Percutaneous coronary intervention for unprotected left main coronary artery stenosis

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Abstract

Hemodynamically significant left main coronary artery stenosis (LMCA) is found in around 4% of diagnostic coronary angiograms and is known as unprotected LMCA stenosis if the left coronary artery and left circumflex artery has no previous patent grafts. Previous randomized studies have demonstrated a significant reduction in mortality when revascularization by coronary artery bypass graft (CABG) surgery was undertaken compared with medical treatment. Therefore, current practice guidelines do not recommend percutaneous coronary intervention (PCI) for unprotected LMCA stenosis [3]. However, with the advancement of techniques and equipment, the percutaneous interventional approach for implantation of coronary stents has been shown to be feasible for patients with unprotected LMCA stenosis [3].

Nonetheless, PCI for unprotected LMCA stenosis is still indicated for patients at high surgical risk or with emergent clinical situations, such as bailout procedure or acute myocardial infarction (MI), as an alternative therapy to CABG, because a recent randomized study failed to prove superiority or at least non-inferiority of DES placement for unprotected LMCA stenosis compared with CABG [3,10]. Nonetheless, PCI for unprotected LMCA stenosis is still indicated for patients at high surgical risk or with emergent clinical situations, such as bailout procedure or acute myocardial infarction (MI), as an alternative therapy to CABG, because a recent randomized study failed to prove superiority or at least non-inferiority of DES placement for unprotected LMCA stenosis compared with CABG [3,10].

In contrast, there is a concern about the long-term safety of DES. The incidence of late stent...
thrombosis has been reported to be higher with DES compared with bare-metal stent (BMS) implantation[32-36]. Indeed, the United States Food and Drug Administration has warned that the risk of stent thrombosis may outweigh the benefits of DES in off-label use, such as for unprotected LMCA stenosis[37].

Patients with LMCA stenosis have been traditionally classified into two subgroups: protected (a previous patient CABG surgery graft to one or more major branches of the left coronary artery) and unprotected LMCA diseases (without such bypasses). In this review, we evaluated the current outcomes of PCI with DES in a series of research studies conducted across several countries.

DEFINITION OF SIGNIFICANT LMCA STENOSIS

Coronary angiography has been the standard tool to determine the severity of coronary artery disease. Although the traditional cutoff for significant coronary stenosis has been a diameter stenosis of 70% in non-LMCA lesions, this cutoff in LMCA has been a diameter stenosis of 50%. However, because the conventional coronary angiogram is only a lumenogram providing information about lumen diameter but yielding little insight into lesion and plaque characteristics themselves, it has several limitations due to peculiar anatomic and hemodynamic factors. In addition, the LMCA segment is the least reproducible of any coronary segment with the largest reported intraobserver and interobserver variabilities[38-40]. Therefore, intravascular ultrasound (IVUS) is often used to assess the severity of LMCA stenosis.

A decision of significant stenosis at the LMCA necessitating revascularization should be determined by the absolute luminal area, not by the degree of plaque burden or area stenosis. Because of remodeling, a larger plaque burden can exist in the absence of lumen compromise[41]. Abizaid et al[42] reported a 1-year follow-up in 122 patients with LMCA. The minimal lumen diameter by IVUS was the most important predictor of cardiac events with a 1-year event rate of 14% in patients with a minimal luminal diameter < 3.0 mm. Fassa et al[43] reported that the long-term outcome of patients having LMCA with a minimal lumen area < 7.5 mm² without revascularization was considerably worse than those who were revascularized. Jasti et al[44] compared fractional flow reserve (FFR) and IVUS in patients with an angiographically ambiguous LMCA stenosis. However, accurate assessment of ostial LMCA is not always possible. Practically, it is important to keep the IVUS catheter coaxial with the LMCA and to disengage the guiding catheter from the ostium so that the guiding catheter is not mistaken for a calcific lesion with a lumen dimension equal to the inner lumen of the guiding catheter. When assessing distal LMCA disease, it is important to begin imaging in the most co-axial branch vessel. Nevertheless, distribution of plaque in the distal LMCA is not always uniform; and it may be necessary to image from more than one branch back into the LMCA.

FFR may play an adjunctive role in determining significant stenosis at the LMCA. FFR is the ratio of the maximal blood flow achievable in a stenotic vessel to the normal maximal flow in the same vessel[45]. A FFR value of < 0.75 is considered a reliable indicator of significant stenosis producing inducible ischemia[46]. In patients with an angiographically equivocal LMCA stenosis, a strategy of revascularization is medical therapy based on an FFR cut-point of 0.75 was associated with an excellent survival and freedom from events for up to 3 years of follow-up[46].

