Left Main Stenting
– Now and Future –
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For several decades, based on clinical trials comparing coronary-artery bypass grafting (CABG) with medical therapy, bypass surgery has been regarded as the treatment of choice for patients with unprotected left main coronary artery (LMCA) disease. However, because of marked advancements in the techniques of percutaneous coronary intervention (PCI) with stenting and CABG and adjunctive pharmacologic therapy, reevaluation and review of current indications for optimal revascularization therapy for LMCA disease are 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 either PCI with stenting or CABG, the only difference being the rate of repeat revascularization. Cumulative and emerging data from several extensive registries and a large clinical trial may have prompted many interventional cardiologists to select PCI with stenting as an alternative revascularization strategy for such patients. In addition, these data not only may change future guidelines, but support the need for prospective, large randomized trials comparing the 2 revascularization treatments. Finally, this evidence will change the current clinical practice of revascularization strategy for unprotected LMCA disease. (Circ J 2011; 75: 749–755)

Key Words: Bypass surgery; Left main coronary disease; Stents

T he standard revascularization choice for unprotected left main coronary artery (LMCA) disease is coronary-artery bypass grafting (CABG), based on the documented efficacy and survival advantage of CABG in reference to medical therapy since the 1970s.1,2 However, because of the anatomically easy accessibility and relatively large caliber of the LMCA, percutaneous coronary intervention (PCI) for LMCA disease has been attractive to the interventional cardiologist. Technical advances in both 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 reevaluation of the role of PCI as a viable alternative treatment for unprotected LMCA disease.3

However, there are limited data regarding the long-term outcomes of PCI and limited numbers of well-conducted, large randomized trials comparing PCI and CABG for such patients. We therefore reviewed the current evidence and future prospects of PCI with stenting of the LMCA and the alternative role of PCI in reference to standard CABG for patients with LMCA disease.

Outcomes of PCI With Stenting
Over the past years, using PCI with bare metal stents (BMS), LMCA intervention has shown its feasibility and acceptable short- and mid-term outcomes. Due to marked improvement in the efficacy of DES compared to BMS, many experienced interventional cardiologists currently perform PCI with DES for patients with unprotected LMCA disease. Several observational studies, although limited by their non-randomized nature, small number of patients, and short follow-up periods, have shown promising outcomes for PCI using DES compared with BMS.4–7 However, there remains some clinical uncertainty regarding the optimal stent type for use in unprotected LMCA disease. The use of DES in left main (LM) disease has been regarded as an off-label application and adverse events associated with DES has been pronounced, in particular late stent thrombosis. Recently, a well-conducted, large meta-analysis comparing outcomes for DES and BMS after PCI for unprotected LMCA disease was reported.8 A total of 44 studies and 10,342 patients who received a DES or BMS were analyzed. The respective (DES vs. BMS) cumulative event rates at 3 years were 8.8% and 12.7% for death, 4.0% and 3.4% for MI, 8.0% and 16.4% for target vessel revascularization/target lesion revascularization (TVR/TLR), and 21.4% and 31.6% for major adverse cardiovascular events (MACE). Adjusted outcomes at 3 years favored DES (Figure).

Ostial and/or Shaft Disease
The feasibility and success of PCI with stent implantation for LMCA disease require careful evaluation of the lesion’s com-
plexity. The probability of procedural success requires consideration of whether the atherosclerotic coronary plaque involves the ostium and/or shaft of the LMCA, or the length of the LM trunk and whether obstructing plaque involves the distal bifurcation with or without extension into the left anterior descending (LAD) or circumflex artery (LCX). With the marked reduction in restenosis with DES and the large caliber and easy accessibility of most LM arteries, which could attenuate this benefit, ostial/shaft disease might be the attractive target for LMCA intervention. A multicenter observational study demonstrated favorable long-term outcomes with DES; procedural success was achieved in 99% of patients, no case of in-hospital Q-wave MI or death, mean late lumen loss of 0.01 mm and restenosis of 0.9% at angiographic follow-up, and favorable long-term clinical outcomes (3.4% cumulative mortality and 4.7% TVR at median 2.4 years). 

