PCI vs. CABG for LMCA revascularisation

CABG has usually been recommended for left main disease in symptomatic patients. Surgical approaches have a distinct advantage in that they can ignore the anatomic complexity and location of the left main coronary lesion, because bypass grafts are placed distally to the left anterior descending and circumflex coronary arteries and complete revascularisation is easily accomplished. While the benefits of CABG are well known, the CABG procedure results in a large portion of myocardium being potentially supplied solely by the venous graft, with a limited duration of patency. By contrast, PCI of LMCA lesions has been relatively technically feasible due to large calibre and easy accessibility, and successful LMCA stenting would ensure complete arterial revascularisation of the entire coronary arterial vasculature.

To date, a large body of data from observational registries to clinical trials supports the feasibility, efficacy and safety of stenting as compared to CABG for treatment of unprotected LMCA disease. Several observational studies comparing DES and CABG for LMCA disease showed that the early clinical events of LMCA stenting were similar or superior to those of bypass surgery because of a significant increase in periprocedural MI or stroke in CABG patients, and that mortality between 30 days and three years was similar in the PCI and CABG groups.[4-7] However, the risk of TVR was consistently higher with PCI than with CABG. Recent long-term follow-up data from the ASAN-MAIN (ASAN Medical Center-Left MAIN Revascularisation) registry, with complete 10-year follow-up comparison of BMS and concurrent CABG and complete 5-year follow-up comparison of DES and concurrent CABG, demonstrated that stenting showed similar long-term mortality and rates of death, Q-wave MI, or stroke.[8] However, stenting, even with DES, was associated with higher rates of TVR than was CABG.

The evidence from randomised trials comparing CABG and PCI in LMCA disease is limited. Although pure treatment effects among the two primary revascularisation methods can be achieved from randomised clinical trials, the use of a composite endpoint, the small number of patients, and the limited duration of follow-up have biased the study findings. There is also bias concerning entry into the trial, which is a major limitation after the trial is completed and the physician needs to extrapolate the data to clinical practice. The available data comes from small numbers of patients (LEMANS trial) and subgroup analysis (SYNTAX [SYNergy Between PCI With TAXUS and Cardiac Surgery] trial). The LEMANS trial showed a significant benefit of ejection fraction improvement and favourable clinical outcomes after PCI than after CABG.[9] In the LMCA subgroup analysis from the SYNTAX trial,[10] PCI demonstrated the 12 month rate of major adverse cardiac or cerebrovascular events, death, myocardial infarction (MI) or stroke, equivalent to those seen after CABG, but a higher rate of target-vessel revascularisation (TVR) was observed in the DES arm, which was offset by an increase in the rate of stroke in the surgical arm. A *post hoc* analysis of the patients with LMCA disease found that those who also had two- or three-vessel disease had, after PCI, a significantly higher rate of the primary outcome than those with LMCA disease alone or in combination with single-vessel disease (19.8% and 19.3% vs. 7.1% and 7.5%, respectively). These overall findings were consistent up to three years of clinical follow-up.[11]

The American Heart Association/American College of Cardiology PCI guidelines have recently been updated to reflect an increasing off-label experience with stenting and clinical studies (particularly the SYNTAX trial) and led to a revision in treatment guidelines, with PCI now receiving a class IIb indication for the treatment of LMCA stenosis.[12] It is likely that further discussion will ensue as to whether the current knowledge basis for LMCA stenting justifies an IIa rather than an IIb recommendation.

Risk-stratification with clinical and angiographic parameters is clinically important to treat patients with high-risk CAD, such as unprotected LMCA disease. A previous study suggested that the surgical-risk parameter (EuroSCORE and the Parsonnet score)[13] and inflammatory biomarkers, such as C-reactive protein (CRP),[14] have been suggested as useful predictors of adverse outcomes after LMCA stenting. Recently, the insight on the relative impact of lesion complexity on outcomes in patients with LMCA disease being treated with CABG vs. DES has been intensified with using the SYNTAX score.[10] The rates of mortality and composite serious outcomes favoured DES implantation over CABG in patients with a "low-risk" of CAD complexity, as measured by the SYNTAX score. By contrast, the rates of these outcomes favoured CABG over PCI in patients with a "high-risk" of complexity. These results suggest that the SYNTAX score might be an effective tool for stratification of patients with complex LMCA disease into several levels of risk, which can then be used to determine the appropriate revascularisation strategy.