OUTCOMES OF DES

Safety in terms of the risk of death, MI or stent thrombosis

Although there are disputes regarding the long-term safety of DES, the possibility of late or very late thrombosis is still the major factor limiting global use of DES, especially for unprotected LMCA stenosis. Table 1 depicts the results of recent studies demonstrating the outcomes of DES implantation for unprotected LMCA stenosis. It is clear that none of the clinical studies showed a significant increase in the cumulative rates of death or MI following DES implantation for unprotected LMCA, as compared with BMS. In three early pilot studies which compared the outcomes of DES with those of BMS, the incidence of death, MI or stent thrombosis were comparable in the two stent types during the procedure and at follow-up[46]. Of interest, in the study by Valgimigli et al[47], DES was associated with a significant reduction in both the rate of MI [hazard ratio (HR) = 0.22, P = 0.006] and the composite of death or MI (HR = 0.26, P = 0.004) compared with BMS. Considering that restenosis can lead to an acute MI in 3.5% to 19.4%, a significant reduction in restenosis achieved by DES might contribute to the better outcome seen with DES. In fact, a previous study suggested that restenosis at the BMS in LMCA could present as late mortality[47]. In addition, more frequent repeat revascularizations to treat BMS restenosis, in which CABG is the standard of care for unprotected LMCA, may also be related to an increase in complications compared with DES. A recent meta-analysis supported the safety of DES which did not increase the risk of death, MI, or stent thrombosis compared with BMS[48]. In this meta-analysis of 1278 patients with unprotected LMCA stenosis, during a median of 10 mo, the mortality rate in DES-based PCI was only 5.5% (3.4% to 7.7%) and was not higher than BMS-based PCI.

Recently, studies assessed the risk of safety outcomes following the use of DES compared with BMS over 2 years[49-51]. After rigorous adjustment using propensity score or the IPTW (inverse-probability-of-treatment weighting) method to avoid selection bias, which was an inherent limitation of the studies, DES was not associated with a long-term increase in death or MI.
interest, Palmerini et al.\textsuperscript{26} showed a survival benefit of DES over 2 years. These studies supported previous pilot studies in that elective PCI with DES for unprotected LMCA stenosis seems to be a safe alternative to CABG.

With regard to the risk of stent thrombosis, in the series of LMCA DES studies, the incidence of stent thrombosis at 1 year ranged from 0% to 4% and was not statistically different from that with BMS\textsuperscript{4,16}. Recently, a multicenter study confirmed this finding, where the incidence of definite stent thrombosis at 2 years was only 0.5% in 731 patients treated with DES\textsuperscript{40}. In addition, the Drug Eluting stent for left main multicenter study, which included 358 patients undergoing LMCA stenting with DES, reported that the incidence of definite, probable, and possible stent thrombosis was 0.6%, 1.1% and 4.4%, respectively, at 3 years\textsuperscript{40}. In recent large multicenter studies for the ISAR-LEFT-MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) study or MAIN-COMPARE (Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) study, the incidence of definite or probable stent thrombosis was less than 1%\textsuperscript{46,48}. However, because these studies were underpowered to completely exclude the possibility of an increased risk of stent thrombosis over this long time period, further research needs to be performed. Previous studies assessing the long-term outcomes of DES for complex lesions showed inhomogeneous outcomes. For example, recent large trials evaluating the safety of DES for complex lesions showed comparable risks of death or MI for the two stent types\textsuperscript{49,50}. The recent large NHLBI (National Heart, Lung, and Blood Institute) study in the United States reported that, the off-label use of DES, compared with BMS, for similar indications was associated with a comparable 1-year risk of death and a lower 1-year risk of MI after adjustment\textsuperscript{49}. Of interest, a large study of 13,353 patients in Ontario found that the 3-year mortality rate in a propensity-matched population was significantly higher with BMS than with DES\textsuperscript{48}. The comparable or lower incidence of death or MI using DES compared with BMS may be due, at least in part, to the off-setting risks of restenosis vs stent thrombosis.