Distal Bifurcation Disease

The distal bifurcation is involved in more than half of all patients (60–90%) with LMCA disease. Several studies suggest that results are less favorable when distal LMCA lesions are treated by a 2-stent approach compared with 1-stent approach. The TLR rate is relatively low (<5%) with a 1-stent approach, even for distal LMCA lesions, and is nearly equivalent to results obtained with DES for ostial or mid-LM lesions. However, patients with distal LMCA lesions treated with 2-stent techniques have shown a TLR rate as high as 25%, with restenosis confined mainly to the LCX ostium. A recent large observation study evaluated the impact of distal bifurcation involvement and the role of 1 vs. 2 stents for 1,111 consecutive patients receiving DES for unprotected LMCA disease. Compared with ostial or midshaft lesions, the distal LM bifurcation was 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 1-stent bifurcation treatment and those with ostial or midshaft LMCA lesions.

Safety of LM Stenting

Concerns have been raised regarding the long-term safety of DES, with particular regard to late stent thrombosis and late mortality. Increasing concern over stent thrombosis, which may have more catastrophic consequences that most likely would result 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. Currently, reported rates of stent thrombosis among several large observational studies in patients who received DES implantation for unprotected LMCA disease range between 1% and 2% within 1–3 years. It 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. In addition, there are very limited data regarding the performance of second- and third-generation DES for unprotected LMCA disease. Since second-generation DES show superior safety and efficacy to first-generation DES, the relative long-term benefits of the new-generation DES compared to first-generation DES or CABG should be reassessed soon for optimal LMCA revascularization.

Technical Aspect of PCI With Stenting

FFR-Guided Decision Making

Recent studies have suggested that fractional flow reserve (FFR)-guided PCI is associated with reduced major adverse cardiac events in patients with multivessel coronary artery disease (CAD). Previous studies have demonstrated that
FFR >0.75–0.80 was a strong predictor of favorable clinical outcomes in patients with intermediate LM disease.\textsuperscript{23–25} Based on an FFR <0.75 vs. ≥0.75, Jasti et al reported that 38-month survival rates were 100% vs. 100% and event-free survival estimates were 100% vs. 90%, respectively (all, P=0.05).\textsuperscript{23} When treatment strategy of equivocal LM stenosis was determined by FFR <0.80 (bypass surgery) vs. ≥0.80 (medical therapy), 5-year survival estimates were similar between surgical and nonsurgical groups (85.4% vs. 89.8%, P=0.48) as were the 5-year event-free survival estimates (74.2% vs. 82.8%, P=0.50).\textsuperscript{26} Thus, FFR measurement is appropriate for identifying patients with intermediate LM stenosis in whom deferral of revascularization is associated with excellent survival and low event rates.

In addition, because angiographic assessment of LM stenosis severity is not accurate, there have been attempts to find intravascular ultrasound (IVUS) measurements that correspond to the functional significance and clinical outcomes and to integrate morphologic, physiologic, and long-term follow-up data. The suggested minimal lumen area (MLA) cut-point has varied from 5.9 to 9.6 mm\(^2\) for identifying significant LM disease, so the optimal cut-off value and its accuracy remains debatable. Therefore, new studies to determine the best IVUS criteria for predicting the physiologic significance of intermediate LM lesions using FFR as the standard are also required.

**IVUS-Guided Optimization**

Because the conventional coronary angiogram is only a lumenogram providing information on lumen diameter but yielding little insight into lesion or plaque characteristics, exact evaluation of LMCA disease is sometimes difficult if there are peculiar anatomic and hemodynamic factors such as large size, a short normal reference segment, overlapping of major vessels, aortic cusp opacification, streaming of contrast agent, and various angulations.

During LMCA stenting, especially PCI for distal LMCA bifurcation lesions, IVUS-assisted PCI might be very helpful for measuring the degree of stenosis, plaque characteristics, and anatomic configuration (with delineation of major side branches) in order to select the appropriate diameter and length of the stent, as well as the optimal stenting strategy, and to detect post-procedural stent underexpansion, incomplete lesion coverage, residual plaque, and stent inapposition. A multicenter 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-alone guidance.\textsuperscript{26}

In addition, there are limited data on the pre- and post-procedural IVUS predictors of adverse events after DES implantation into distal LM bifurcation stenoses. Kang et al\textsuperscript{27} evaluated a total of 168 patients with distal LM bifurcation stenting with DES. Their independent predictors for post-stenting minimal stent area (MSA) within the distal portion of the LM above the LAD carina were pre-procedural lumen area of the LAD carina (β=0.253, 95% confidence interval [CI] 0.10–0.36, P=0.001) and pre-procedural MLA within the polygon of confluence (POC=confluent zone of LAD and LCX) (β=0.205, 95%CI 0.04–0.23, P=0.008). On their multivariable Cox model, female gender (adjusted hazard ratio [HR] 2.56, 95%CI 1.173–5.594, P=0.018) and pre-procedural MLA within the POC (adjusted HR 0.829, 95% CI 0.708–0.971, P=0.020) were the independent predictors for the occurrence of events at 3-year follow-up. Thus, as assessed by simple LAD pullback, the pre-procedural MLA within the POC was a surrogate for the overall severity of LM bifurcation disease, contributing to post-stenting MSA within the distal segment of the LM bifurcation, and was a predictor of long-term clinical outcomes during follow-up.

