Hemodynamically significant left main coronary artery (LMCA) stenosis is found in approximately 4% of diagnostic coronary angiograms and is known as unprotected LMCA stenosis if the left coronary artery and left circumflex artery has no patent previous grafts. Previous randomized studies 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 such a lesion because of the proven benefit of surgery and high rates of restenosis with the use of bare-metal stents. However, with the advent of drug-eluting stents (DES), the long-term outcomes of PCI with DES to treat unprotected LMCA stenoses have been reported to be acceptable. Therefore, despite the current guidelines, PCI for the treatment of unprotected LMCA stenosis is often undertaken in many countries in individuals who are at a very high risk with CABG or refuse to undergo a sternotomy. Future randomized studies comparing CABG versus PCI using DES for the treatment of unprotected LMCA stenosis would add to our clinical knowledge, and help to lead to the adoption of appropriate treatment.

Keyvords: bypass surgery · coronary artery · left main · prognosis · restenosis · stent

Owing to the long-term benefit of coronary artery bypass graft (CABG) surgery compared with medical therapy, CABG has been the standard treatment for unprotected left main coronary artery (LMCA) stenosis [1–3]. However, with advances in technique and equipment, the percutaneous interventional approach for implantation of coronary stents has been shown to be feasible for patients with unprotected LMCA stenosis [3]. In particular, the recent introduction of drug-eluting stents (DES), together with advances in periprocedural and postprocedural adjunctive pharmacotherapies, have improved outcomes of percutaneous coronary interventions (PCI) for these complex coronary lesions [4–29]. Nonetheless, PCI for unprotected LMCA stenosis is still only indicated for patients at a high surgical risk or for emergent clinical situations, such as bailout procedure or acute myocardial infarction (MI), as an alternative therapy to CABG, as the recent registry and randomized study failed to prove superiority, or at least non-inferiority, of DES placement for unprotected LMCA stenosis, as compared with CABG [21,30,31]. By contrast, there is concern regarding 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 US FDA 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]. Therefore, in this review, we evaluate the current techniques and outcomes of PCI with either BMS or DES compared with CABG in a series of studies conducted in several countries.

Significant left main coronary artery stenosis
Coronary angiography has been the standard tool to determine the severity of coronary artery disease. Although a traditional cut-off for significant coronary stenosis has been diameter stenosis of 70% in non-LMCA lesions, its cut-off in LMCA has been a diameter stenosis of 50%. However, because the conventional coronary angiogram is only a lumenogram, providing information regarding 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 intra- and inter-observer variabilities [38–40]. Therefore, intravascular ultrasound (IVUS) is often used to assess the severity of LMCA stenosis.

A diagnosis 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. reported 1-year follow-up in 122 patients with LMCA disease. The minimum lumen diameter by IVUS was the most important predictor of cardiac events, with a 1-year event rate of 14% in patients with a minimum luminal diameter of less than 3.0 mm [42]. Fassa et al. reported that the long-term outcome of patients with a LMCA with a minimum lumen area of less than 7.5 mm² without revascularization were considerably worse than those who were revascularized [43]. Jasti et al. compared fractional flow reserve (FFR) and IVUS in patients with an angiographically ambiguous LMCA stenosis [44]. However, accurate assessment for ostial LMCA is not always possible. Practically, it is important to keep the IVUS catheter co-axial 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.

Fractional flow reserve 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]. An FFR value of less than 0.75 is considered to be a reliable indicator of significant stenosis producing inducible ischemia [46]. In patients with an angiographically equivocal LMCA stenosis, a strategy of revascularization versus medical therapy based on an FFR cut-point of 0.75 was associated with excellent survival and freedom from events for up to 3 years follow-up [44].