### Table 1 Outcomes of drug-eluting stents for unprotected left main coronary artery stenosis

<table>
<thead>
<tr>
<th>Stent type</th>
<th>Chieffo et al.\textsuperscript{23}</th>
<th>Valgimigli et al.\textsuperscript{11}</th>
<th>Park et al.\textsuperscript{22}</th>
<th>de Lezo et al.\textsuperscript{29}</th>
<th>Price et al.\textsuperscript{41}</th>
<th>Kim et al.\textsuperscript{20}</th>
<th>Meliga et al.\textsuperscript{29}</th>
<th>Mehlli et al.\textsuperscript{40}</th>
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<td>Single center study</td>
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<td>Single center study</td>
<td>Single center study</td>
<td>Multicenter study</td>
<td>Multicenter randomized study</td>
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<td>64</td>
<td>58</td>
<td>63</td>
<td>52</td>
<td>50</td>
<td>63</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>51*</td>
<td>57</td>
<td>41</td>
<td>42</td>
<td>60</td>
<td>62</td>
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<td>50</td>
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<tr>
<td>Acute myocardial infarction (%)</td>
<td>NA</td>
<td>NA</td>
<td>17</td>
<td>20*</td>
<td>9.8</td>
<td>6.6</td>
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<td>Bifurcation involvement (%)</td>
<td>81*</td>
<td>58</td>
<td>65</td>
<td>66</td>
<td>71*</td>
<td>43</td>
<td>42</td>
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<td>Two-stent technique (%)</td>
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<td>15</td>
<td>41*</td>
<td>18</td>
<td>18</td>
<td>89</td>
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<td>Initial clinical outcomes</td>
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<td>In-hospital</td>
<td>30 d</td>
<td>In-hospital</td>
<td>30 d</td>
<td>In-hospital</td>
<td>30 d</td>
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<tr>
<td>Death (%)</td>
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<td>11</td>
<td>7</td>
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<td>Myocardial infarction (%)</td>
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<td>4</td>
<td>9</td>
<td>7</td>
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<td>8</td>
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<td>Stent thrombosis (%)</td>
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<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
</tr>
<tr>
<td>Long-term outcomes (%)</td>
<td>In-hospital</td>
<td>30 d</td>
<td>In-hospital</td>
<td>30 d</td>
<td>In-hospital</td>
<td>30 d</td>
<td>In-hospital</td>
<td>30 d</td>
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<tr>
<td>Mean follow-up (mo)</td>
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<td>6</td>
<td>17</td>
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<td>4</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>10</td>
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<tr>
<td>Myocardial infarction (%)</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Stent thrombosis (%)</td>
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<td>0.0</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>TVR (%)</td>
<td>19</td>
<td>31</td>
<td>6</td>
<td>12</td>
<td>2</td>
<td>17</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>Any MACE (%)</td>
<td>NA</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
</tr>
</tbody>
</table>

\(a\) \textit{p}< 0.05 between drug-eluting stent (SES and/or PES) vs BMS. BMS: Bare metal stent; NA: Not available; MACE: Major adverse cardiac events including death, myocardial infarction, and TVR; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; TVR: Target vessel revascularization; DELFT: Drug Eluting stent for left main.


**Prognostic factors**

Several attempts have been made to predict the long-term outcome of complex LMCA intervention. Predictably, periprocedural and long-term mortality strongly depend on the patient’s clinical presentation. In the ULTIMA (Unprotected Left Main Trunk Investigation Multicenter Assessment) multicenter study, which included 279 patients treated with BMS, 46% of whom were inoperable or high surgical risk, the in-hospital mortality was 13.7%, and the 1-year incidence of all-cause mortality was 24.2%[13]. On the other hand, in the 32% of patients with low surgical risk (age < 65 years and ejection fraction > 30%), there were no periprocedural deaths and the 1-year mortality was 3.4%. Similarly, in patients with DES implantation, high surgical risk represented by high EuroSCORE or Parsonnet score, was the independent predictor of death or MI[13][20]. Therefore, it is recommended that continued attention should be paid to this procedure in patients at high surgical risk. More recently, the ‘SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery score)’, which was an angiographic risk stratification model, has been created to predict long-term outcome after coronary revascularization with either PCI or CABG[20]. In the recent SYNTAX study comparing PCI with paclitaxel-eluting stent vs CABG for multivessel or LMCA disease, the long-term mortality was significantly associated with the SYNTAX score[20]. Therefore, for patients with high clinical risk profiles or complex lesion morphologies, who are defined using these risk stratification models, the PCI procedures need to be performed by experienced interventionalists with the aid of IVUS, mechanical hemodynamic support, and optimal adjunctive pharmacotherapies, after judicious selection of patients.

**Recurrent revascularization**

Compared with BMS, DES reduced the incidence of angiographic restenosis and subsequently the need for repeat revascularization in unprotected LMCA stenosis. In early pilot studies, the 1-year incidence of repeat revascularization following DES implantation was 2%-19% as compared with 12%-31% following BMS implantation (Table 1)[4-6,21]. Fortunately, in a long-term study of 3 years, the incidence of repeat revascularization remained steady without significant observation of the “late catch-up” phenomenon of late restenosis noted after coronary brachytherapy[21]. Recently, two larger studies confirmed the efficacy of DES[20,27]. The risk of target lesion revascularization over 3 years was reduced by 60% with use of DES[27].

The risk of restenosis was significantly influenced by lesion location. DES treatment for ostial and shaft LMCA lesions had a very low incidence of angiographic or clinical restenosis[14]. In a study which included 144 patients with ostial or shaft stenosis in three cardiac centers, angiographic restenosis and target vessel revascularization at 1 year occurred in only 1 (1%) and 2 (1%) patients, respectively. Although, in those studies, the lack of availability of DES sizes larger than 3.5 mm imposed an overdilation strategy to match the LMCA reference diameter, there were no cardiac deaths, MI or stent thrombosis in this study.