### Optimal Management of In-Stent Restenosis After LM Stenting

Few data on the clinical course and management of patients experiencing restenosis after DES treatment for unprotected LMCA disease have appeared. FAILS (Failure in Left Main Study)\textsuperscript{28} evaluated 70 patients with post-DES restenosis after LMCA stenting. Among them, 59 (84.3%) were treated with repeated PCI (DES, BMS, or balloon angioplasty only), whereas 7 (10%) patients underwent CABG, and 4 (5.7%) were treated medically. During follow-up of 27 months, the cumulative incidence of long-term MACE (death, MI, TLR) was 50% in the medical group, 25% in the PCI group, and 14% in the CABG group. Lee et al\textsuperscript{29} also evaluated 71 cases of in-stent restenosis (ISR; 17.6%) among 402 patient who received DES implantation for LMCA disease; 57 cases were focal-type and 14 were diffuse-type ISR. Of the patients, 40 (56.3%) underwent repeated PCI, 10 (14.1%) underwent bypass surgery, and 21 (29.6%) were treated medically. During long-term follow-up (median 31.7 months), the incidence of MACE was 14.4% in the medical group, 13.6% in the PCI group, and 10.0% in the bypass surgery group (P=0.91). These data suggested that the long-term clinical prognosis of patients with DES-ISR associated with LMCA stenting was benign, regardless of treatment type, which depended mainly on physician discretion.

### Efficacy and Safety of PCI vs. CABG

CABG has usually been recommended for LM disease in symptomatic patients. Surgical approaches have a distinct advantage, because bypass grafts are placed distally to the LAD and LCX, meaning anatomic complexity and the location of the LM coronary lesion can be ignored, and complete revascularization is easily accomplished. Although the benefits of CABG are well known, the procedure results in a large portion of myocardium being potentially supplied solely by a venous graft with a limited duration of patency. By contrast, PCI of LMCA lesions is relatively technically feasible due to the large vessel caliber and its easy accessibility, and successful LMCA stenting would ensure complete arterial revascularization of the entire coronary arterial vasculature.\textsuperscript{30}

Table 1 summarizes key observational studies, meta-analyses, and randomized trials comparing PCI with DES with CABG.

#### Registry Data

Although several studies have reported on the mid-term safety and feasibility of stenting in LMCA disease, the long-term benefits of PCI compared with bypass surgery are less clear, in part because they have been evaluated less extensively. Several small observational studies have compared PCI with stenting of unprotected LMCA to CABG.\textsuperscript{31–35} The early clinical events of LM stenting are similar or superior to those of bypass surgery because of the significant increase in peri-procedural MI\textsuperscript{31} or cerebrovascular events\textsuperscript{32} in the CABG patients. Longer-term mortality up to approximately 1 year was similar in the PCI and the CABG groups. However, the risk of TVR was consistently higher with PCI than with CABG.
The MAIN-COMPARE registry is a large, multicenter, long-term follow-up study comparing PCI with BMS or DES and CABG for unprotected LMCA disease. This registry included 2,240 patients with unprotected LMCA disease who underwent stenting (BMS 318; DES 784) or CABG (1,138) at 12 major cardiac centers in Korea. First report at 3 years after propensity-matching showed that the risks of death and the composite of death, Q-wave MI, or stroke were similar in the PCI and CABG groups and these results were consistent when either BMS or DES was compared with concurrent CABG. However, the rate of TVR was significantly lower in the CABG group than in the PCI group with hazard ratios varying by the type of stent. DES recipients were almost 6-fold more likely, and BMS recipients almost 10-fold more likely, to require revascularization, compared to those who underwent surgery. Recently, more long-term, 5-year results of the MAIN-COMPARE registry were reported. After adjustment for differences in baseline risk factors with the inverse probability of treatment weighting, the 5-year risk of death (HR: 1.13; 95% CI: 0.88–1.44, P=0.35) and the combined risk of death, Q-wave MI, or stroke (HR: 1.07; 95% CI: 0.84–1.37, P=0.59) were not significantly different for patients undergoing stenting vs. CABG. The risk of TVR was significantly higher in the stenting group than in the CABG group (HR: 5.11; 95% CI: 3.52–7.42, P=0.001).