**Outcomes with DES**

**Safety compared with BMS**

Although there are disputes regarding the long-term safety of DES, the possibility of late or very late thrombosis has still been 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 in DES implantation for unprotected LMCA, as compared with BMS. In the three early pilot studies comparing the outcomes of DES with those of BMS, the incidences of death, MI or stent thrombosis were comparable in the two stent types during the procedure and at follow-up [4–6]. Of interest, in the study of Valgimigli et al., DES were associated with significant reductions 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 [6]. Considering that restenosis can lead to an acute MI in 3.5–19.4%, a significant reduction of restenosis achieved by DES might contribute to the better outcome. In fact, a previous study suggested that the episode of restenosis at the BMS in LMCA could present as late mortality [47]. In addition, more frequent repeat revascularization to treat BMS restenosis, in which CABG is the standard of care at the unprotected LMCA, may also be related to the increase in hazardous accidents compared with DES. A recent meta-analysis supported the safety of DES, showing that DES did not increase the risk of death, MI or stent thrombosis compared with BMS [18]. In this meta-analysis of 1278 patients with unprotected LMCA stenosis, for a median of 10 months, mortality rate in DES-based PCI was only 5.5% (3.4–7.7%) and was not higher than BMS-based PCI.

Recently, three registry studies assessed the risk of safety outcomes with the use of DES compared with BMS over 2 years, as shown in Figure 1 [25–27]. After rigorous adjustment using propensity score or the inverse-probability-of-treatment weighting method to avoid selection bias, which was an inherent limitation of the registry study, DES was not associated with long-term increase in death or MI. Of interest, the report of Palmerini et al. showed the survival benefit of DES over 2 years. These studies supported the previous pilot studies that elective PCI with DES for unprotected LMCA stenosis seems to be a safe alternative to CABG.

Regarding 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 in BMS [4–6]. Recently, a multicenter study confirmed the finding that the incidence of definite stent thrombosis at 2 years was only 0.5% in 731 patients treated with DES [19]. In addition, the Drug Eluting Stent for Left Main (DELFIT) multicenter registry, 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% at
Table 1. Outcomes with drug-eluting stents for unprotected left main coronary artery stenosis.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>SES, PES</td>
<td>SES, PES</td>
<td>BMS</td>
<td>SES, PES</td>
<td>BMS</td>
<td>SES</td>
<td>SES</td>
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</tr>
<tr>
<td>Age (years)</td>
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<td>95</td>
<td>86</td>
<td>102</td>
<td>121</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>63</td>
<td>66</td>
<td>64</td>
<td>66</td>
<td>60</td>
<td>58</td>
<td>63</td>
<td>69</td>
</tr>
<tr>
<td>Acute myocardial infarction (%)</td>
<td>51*</td>
<td>57</td>
<td>41</td>
<td>42</td>
<td>60</td>
<td>62</td>
<td>57</td>
<td>NA</td>
</tr>
<tr>
<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>
<td>94</td>
</tr>
<tr>
<td>Two-stent technique (%)</td>
<td>74</td>
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<td>40</td>
<td>40</td>
<td>15</td>
<td>41*</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Initial clinical outcomes</td>
<td>In-hospital</td>
<td>30 days</td>
<td>In-hospital</td>
<td>In-hospital</td>
<td>In-hospital</td>
<td>In-hospital</td>
<td>In-hospital</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Death (%)</td>
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<td>0</td>
<td>11</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>8</td>
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<tr>
<td>Stent thrombosis (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>TVR (%)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Any events (%)</td>
<td>NA</td>
<td>NA</td>
<td>15</td>
<td>19</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>10</td>
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<tr>
<td>Long-term outcomes</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>Cumulative</td>
<td>After discharge</td>
<td>Cumulative</td>
<td>3 years</td>
<td>2 years</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
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<td>6</td>
<td>17</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Death (%)</td>
<td>4</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<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>
<td>0.1</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>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>NA</td>
<td>24*</td>
<td>45</td>
<td>8*</td>
<td>26</td>
<td>NA</td>
<td>44</td>
</tr>
</tbody>
</table>