In contrast, PCI for LMCA bifurcation has been more challenging although the prevalence was more than 60% in previous studies[4,6,10,21]. However, repeat revascularization was exclusively performed in patients with PCI for bifurcation stenosis[5,24]. A recent study assessing the outcomes of LMCA DES showed that the risk of target vessel revascularization was 6-fold (95% CI: 1.2-29) in bifurcation stenosis compared with non-bifurcation stenosis (13% vs 3%)[13]. The risk of bifurcation stenosis was highlighted in a recent study by Price et al[13] where the target lesion revascularization rate after sirolimus-eluting stent implantation was 38% (11). In this study, 94% (47/50) of patients had lesions at the bifurcation and 98% underwent serial angiographic follow-up at 3 and/or 9 mo. This discouraging result questioned the efficacy of DES and suggested the need for meticulous surveillance using angiographic follow-up in PCI for LMCA bifurcation stenosis. However, this study was limited by the exclusive use of a complex stenting strategy (two stents in both branches) in 84% of patients, which may have increased the need for repeat revascularization. Although, there is an ongoing debate[23], a recent report proposed that the complex stenting technique might be associated with the high occurrence of restenosis compared with the simple stenting technique[26]. A subgroup analysis of a large Italian study supported this hypothesis that a single stenting strategy for bifurcation LMCA lesions had a comparable long-term outcome to that for non-bifurcation lesions[24]. Taken together, these findings suggest that the simple stenting approach (LMCA to left anterior descending artery with optional treatment in the circumflex artery) is primarily recommended in patients with a relatively patent or diminutive circumflex artery. Furthermore, future stent platforms specifically designed for LMCA bifurcation lesions may provide better scaffolding and more uniform drug delivery to the bifurcation LMCA stenosis.

With regard to the differential benefit of the type of DES used for the prevention of restenosis, the two most widely used DESs, sirolimus- and paclitaxel-eluting stents, were evaluated in previous studies. In an early study, the research trial, which compared these two DESs, a comparable incidence of major adverse cardiac events was shown with 25% in the sirolimus (55 patients) and 29% in the paclitaxel-eluting stent (55 patients)[22]. The recent ISAR-Left-Main study compared 305 patients receiving sirolimus- and 302 patients receiving paclitaxel-eluting stents in a prospective randomized design[48]. At 1 year, major adverse events occurred in 13.6% of the paclitaxel- and 15.8% of the sirolimus-eluting stent groups with 16.0% and 19.4% of restenosis, respectively (P = NS). The use of a second generation DES is being evaluated in many studies.
Lesion restricted to the LMCA ostium or shaft
In-stent restenosis at the LMCA, in which repeat PCI is not likely to be performed
Contraindication to antiplatelet therapy including aspirin, heparin, and ticlopidine
History of serious allergic reaction to stainless steel, drugs on drug-eluting stents, and contrast agent
History of known coagulopathy or bleeding diathesis
Pregnant women
Complex coronary anatomies at LMCA, unsuitable for stenting (e.g. severe calcification, severe tortuosity, etc.)
Total occlusions at other major epicardial coronary arteries (≥ 2)
Multivessel stenosis except LMCA
Decreased left ventricular dysfunction (< 40%)
Extensive peripheral vascular disease, in which placement of guiding catheter or intra-aortic balloon pump is not likely to be performed
In-stent restenosis at the LMCA, in which repeat PCI is not likely to be performed

Table 2 Features favoring PCI or CABG

<table>
<thead>
<tr>
<th>Indications favoring PCI</th>
<th>Indications in favor of CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute</strong></td>
<td></td>
</tr>
<tr>
<td>Suitable coronary anatomy for stenting with preserved left ventricular function (≥ 40%)</td>
<td>Patient who refuses PCI</td>
</tr>
<tr>
<td>Patient who refuses PCI</td>
<td></td>
</tr>
<tr>
<td><strong>Relative</strong></td>
<td></td>
</tr>
<tr>
<td>Lesion restricted to the LMCA ostium or shaft</td>
<td></td>
</tr>
<tr>
<td>Isolated LMCA lesion</td>
<td></td>
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<tr>
<td>Bail-out procedure (e.g. dissection at the LMCA complicated during angiography or PCI)</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction at the LMCA, in which emergent revascularization is necessary</td>
<td></td>
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<tr>
<td>Cardiogenic shock due to LMCA stenosis, in which emergent revascularization is necessary</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 80 yr</td>
<td></td>
</tr>
<tr>
<td>Serious co-morbid disease (e.g. chronic lung disease, poor general performance, etc.)</td>
<td></td>
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<tr>
<td>Limited life expectancy of less than 1 yr</td>
<td></td>
</tr>
<tr>
<td>Prior CABG</td>
<td></td>
</tr>
<tr>
<td>Coronary anatomy, unsuitable for CABG (e.g. poor distal run-off)</td>
<td></td>
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</tbody>
</table>

CABG: Coronary artery bypass graft surgery; LMCA: Left main coronary artery; PCI: Percutaneous coronary intervention.