Who is the good candidate for left main stenting in current practice?

The choice of PCI or CABG for treatment of unprotected LMCA disease depends on several clinical and anatomic features, making optimal patient selection crucial for appropriate treatment of LMCA disease and achievement of favourable long-term outcomes. Although confirmative evidence based on large clinical trials is lacking, selected patient populations with unprotected LMCA disease for whom revascularisation with PCI has comparable safety and efficacy outcomes to CABG are listed in Table 1.

Table 1. Selected group of patients with unprotected left main disease who are expected to have favourable clinical outcomes as standard bypass surgery.

Left main patient subsets
– Ostial and/or shaft left main disease
– Isolated left main disease
– Left main disease plus single-vessel disease
– Distal bifurcation left main disease treatable by single stent cross-over approach
– Low-or-intermediate concomitant disease complexity; Syntax score <33

Technical consideration, efficacy and safety concerns of stenting for distal LMCA bifurcation lesions

Lesion characteristics, techniques and efficacy issues

The feasibility and success of PCI with stent implantation for LMCA disease require a careful evaluation of lesion complexity. The probability of procedural success requires a consideration of whether the atherosclerotic coronary plaque involves the ostium and/or shaft of the LMCA, or the length of the left main trunk and whether obstructing plaque involves the distal bifurcation with or without extension into the left anterior descending or circumflex arteries. The distal bifurcation portion is involved in more than half of all patients (60% to 90%) with LMCA disease. Atherosclerotic distal bifurcation lesions are bulky, and PCI is frequently complicated by plaque shifting. Despite improvements in outcomes with the use of DES, clinical or angiographic restenosis remains common and bifurcation lesions have emerged as major predictors of stent thrombosis. A recent, large observation study evaluated the impact of distal bifurcation involvement and the role of one vs. two stents for 1,111 consecutive patients receiving DES for unprotected LMCA disease.[15] Compared with ostial or mid-shaft lesions, distal left main bifurcations were associated with a 50% excess risk of adverse outcomes, which was mainly driven by bifurcation lesions that were treated with complex stenting, as no difference in outcomes was observed between patients with single-stent bifurcation treatment and those with ostial or mid-shaft LMCA lesions. Other, currently available evidence, always suggests that results are less favourable when distal LMCA and non-LMCA bifurcation lesions are treated by a two-stent approach as compared with the single-stent approach.[16-18], with increases in MI, stent thrombosis, and repeat revascularisation. Moreover, the technical difficulties inherent in deploying two vs. one stent can increase procedural time, contrast volume and radiation exposure.

For treating distal LMCA bifurcation lesions, the relative benefits of provisional stenting of bifurcation lesions, in which a single main-vessel stent is deployed and side branch stenting is only used in cases of suboptimal angiographic results, as compared with a complex approach, in which stenting is performed in both the main and side branch, has been a long-standing debate for which there is now a general consensus.[3] A single-stent technique, in which a stent is placed across the side branch (usually the circumflex coronary artery), is preferred in patients with diminutive or normal-appearing side branches.[19] However, if the operators decide on a single stent approach, it is almost always possible to place the second stent on the side branch if stenting crossover does not yield an optimal result. A number of two-stent techniques, with various levels of complexity and indications, can be used to treat distal LMCA bifurcation stenosis. These techniques fall mainly into four broad categories (Figure 1): T-stenting, crush stenting, culotte stenting, and simultaneous kissing stenting (SKS) or Y-stenting. The decision for specific types of complex stenting approaches for distal LMCA lesions is usually performed on the basis of the vessel size, bifurcation angulation and obstructive degree of the major side