*p < 0.05 between drug-eluting stent (SES and/or PES) vs BMS.
BMS: Bare-metal stent; DELFT: Drug-eluting stent for left main; MACE: Major adverse cardiac events including death, myocardial infarction and TVR; NA: Not available; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; TLR: Target lesion revascularization; TVR: Target vessel revascularization.
In recent large, multicenter studies, in the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions [ISAR-LEFT-MAIN] or the Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization [MAIN-COMPARE]), the incidence of definite or probable stent thrombosis was less than 1% [21,48]. However, because these studies are still underpowered to completely exclude the possibility of increased risk of stent thrombosis in the long term, further studies need to be performed to determine this. The previous studies assessing the long-term outcomes of DES for complex lesions showed various outcomes. For example, recent large registries evaluating the safety of DES for complex lesions showed comparable
risks of death or MI for the two stent types [49,50]. The recent large National Heart, Lung, and Blood Institute (NHLBI) registry in the USA 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 [49]. Of interest, a large registry 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 [50]. The comparable or lower incidence of death or MI with the use of DES compared with BMS may be due, at least in part, to the off-setting risks of restenosis versus stent thrombosis.

Risk stratification of long-term safety
Several attempts have been made to predict long-term outcomes of complex LMCA intervention. Predictably, periprocedural and long-term mortality depend strongly on the patient’s clinical presentation. In the Unprotected Left Trunk Investigation Multicenter Assessment (ULTIMA) multicenter registry, which included 279 patients treated with BMS, 46% of whom were inoperable or a high surgical risk, the inhospital mortality was 13.7% and the 1-year incidence of all-cause mortality was 24.2% [51]. On the other hand, in the 32% of patients at low surgical risk (age <65 years and with an ejection fraction >30%), there were no periprocedural deaths and the 1-year mortality was 3.4%. Similarly, with DES implantation, high surgical risk represented by high EuroSCORE or Parsonnet score was an independent predictor of death or MI [13,52]. Therefore, it is recommended that a lot of attention should continue to be paid to procedure in patients at high surgical risk. More recently, the Synergy between PCI with Taxus and Cardiac Surgery score (SYNTAX), an angiographic risk stratification model, has been created to predict long-term outcomes after coronary revascularization with either PCI or CABG [30]. In the recent SYNTAX study comparing PCI with paclitaxel-eluting stent versus CABG for multivessel or LMCA disease, there was significant interaction between the treatment type and the SYNTAX score [30]. In patients with a high SYNTAX score, CABG, as compared with stenting, had a better outcome in terms of the incidence of major adverse cardiac and cerebrovascular events. Therefore, for patients with high clinical risk profiles or complex lesion morphologies who are defined using these risk stratification models, PCI procedures need to be performed by experienced interventionalists with the aid of IVUS, mechanical hemodynamic support and optimal adjunctive pharmacotherapies, after the judicious selection of patients.

Restenosis & repeat revascularization
Compared with BMS, DES reduced the incidence of angiographic restenosis and subsequently the need for repeat revascularization in unprotected LMCA stenosis. In the early pilot studies, the 1-year incidence of repeat revascularization in DES implantation was 2–19% as compared with 12–31% in BMS (Table 1) [4–6]. Fortunately, in the long-term study up to 3 years, the incidence of repeat revascularization remained steady without the significant observation of ‘late catch-up’ phenomenon of late restenosis noted after coronary brachytherapy [21]. Recently, two larger registries confirmed the efficacy of DES [25,27]. The risk of target lesion revascularization over 3 years was reduced by 60% with use of DES as shown in Figure 1 [27].

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

By contrast, PCI for LMCA bifurcation has been more challenging, although prevalence was more than 60% across the previous studies [4–6,10,21]. However, repeat revascularization was exclusively performed in patients with PCI for bifurcation stenosis [4–6]. A recent study assessing the outcomes of LMCA DES showed that the risk of target vessel revascularization was sixfold higher (95% CI: 1.2–29) in bifurcation stenosis compared with nonbifurcation stenosis (13 vs 3%) [13]. The risk of bifurcation stenosis was further highlighted in a recent study of Price et al., which showed that the target lesion revascularization rate after sirolimus-eluting stent implantation was 44% [11]. In this study, 94% (47 out of 50) of patients had lesions at the bifurcation and 98% underwent serial angiographic follow-up at 3 and/or 9 months. This discouraging result led to caution over the efficacy of DES and highlighted
the need for meticulous surveillance of 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 increase the need for repeat revascularization. Although there was a debate [53], a current report suggested the probability that the complex stenting technique might be associated with a high occurrence of restenosis compared with the simple stenting technique [8]. A subgroup analysis of the large Italian registry supported this with the hypothesis that a single stenting strategy for bifurcation LMCA lesions had comparable long-term outcomes with nonbifurcation lesions [24]. Taken together, before a novel treatment strategy is settled, 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.