COMPARISON WITH CORONARY ARTERY BYPASS SURGERY

It is surprising to note that current guidelines for unprotected LMCA treatment, in which elective PCI for patients who are treatable with bypass surgery is a contraindication, is based mostly on 20-year-old clinical trials[1-3]. These studies demonstrated a definite benefit of survival with CABG in LMCA stenosis compared with medical treatment. However, application of these results to current practice seems inappropriate because surgical technique as well as medical treatment in these studies is outdated by today’s standards and no randomization studies between PCI and CABG with enough power have been conducted. The lack of data on the current CABG procedure used in unprotected LMCA stenosis further precludes a theoretical comparison of the two revascularization strategies. Table 2 lists the patient and lesion characteristics favoring PCI or CABG based on current expert opinion and evidence.

Recently, several non-randomized studies comparing the safety and efficacy of DES treatment for unprotected LMCA stenosis, compared with CABG, were published (Table 3). Chieffo et al[7] compared retrospectively the outcomes of 107 patients undergoing DES placement with 142 patients undergoing CABG. They showed that DES was associated with a non-significant mortality benefit (odds ratio = 0.331, P = 0.167) and a significantly lower incidence of composites of death or MI (0.260, P = 0.0005) and death, MI, or cerebrovascular accident (odds ratio = 0.385, P = 0.01) at 1-year follow-up. Conversely, CABG was correlated with a lower occurrence of target vessel revascularization (3.6% vs 19.6%, P = 0.0001). These findings were supported by Lee et al[9], in 50 patients with DES placement and 123 patients with CABG. In this study, although the DES group had slightly higher surgical risk, the rate of mortality or MI at 30 d was comparable between the two treatments. At 1-year follow-up, DES patients had a non-significantly better clinical outcome compared with CABG, reflected by overall survival (96% vs 85%) and survival freedom from death, MI, target vessel revascularization, or adverse cerebrovascular events (83% vs 75%). However, the survival freedom from repeat revascularization at 1 year remained non-significantly higher for CABG compared to the DES (95% vs 87%). The results of a recent multicenter study were in agreement with the previous two reports with regard to the safety outcomes[10-11]. The PCI group treated with BMS or DES (60%) had a similar incidence of death and/or MI, but a higher incidence of target lesion revascularization compared with the CABG group. Similar safety with PCI compared with CABG was observed in older patients (age ≥ 75 years) by Palmerini et al[8]. Recently, a randomized study comparing PCI (n = 52) vs CABG (n = 53) was undertaken in 105 patients with unprotected LMCA stenosis[12]. PCI was performed using either BMS (65%) or DES (35%). The primary end point was the change in left ventricular ejection fraction 12 mo after the intervention. A significant increase in ejection fraction was noted only in the PCI group (3.3% ± 6.7% vs PCI 0.5% ± 0.8% after CABG, P = 0.047). In contrast, at 1-year after the procedure, repeat revascularization was significantly lower in the CABG group (n = 5) than in the PCI group (n =
Table 3  Comparison of drug-eluting stents to coronary artery bypass surgery for unprotected left main coronary artery stenosis