Randomized Clinical Trial Data

The evidence from randomized trials comparing CABG and PCI in LMCA disease is limited. Although assessment of pure treatment effects among 2 primary revascularization methods can be achieved from randomized clinical trials, the use of composite endpoints, small numbers of patients, and the limited duration of follow-up have biased the studies’ findings. There is also bias to entry into the trial, which is a major limitation after the trial is over and the physician needs to extrapolate the data to clinical practice.

The LeMANS trial was the first randomized comparison of PCI with stenting (52 patients) and CABG (53 patients) for treatment of unprotected LMCA stenosis, with or without multivessel CAD. DES were placed in 35% of PCI patients and left internal mammary artery grafts were used in 72% of CABG patients. At 1 year, the primary endpoint of absolute change in left ventricular ejection fraction was significantly greater in the PCI than in the CABG group (3.3±6.7% vs. 0.5±0.8%; P=0.047), whereas the secondary endpoints, survival and major adverse cardiac or cerebrovascular events (MACCE), were comparable in the 2 groups. However, this first trial is limited by the small number of patients and the nonspecific and inconclusive primary endpoint chosen to evaluate treatment effects.

In subgroup LMCA analysis from the SYNTAX trial, PCI demonstrated 12-month rates of MACCE, death, MI, or stroke, equivalent to those seen after CABG, but a higher rate of 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 2- or 3-vessel disease had, after PCI, a significantly higher rate of the primary outcome than those with LMCA disease alone or in combination with 1-vessel disease (1VD) (19.8% and 19.3% vs. 7.1% and 7.5%, respectively). These overall findings were consistent up to 3 years of clinical follow-up.

Recently, Boudriot et al reported the results of randomized trial comparing sirolimus-eluting stenting (n=100) with CABG (n=101) for patients with unprotected LMCA disease. The primary end point was noninferiority in free of multivessel CAD. DES were placed in 35% of PCI patients and left internal mammary artery grafts were used in 72% of CABG patients. At 12 months, the incidence of the primary end point was 13.9% in the CABG group and 19.0% in the PCI group (P=0.19 for noninferiority). The combined rates for death and MI were similar (7.9% in CABG vs. 5.0% in PCI), but repeat revascularization was significantly higher in the PCI group (14.0% vs. 5.9% of CABG).

Two large randomized trials, the PRECOMBAT (Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Disease) and the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trials, have recently been reported, using DES with everolimus and zotarolimus, respectively. Although both trials have similar methods, PRECOMBAT is set to be the largest randomized trial comparing PCI and CABG for LMCA disease.
Current recommendation
Past recommendation
Whether or not the results achieved with coronary stenting for LMCA disease with follow-up durations of 5–10 years is available on the comparative outcomes after PCI or CABG.
Current guideline for LMCA stenting justifies the IIa indication for the treatment of LMCA stenosis.

**Conclusions: LM Stenting Now and in the Future**

Current evidence from clinical trials and extensive off-label experience indicates that stenting yields mortality and morbidity rates that compare favorably with CABG, updating the current guidelines for LMCA revascularization, and might have prompted many interventional cardiologists to choose PCI with DES as a good treatment option for patients with LMCA disease. Large randomized clinical trials with long-term follow-up, such as the PRECOMBAT and EXCEL trials, can provide more confirmation. An integrated approach that considers the relative efficacy and safety of PCI with DES and CABG for patients with unprotected LMCA disease.

**Meta-Analysis**

A systemic review conducted by Taggart et al suggested that early (in-hospital, to 30 days) and longer-term (1–2 year) mortality rates were better after CABG (early, 2–4%; average 3%; late, 5–6%; average 5%) than PCI with BMS (early, 0–14%; average 6%; late, 3–31%, average 17%) or DES (early, 0–10%, average 2%; late, 0–14%, average 7%).

Takagi et al reported a meta-analysis of 2,181 patients with unprotected LMCA disease who underwent stenting (n=1,006) or CABG (n=1,175) in 6 studies (1 randomized and 5 observational studies). Analytic results demonstrated no significant difference in death rate between stenting and CABG (odds ratio [OR] 0.99, 95%CI 0.69–1.43, P=0.97), but a statistically significant increase in repeated revascularization with stenting (OR 5.05, 95%CI 3.07–8.30, P<0.001), and a statistically nonsignificant benefit of stenting relative to CABG (OR 0.68, 95%CI 0.32–1.46, P=0.32).