Regarding the differential benefit of DES for the prevention of restenosis, the two most widely applicable DES – sirolimus- and paclitaxel-eluting stents – were evaluated in previous studies. An early study comparing the two DES from a RESEARCH registry showed a comparable incidence of major adverse cardiac events with 25% in sirolimus- (55 patients) and 29% in paclitaxel-eluting stents (55 patients) [12]. The recent ISAR-LEFT-MAIN study compared 305 patients receiving sirolimus- and 302 patients receiving paclitaxel-eluting stents with 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% restenosis, respectively (p = not significant). Use of second-generation DES is being evaluated in many studies.

Comparison with CABG

It is surprising to note that current guidelines for the treatment of unprotected LMCA, in which elective PCI for patients who are treatable with bypass surgery is a contraindication, are based mostly on 20-year-old clinical trials [1–3]. These studies demonstrated a definite benefit in survival of CABG in LMCA stenosis compared with medical treatment. However, the application of these results to current practice seems inappropriate as surgical technique as well as medical treatment in these studies is outdated by current 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. Box 1 lists the patient and lesion characteristics favoring PCI or CABG based on current expert opinion and evidence.

Currently, several nonrandomized studies comparing the safety and efficacy of DES treatment for unprotected LMCA stenosis, compared with CABG, have been published (Table 2). Chieffo et al. retrospectively compared the outcomes of 107 patients undergoing DES placement with 142 patients undergoing CABG [7]. They showed that DES was associated with a nonsignificant benefit in mortality (OR: 0.331; p = 0.167) and significantly lower incidence of composites of death or MI (OR: 0.260; p = 0.0005) and death, MI or cerebrovascular accident (OR: 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 the report of Lee et al., which consisted of 50 patients with DES placement and 123 patients with CABG [9]. In this study, although the DES group had a slightly higher surgical risk, the rate of mortality or MI at 30 days was comparable between the two treatments. At 1-year follow-up, the DES had nonsignificantly better clinical outcomes compared with CABG, reflected in 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 nonsignificantly higher for the CABG compared with the DES (95 vs 87%). The results of a recent multicenter registry were in agreement with the previous two reports with regards to the safety outcomes [10]. 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. A similarity in safety with the use of PCI compared with CABG was ascertained for older patients (age >75 years) by Palmerini et al. [15]. Recently, a randomized study comparing PCI (n = 52) with CABG (n = 53) was undertaken for 105 patients with unprotected LMCA stenosis [17]. PCI was performed using either BMS (65%) or DES (35%). The primary end point was the change in left ventricular ejection fraction 12 months after the intervention, in which a significant increase...
in ejection fraction was noted only in the PCI group (3.3 ± 6.7% after PCI vs 0.5 ± 0.8% after CABG; p = 0.047). By contrast, at 1 year after procedure, repeat revascularization was significantly lower in the CABG group (n = 5) than in the PCI group (n = 15), although the incidence of death or MI was comparable between the two groups. However, this study was still 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 the recent large registry, the MAIN-COMPARE study [21]. They analyzed data 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 nonrandomized study design, a novel adjustment was performed using propensity-score matching in overall population and separate periods. In the first and second waves, BMS and DES were exclusively used, respectively. The outcomes of stenting in the overall patients and each wave were compared with those of concurrent CABG as shown in Figure 2. During 3 years of follow-up, patients treated with stenting were nearly four-times as likely to need a repeat revascularization when compared with 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 the use of stenting compared with CABG, as shown in Figure 1. 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 revascularization in PCI patients were treated with repeat PCI instead of CABG. Given the fact that the recommendation for CABG for unprotected LMCA disease has been 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, a current recommendation of routine angiographic surveillance at 6–9 months after PCI for unprotected LMCA stenosis might increase unnecessary repeat revascularization due to the ‘oculo-stenotic’ reflex.