<table>
<thead>
<tr>
<th>Study design</th>
<th>Registry</th>
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<td>Ejection fraction (%)</td>
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<td>52</td>
<td>52</td>
<td>55</td>
<td>54</td>
<td>54</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>EuroSCORE or Parsonnet score (Lee)</td>
<td>4.4</td>
<td>4.3</td>
<td>18.0^</td>
<td>13.0</td>
<td>6.0*</td>
<td>5.0</td>
<td>3.3</td>
<td>3.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Initial clinical outcomes</td>
<td>In-hospital</td>
<td>30 d</td>
<td>30 d</td>
<td>30 d</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (%)</td>
<td>0.0</td>
<td>2.0</td>
<td>2.0</td>
<td>5.0</td>
<td>3.2</td>
<td>4.5</td>
<td>0.0</td>
<td>0.0</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Myocardial infarction (%)</td>
<td>9.0</td>
<td>26.0</td>
<td>0.0</td>
<td>2.0</td>
<td>4.5</td>
<td>1.9</td>
<td>1.9</td>
<td>3.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TVR (%)</td>
<td>0.0</td>
<td>2.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.6</td>
<td>0.6</td>
<td>1.9</td>
<td>0.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Any MACE (%)</td>
<td>NA</td>
<td>NA</td>
<td>0.0</td>
<td>8.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cerebrovascular accident (%)</td>
<td>0.0</td>
<td>1.4</td>
<td>2.0*</td>
<td>17.0</td>
<td>NA</td>
<td>NA</td>
<td>0.0</td>
<td>2.0</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Long-term clinical outcomes</td>
<td>Cumulative after discharge</td>
<td>Kaplan-Meier</td>
<td>Cumulative</td>
<td>Kaplan-Meier</td>
<td>At 1 yr</td>
<td>Kaplan-Meier at 3 yr for propensity-matched cohort</td>
<td></td>
<td></td>
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<tr>
<td>Mean follow-up (mo)</td>
<td>12.0</td>
<td>12.0</td>
<td>6.0</td>
<td>6.0</td>
<td>14.0</td>
<td>14.0</td>
<td>NA</td>
<td>NA</td>
<td>33.9</td>
<td>38.4</td>
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<tr>
<td>Death (%)</td>
<td>2.8</td>
<td>6.4</td>
<td>4.0</td>
<td>13.0</td>
<td>13.4</td>
<td>12.3</td>
<td>1.9</td>
<td>7.5</td>
<td>7.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>0.9</td>
<td>1.4</td>
<td>NA</td>
<td>NA</td>
<td>8.3</td>
<td>4.5</td>
<td>1.9</td>
<td>5.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TVR (%)</td>
<td>19.6*</td>
<td>3.6</td>
<td>7.0</td>
<td>1.0</td>
<td>25.5*</td>
<td>2.6</td>
<td>28.8*</td>
<td>9.4</td>
<td>12.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Cerebrovascular accident (%)</td>
<td>0.9</td>
<td>0.7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.0</td>
<td>3.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Any events (%)</td>
<td>NA</td>
<td>NA</td>
<td>11.0</td>
<td>17.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

\*P < 0.05 between PCI vs CABG.

15), although the incidence of death or MI was comparable between the two groups. However, this study was underpowered to assess the long-term clinical effectiveness of PCI compared with CABG.

Stronger evidence for the feasibility of PCI as an alternative to CABG comes from a recent large trial, the MAIN-COMPARE study\[21\]. In this study, data were analyzed from 2240 patients with unprotected LMCA disease treated at 12 medical centers in Korea. Of these, 318 were treated with BMS, 784 were treated with DES, and 1138 underwent CABG. To avoid bias due to the non-randomized study design, a novel adjustment was performed using propensity-score matching in the overall population at separate periods. In the first and second waves, BMS and DES were exclusively used, respectively. The outcome of stenting in the overall population and each wave were compared with those of concurrent CABG. During 3 years of follow-up, patients treated with stenting were nearly 4 times as likely to need a repeat revascularization compared to those who underwent CABG (HR = 4.76, 95% CI: 2.80-8.11). However, the rates of death (HR = 1.18, 95% CI: 0.77-1.80) and the combined rates of death, MI and stroke (HR = 1.10, 95% CI: 0.75-1.62) were not significantly higher with stenting compared with CABG. A similar pattern was also observed in patients treated with DES or BMS. Another interesting finding in this study was that the majority of repeat revascularizations in PCI patients were treated with repeat PCI instead of CABG. Given the fact that the recommendation for CABG for unprotected LMCA disease was based mostly on survival benefit compared with medical treatment, the lack of a statistically significant difference in mortality may support PCI as an alternative option to bypass surgery. In addition, the current recommendation of routine angiographic surveillance at 6-9 mo after PCI for unprotected LMCA stenosis might increase the unnecessary need for repeat revascularization due to ‘oculo-stenotic’ reflex.

The ultimate proof of the relative values of PCI vs CABG for unprotected LMCA stenosis clearly depends on the results of randomized clinical trials comparing the two treatment strategies. The trials involve a number of technical considerations that could significantly alter angioplasty outcomes. The SYNTAX trial compared the outcomes of PCI with paclitaxel-eluting stents vs CABG for unprotected LMCA stenosis in a subgroup from the randomized study cohort\[30\]. As shown in the subset of patients with LMCA disease comprising 348 patients receiving CABG and 357 receiving PCI (15.8%) demonstrated equivalent 1-year clinical outcomes of major adverse cardiac and cerebrovascular events including death, MI, stroke and repeat revascularization with CABG (13.7%, P = 0.44). When the patients were stratified according to the vascular involvement, the event rate in the PCI group was numerically higher for patients with 2-vessel (19.8% vs 14.4%, P = 0.29) and 3-vessel (19.3% vs 15.4%, P = 0.42) disease. However, the incidence of these events were numerically lower in the PCI group for patients with isolated LMCA (7.1% vs 8.5%, P = 1.0) or 1-vessel disease (7.5% vs 13.2%, P = 0.27). Of interest, the higher rate of repeat revascularization with PCI (11.8% vs 6.5%, P = 0.02) was offset by a higher incidence of stroke with CABG (2.7% vs 0.3%, P = 0.01). However, it should be noted that the analysis for LMCA disease was not the primary objective analysis but the post-
hoc analysis, which is hypothesis-generating. Therefore, further randomized studies are warranted to provide a definite answer to this question for a specific cohort of patients having unprotected LMCA stenosis. Another randomized study, the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery vs Angioplasty using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial, performed in Korea randomized 600 patients with unprotected LMCA to either CABG or PCI with sirolimus-eluting stents. This study has a non-inferiority design with the primary end point of major adverse cardiac and cerebrovascular events at a mean of 2 years. A more global randomized trial, the EXCEL (Evaluation of XIENCE PRIME™ vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), is also being carried out to compare PCI and CABG for approximately 2500 patients with unprotected LMCA stenosis.