Recently, Lee et al also performed a similar meta-analysis (2,905 patients from 8 clinical studies: 2 randomized trials and 6 observational studies) comparing CABG and PCI with DES for unprotected LMCA disease. At 1-year follow-up, there was no significant difference between the CABG and DES groups in the risk for death (OR 1.12, 95%CI 0.80–1.56) or the composite endpoint of death, MI, or stroke (OR 1.25, 95%CI 0.86–1.82). The risk for TVR was significantly lower in the CABG group as compared to the DES group (OR 0.44, 95%CI 0.32–0.59). However, these results of systemic review and meta-analysis should be interpreted with caution and regarded as only exploratory findings, given the limited number of patients, the selection or publication bias in the literature reviewed, and caveats on the internal validity of the included clinical studies.

**Very-Long-Term Clinical Outcomes**

Several reports have shown the successful use of coronary stenting compared with CABG in patients with unprotected LMCA disease. However, there are currently limited data available on the comparative outcomes after PCI or CABG for LMCA disease with follow-up durations of 5–10 years. Whether or not the results achieved with coronary stenting would be stable for 5–10 years remains to be determined in unprotected LMCA disease. The ASAN–MAIN (ASAN Medical Center–Left MAIN Revascularization) registry is the longest follow-up study, reporting 10-year results of BMS and 5-year results of DES as compared to concurrent CABG.

In the 10-year follow-up cohort of BMS and concurrent CABG, the adjusted risks of death (HR 0.81, 95%CI 0.44–1.50; P=0.50) and the composite of death, Q-wave MI, or stroke (HR 0.92; 95%CI 0.55–1.53; P=0.74) were similar between the 2 groups. The rate of TVR was significantly higher in the BMS group (HR 10.34; 95%CI 4.61–23.18; P<0.001). In the 5-year follow-up cohort of DES and concurrent CABG, there was no significant difference in the adjusted risk of death (HR 0.83; 95%CI 0.34–2.07; P=0.70) or the risk of the composite outcome (HR 0.91; 95%CI 0.45–1.83; P=0.79). The rates of TVR were also higher in the DES group than the CABG group (HR 6.22; 95%CI 2.26–17.14; P=0.001).

**Current Changes to ACC/AHA and ESC Guidelines**

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

Recent guideline from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) also reported their indications of PCI relative to CABG for myocardial revascularization of LMCA disease: (1) isolated or 1VD, ostium/shaft; class IIa B, (2) isolated or 1VD, distal bifurcation; class IIb B, LM+2VD or 3VD, SYNTAX score ≤32; class IIb B, LM+2VD or 3VD, SYNTAX score >33; III B.

Coronary Artery Disease) and EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), might provide more confirmatory information regarding the relative efficacy and safety of PCI with DES and CABG for patients with unprotected LMCA disease.

ACC/AHA, American Heart Association/American College of Cardiology; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; CABG, coronary-artery bypass grafting; LM, left main; VD, vessel disease.

### Table 2. Changes to ACC/AHA and ESC Guidelines for PCI for Unprotected LM Coronary Artery Disease

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<th>Guideline</th>
<th>Past recommendation</th>
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<tr>
<td>ACC/AHA Guideline</td>
<td>2005 PCI Guideline → Class III B PCI is not recommended in patients with LM disease and eligibility for CABG (Level of Evidence: C)</td>
<td>2009 PCI Guideline → Class IIb B PCI of the LM coronary artery with stents as an alternative to CABG may be considered in patients with anatomic conditions that are associated with a low risk of PCI procedural complications and clinical conditions that predict an increased risk of adverse surgical outcomes (Level of Evidence: B)</td>
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<tr>
<td>ESC Guideline</td>
<td>2005 PCI Guideline → Class III B Stenting for unprotected LM disease should only be considered in the absence of other revascularization options</td>
<td>2010 PCI Guideline → Class IIa B → III B LM (isolated or 1VD, ostium/shaft): IIa B, LM (isolated or 1VD, distal bifurcation): IIb B, LM+2VD or 3VD, SYNTAX score ≤32: IIb B, LM+2VD or 3VD, SYNTAX score &gt;33: III B</td>
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ESC=European Society of Cardiology; PCI=percutaneous coronary intervention; LM=left main; VD=vessel disease.
combines more advanced devices with specialized techniques, adjunctive physiologic and imaging support, and adjunctive pharmacologic agents has greatly improved PCI success rates and long-term clinical outcomes for these complex lesions.

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Both authors have read the manuscript and agree with the contents.

References