The ultimate proof of the relative values of PCI versus CABG for unprotected LMCA stenosis clearly depends on the results of randomized clinical trials comparing the two treatment strategies. The trials will involve a number of technical considerations that could significantly alter angioplasty outcomes. The SYNTAX trial

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**Box 1. Features favoring percutaneous coronary intervention or coronary artery bypass graft surgery.**

**Indications in favor of percutaneous coronary intervention**

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>Suitable coronary anatomy for stenting with preserved left ventricular function (&gt;40%)</td>
</tr>
<tr>
<td>Relative</td>
<td>Patient who refuses surgery</td>
</tr>
</tbody>
</table>

**Indications in favor of coronary artery bypass graft surgery**

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>Patient who refuses PCI</td>
</tr>
<tr>
<td>Relative</td>
<td>Complex coronary anatomic at LMCA, unsuitable for stenting (e.g., severe calcification and severe tortuosity)</td>
</tr>
</tbody>
</table>

CABG: Coronary artery bypass graft; LMCA: Left main coronary artery; PCI: Percutaneous coronary intervention.
Park & Kim compared the outcomes of PCI with paclitaxel-eluting stents versus CABG for unprotected LMCA stenosis in a subgroup analysis from the randomized study cohort [30]. As shown in the subset of LMCA disease comprising 348 patients receiving CABG and 357 receiving PCI, PCI (15.8%) demonstrated equivalent 1-year clinical outcomes compared with CABG (13.7%; \( p = 0.44 \)). Of interest was the CABG (13.7%) versus PCI (15.8%) revascularization benefit as the primary endpoint of the study. This study was the first to provide a comparative answer to the question of a specific cohort of patients with unprotected LMCA stenosis.

Another randomized study, the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial, is being performed in Korea randomizing 600 patients with unprotected LMCA patients with either CABG or PCI with sirolimus-eluting stents. This study is a noninferiority design with the primary endpoint of the study.

### Technical considerations

**Stenting procedure**

- Stenting for ostial or body LMCA lesions appears to be a simple alternative stenting technique for nonbifurcation LMCA coronary lesions. For instance, a brief and maximal stent expansion is required to get optimal stent expansion and to avoid ischemic complication.

- 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, is more complex and technically demanding. In general, the selection of an appropriate stenting strategy is dependent on the plaque configuration of the LMCA bifurcation. The selection of an appropriate stenting strategy is determined by the plaque configuration of the LMCA bifurcation. For instance, a brief and maximal stent expansion is required to get optimal stent expansion and to avoid ischemic complication.

### Table 2. Comparing drug-eluting stents to coronary artery bypass graft surgery for unprotected left main coronary artery stenosis.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Registry</th>
<th>Registry</th>
<th>Registry</th>
<th>Randomized study</th>
<th>Registry</th>
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</thead>
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<td>PCI with SES, CABG</td>
<td>PCI with SES, CABG</td>
<td>PCI with BMS, DES</td>
<td>PCI with BMS, DES</td>
</tr>
<tr>
<td>No. of patients</td>
<td>107</td>
<td>142</td>
<td>50</td>
<td>123</td>
<td>157</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64</td>
<td>68</td>
<td>72</td>
<td>70</td>
<td>73*</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>52</td>
<td>52</td>
<td>51</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>EuroSCORE or Parsonnet score (Lee)</td>
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<td>4.3</td>
<td>18*</td>
<td>13</td>
<td>6*</td>
</tr>
</tbody>
</table>

### Initial clinical outcomes

<table>
<thead>
<tr>
<th>In-hospital</th>
<th>30 days</th>
<th>30 days</th>
<th>30 days</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>9</td>
<td>26</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>TVR (%)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Any MACE (%)</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Cerebrovascular accident (%)</td>
<td>0</td>
<td>1.4</td>
<td>2*</td>
<td>17</td>
</tr>
</tbody>
</table>

### Long-term clinical outcomes

<table>
<thead>
<tr>
<th>Cumulative after discharge</th>
<th>Kaplan–Meier</th>
<th>Cumulative</th>
<th>At 1 year</th>
<th>Kaplan–Meier at 3 years for propensity-matched cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up (months)</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Death (%)</td>
<td>2.8</td>
<td>6.4</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>0.9</td>
<td>1.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TVR (%)</td>
<td>19.6*</td>
<td>3.6</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular accident (%)</td>
<td>0.9</td>
<td>0.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Any events (%)</td>
<td>NA</td>
<td>NA</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

*p < 0.05 between PCI vs CABG.