**TECHNICAL ISSUES**

**Stenting techniques**

Stenting for ostial or body LMCA lesions seems very simple as the other stenting technique for non-LMCA coronary lesions. For instance, a brief stent expansion is required to obtain optimal stent expansion and to avoid ischemic complications. In ostial LMCA lesions, the coronary stent is generally positioned outside the LMCA for complete lesion coverage of the ostium. Stenting for bifurcation LMCA lesions, however, are technically demanding and should be performed by experienced operators. In general, the selection of an appropriate stenting strategy is dependent on the plaque configuration surrounding the LMCA. However, in spite of recent randomized studies comparing single-stent vs two-stent treatment for bifurcation coronary lesions [54,55], the optimal stenting strategy for LMCA bifurcation lesions has not yet been determined. The current consensus is that the two-stent strategy does not have long-term advantages in terms of the incidence of any major cardiac events compared with the single-stent strategy. Therefore, systemic treatment with the two-stent strategy for all LMCA bifurcation lesions, such as T-stenting, Kissing stenting, Crush technique, or Culotte technique is not generally recommended. Instead, a provisional stenting strategy should be considered as the first-line treatment for LMCA bifurcations without significant side branch stenosis.

**IVUS**

IVUS is considered a useful invasive diagnostic modality in determining anatomical configuration, selecting treatment strategy, and defining optimal stenting outcomes in either the BMS or DES era [56]. Although a retrospective study showed that the clinical impact of IVUS-guided stenting for LMCA with DES did not show a significant clinical long-term benefit compared with the angiography-guided procedure [57], the usefulness of IVUS guided-stenting may not be hampered by this underpowered retrospective study. The information gathered by IVUS may be crucial for the optimal stenting procedure in unprotected LMCA stenosis with excellent intraclass correlation in the measurement of area and plaque [58]. In fact, angiography has a limitation in assessing the true luminal size of the LMCA because this artery is often short and lacks a normal segment for comparison. Therefore, the severity of LMCA stenosis is often underestimated by misinterpretation of the normal segment adjacent to focal stenosis. In addition to the actual assessment of LMCA lesions before a procedure, use of IVUS is very helpful to obtain an adequate expansion of the DES, to prevent stent inapposition, and to achieve full lesion coverage with the DES.

A recent subgroup analysis from the MAIN-COMPARE study reported a very interesting finding in that IVUS-guidance was associated with improved long-term mortality compared with the conventional angiography-guided procedure [59]. With an adjustment using propensity-score matching for 201 matched pairs, there was a strong tendency for a lower risk of 3-year mortality with IVUS-guidance compared with angiography-guidance (6.3% vs 13.6%, log-rank \( P = 0.063, \) HR = 0.54, 95% CI: 0.28-1.03). In particular, for 145 pairs of patients receiving DES, the 3-year incidence of mortality was lower with IVUS-guidance compared with angiography-guidance (4.7% vs 16.0%, log-rank \( P = 0.048, \) HR = 0.39, 95% CI: 0.15-1.02). Of interest, mortality started to diverge 1 year after the procedure. Therefore, in spite of inherent limitations of the non-randomized study design, this study indicated that IVUS-guidance may play a role in reducing very late stent thrombosis and subsequent long-term mortality. In fact, IVUS evaluations of stent underexpansion, incomplete lesion coverage, small stent area, large residual plaque and inapposition have been found to predict stent thrombosis after DES placement [56-63]. Therefore, we strongly recommend the mandatory use of IVUS in PCI for unprotected LMCA.