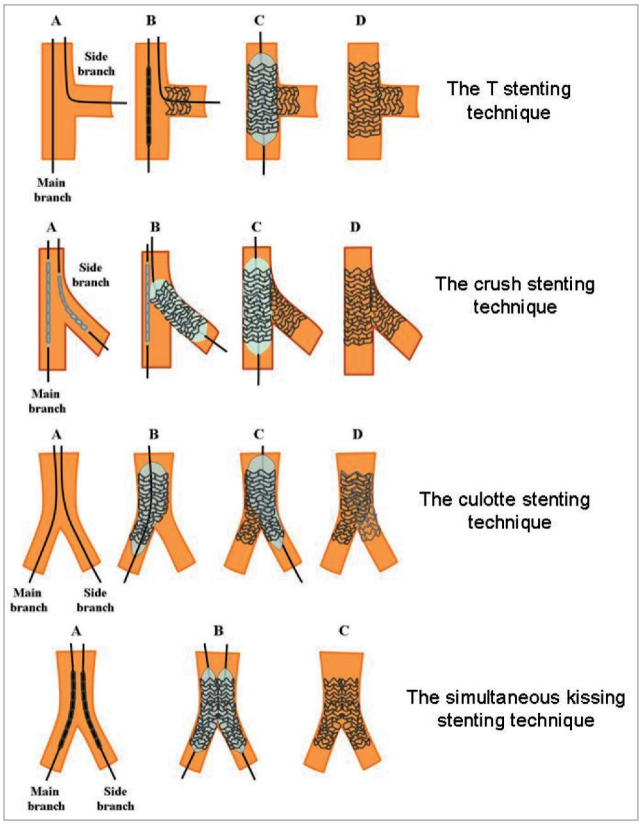
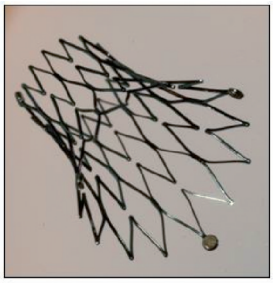


Figure 1. Complex stenting techniques used to treat left main coronary artery stenosis involving distal true bifurcation lesions.

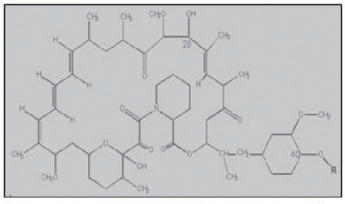
branch. There is little consensus, and few data, on the optimal complex two stent approach. Because restenosis or stent thrombosis can be catastrophic at LMCA locations, all measures for achieving optimal final results should be considered, and intravascular ultrasound (IVUS) assessment is advocated in most cases for stent optimisation. In addition, because of the measurable risk of restenosis and revascularisation after complex stenting, the use of dedicated LMCA bifurcation stents is currently being explored.[20] The Axxess Plus LM system is currently the only available dedicated LMCA device (Figure 2).[21]

An important technical issue in performing PCI with DES for distal LMCA bifurcation lesions is whether there is difference of long-term efficacy and safety among currently available DES. Several observation data and a large randomised trial (the ISAR-LEFT MAIN trial) found that sirolimus-eluting stents and paclitaxel-eluting stents were equally effective and safe in patients undergoing unprotected LMCA stenting, showing comparable risks of death, MI, repeat revascularisation and stent thrombosis.[22-25] There are very limited data regarding the performance of second and third generation DES for unprotected LMCA stenting. Since second generation DES show superior safety and efficacy to first generation DES,[26,27] the relative long-term benefits of new generation DES compared to first generation DES or CABG should be reassessed soon for optimal LMCA revascularisation.