**Debulking atherectomy**

In the BMS era, debulking coronary atherectomy before stenting had been used widely in an attempt to reduce restenosis by removal of plaque burden. However, following the introduction of DES, the role of debulking was restricted due to the dramatic benefit of restenosis reduction. One study suggested a viable role for debulking atherectomy even in the DES era for 99 patients with coronary bifurcations [64]. Of interest, debulking in the main branch and side branch for LMCA stenoses allowed single-stenting in 60 of the 63 LMCA bifurcation stenoses. Surprisingly, during the 1-year follow-up, no serious adverse events occurred. This study indicated that debulking may be preferred in LMCA bifurcations in order to aid a provisional single stenting strategy. In addition, debulking still plays a limited role in facilitating stent delivery. Debubling is used to remove plaque in the LMCA which inhibited advancement of the wire into
the left anterior descending artery. Similarly, a rotablator has been used prior to stenting when calcification in the proximal segment prevents stent delivery or the calcified target lesion is not sufficiently dilated. Therefore, although the data is limited, debulking atherectomy or rotablator still have a limited role even in DES treatment to improve lesion compliance.

Hemodynamic support

Patients in an unstable hemodynamic condition need pharmacological- or device-based hemodynamic support during the procedure for LMCA stenosis. Old age, MI, cardiogenic shock and decreased left ventricular ejection fraction are common clinical conditions requiring elective or provisional hemodynamic support. Hemodynamic support devices include the intra-aortic balloon pump, percutaneous hemodynamic support devices, and left ventricular assist devices. The intra-aortic balloon pump has been used most frequently. Although there is no doubt that the provisional use of an intra-aortic balloon pump in patients with hemodynamic compromise is necessary for a successful procedure, from the literature, the planned use of the balloon pump ranges widely. A study recently suggested the role of intra-aortic balloon pump support in 219 elective LMCA interventions. These authors used a prophylactic balloon pump for a broad range of patients with distal LMCA bifurcation lesions, low ejection fraction of < 40%, use of debulking devices, unstable angina, and critical right coronary artery disease. In that study, interestingly, although the patients receiving elective intra-aortic balloon pump support had more complex clinical risk profiles, the rate of procedural complications was lower than in those not receiving intra-aortic balloon pump support (1.4% vs 9.3%, P = 0.032). Therefore, the elective use of intra-aortic balloon pump support needs to be considered in patients at a high risk with multivessel disease, complex LMCA anatomy, low ejection fraction or unstable presentations. Hopefully, the new support devices, such as Tandem-Heart (CardiacAssist, Pittsburgh, Pennsylvania, USA) or the Impella Recover LP 2.5 System (Impella Cardio-Systems, Aachen, Germany) may improve the feasibility of implementation and the complication rate related to these devices.

Antithrombotics

Although the reported incidence of stent thrombosis in DES treatment for LMCA lesions is very low, the fear of stent thrombosis remains a major concern and prevents the more generalized use of DES. Therefore, careful administration of antiplatelet agents is very important to prevent the occurrence of stent thrombosis. In fact, premature discontinuation of clopidogrel was strongly associated with stent thrombosis in several studies. Therefore, as generally recommended, dual antiplatelet therapy including aspirin and clopidogrel (or ticlopidine) should be maintained for 1 year. If the patients are at high risk, a high loading dose (600 mg) or lifelong administration of clopidogrel needs to be considered. A recent study added the benefit of aggressive use of clopidogrel in the early period after DES implantation. After stopping clopidogrel between 31 and 180 d, the hazard of cardiac death or MI was 4.20 (P = 0.009) compared with stopping clopidogrel between 181 and 36 d. Furthermore, in some institutions in Asian countries, the adjunctive administration of cilostazol has been used to reduce thrombotic complications.

Aggressive use of antithrombotics should also be considered for complex lesion anatomy or unstable coronary conditions. For example, as shown in previous studies, the use of glycoprotein II b/III a inhibitor may play a role in reducing procedure-related thrombotic complications including death or MI. However, the additive role of the glycoprotein II b/III a inhibitor, cilostazol, low molecular weight heparin, direct thrombin inhibitor or other new drugs in DES treatment for LMCA lesions needs to be investigated in future research. Until evidence is accumulated, we have to consider an aggressive combination of antithrombotic drugs before, during or after the procedure to avoid thrombotic complications in high-risk patients. Although the features of high risk are not well delineated, off-label use of DES, such as in diabetes mellitus, multiple stenting, long DES, chronic renal failure, or presentation with MI, is a good index of a high-risk procedure.

CONCLUSION

The current studies, although they are limited by the non-randomized study design, small sample size, and short-term follow-up, have demonstrated the promising procedural and mid-term safety and effectiveness of DES compared with BMS or CABG. With these findings, in our opinion, PCI with DES will progressively increase and can be recommended as the reliable alternative to bypass surgery for patients with unprotected LMCA stenosis, especially as the first line-therapy for ostial or shaft stenosis. Although bifurcation stenosis remains challenging using the percutaneous approach, we are still optimistic as further research into novel procedural techniques, new dedicated stent platforms, and optimal pharmacotherapies may improve patient outcome. Furthermore, we hope, with the upcoming results from randomized clinical trials comparing PCI to CABG for unprotected LMCA stenosis, more confidence in the long-term safety, durability, and efficacy of PCI will be accrued in the near future.

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