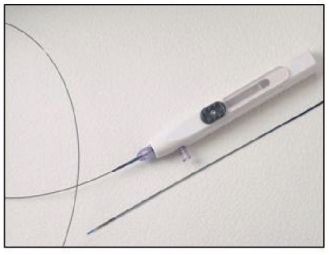
During LMCA stenting, especially PCI for distal LMCA bifurcation lesions, IVUS-assisted PCI might be very helpful to measure the degree



"Stent platform"
Flared (6, 8, 10 or 12 mm flare diameter) distal-end stent design and self-expanding a nickel-titanium alloy in the austenitic phase with a 0.006-inch (0.015 mm) strut thickness



"Coated drug" Biolimus A9, sirolimus analog, suspended within a polylactic acid bioabsobable coating



"4.8 Fr Rx delivery system"

Figure 2. A dedicated distal bifurcation stent system (Axxess Plus LM system; DiVAXX, Irvine, CA, USA).

of stenosis, plaque characteristics, and anatomic configuration (with delineation of major side branches), to select the appropriate diameter and length of the stent as well as the optimal stenting strategy, and to detect postprocedural stent underexpansion, incomplete lesion coverage, residual plaque, and stent in-apposition. A multicentre, observational study suggested that elective DES implantation with IVUS guidance might reduce the long-term mortality rate for unprotected LMCA as compared with conventional angiography guidance alone.[28] At present, more data are needed to test the definite benefit of the routine use of IVUS on the long-term clinical outcomes after PCI with stenting for unprotected LMCA disease.

Safety issues

Recently, concerns have been raised regarding the long-term safety of DES, with particular regard to late stent thrombosis and late mortality.[29-31] Increasing concern over stent thrombosis, which may have more catastrophic consequences most likely resulting in sudden death in patients who received unprotected LMCA stenting, and a lack of long-term clinical data, have hampered the widespread use of PCI with DES as an alternative to CABG. However, recent data alleviate concerns about the safety of PCI with DES for the treatment of unprotected LMCA disease.[6,32-34] Currently, reported rates of stent thrombosis in patients who received DES implantation for unprotected LMCA disease in several large observational studies have been reported to range between 1-2% within 1-3 years. This provides further evidence that LMCA PCI with DES results in lower or, at worst, similar rates of stent thrombosis than rates reported among patients with other coronary lesions in routine clinical practice.

Other important considerations after LMCA stenting include the optimal drug intensity and duration of antiplatelet therapy. Despite the lack of long-term, prospective, large clinical trial data, many clinicians have suggested indefinite use of dual antiplatelet therapy for patients receiving DES implantation for unprotected LMCA disease, owing to the catastrophic consequences associated with stent thrombosis in this location. By contrast, Park et al demonstrated that continuing dual antiplatelet therapy beyond one year in patients who received DES was no more effective in reducing major adverse events than aspirin monotherapy.[35] Other studies suggested use of routine platelet function testing in patients who have received stents for LMCA disease, with a recommendation to increase clopidogrel dose to 150 mg daily if platelet aggregation is >50%.[36] Additional studies with larger populations and longer-term follow-up are warranted to evaluate the antithrombotic benefit vs. major bleeding risk of long-term clopidogrel use, and to determine the optimal duration of clopidogrel therapy after DES placement in patients with LMCA disease.

Conclusion: "left main stenting is clearly a different animal"

Current evidence from clinical trials and large off-label experience indicate that stenting yields mortality and morbidity rates that compare favourably with CABG, updating the current guideline for LMCA revascularisation, which might have prompted many interventional cardiologists to choose PCI with DES as a good treatment option for patients with LMCA disease. Large randomised clinical trials with long-term follow-up, such as the PRECOMBAT (Randomised Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) or the EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation) can provide more confirmative answers. However, despite their success, high-risk lesion subsets – such as distal LMCA bifurcation lesions – continue to present considerable challenges and require unique approaches for optimal results. An integrated approach that combines more advanced devices with specialised techniques, adjunctive physiologic and imaging support, as well as adjunctive pharmacologic agents has greatly improved PCI success rates and long-term clinical outcomes for these complex lesions.

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