BMS: Bare-metal stent; CABG: Coronary artery bypass graft; DES: Drug-eluting stent; MACE: Major adverse cardiac events including death, myocardial infarction and TVR; NA: Not available; PCI: Percutaneous coronary intervention; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; TVR: Target vessel revascularization.
single-stent strategy. Therefore, systemic treatment with a two-stent strategy for all LMCA bifurcation lesions, such as T-stenting, Kissing stenting, the 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.

### Intravascular ultrasound

Intravascular ultrasound is considered to be 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 suggested that the clinical impact of IVUS-guided stenting for LMCA with DES did not show a significant clinical long-term benefit compared with 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 optimal stenting procedure in unprotected LMCA stenosis. In fact, angiography is limited in assessing the true luminal size of the LMCA because the left main artery is often short and lacks a normal segment for comparison. Therefore, the severity of LMCA stenosis is often underestimated by the misinterpretation of the normal segment adjacent to the focal stenosis. In addition to the actual assessment of LMCA lesions before the procedure, use of IVUS is very helpful to get 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 registry reported the very interesting finding that IVUS guidance was associated with improved long-term mortality compared with conventional angiography-guided procedures [23]. With an adjustment using propensity-score matching, for 201 matched pairs, there was a strong tendency to 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 beyond 1 year. Therefore, despite inherent limitations of nonrandomized registry design, this study indicates that IVUS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Any stent (542 pairs)</td>
<td>1.18 (0.77, 1.80)</td>
</tr>
<tr>
<td></td>
<td>BMS (207 pairs)</td>
<td>1.04 (0.59, 1.83)</td>
</tr>
<tr>
<td></td>
<td>DES (396 pairs)</td>
<td>1.36 (0.80, 2.30)</td>
</tr>
<tr>
<td>Death, MI or stroke</td>
<td>Any stent</td>
<td>1.10 (0.75, 1.62)</td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td>0.86 (0.50, 1.49)</td>
</tr>
<tr>
<td></td>
<td>DES</td>
<td>1.40 (0.33, 2.22)</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>Any stent</td>
<td>4.76 (2.80, 8.11)</td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td>10.70 (3.80, 29.90)</td>
</tr>
<tr>
<td></td>
<td>DES</td>
<td>5.96 (2.51, 14.10)</td>
</tr>
</tbody>
</table>

**Figure 2. Hazard ratios for clinical outcomes after stenting as compared with coronary artery bypass graft among propensity-matched patients from the MAIN-COMPARE registry.** Hazard ratios were measured between any stent versus any CABG, BMS vs contemporary CABG, and DES versus contemporary CABG after propensity-matching adjustment in each cohort. BMS: Bare-metal stent; CABG: Coronary artery bypass graft; DES: Drug-eluting stent; MI: Myocardial infarction.

Data taken from [21].
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 [58–62]. 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 was widely used in an attempt to reduce restenosis by the removal of plaque burden. However, after the introduction of DES, the role of debulking is more limited due to the dramatic benefit in restenosis reduction. A study suggested a viable role of debulking atherectomy even in the DES era for 99 coronary bifurcations [63]. Of interest, debulking in the main branch and side branch for LMCA stenoses allowed single-stenting in 60 out of the 63 LMCA bifurcation stenoses. Surprisingly, at 1-year follow-up, no serious adverse event had occurred. This study indicates that debulking may be preferably used in LMCA bifurcations in order to aid a provisional single-stenting strategy. In addition, debulking still plays a limited role in facilitating stent delivery. In a patient illustrated in Figure 3, debulking was used to remove the plaque in the LMCA inhibiting advancement of the wire into the left anterior descending artery. Similarly, 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 are limited, debulking atherectomy or rotablator still has 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.

Figure 3. Debuling coronary atherectomy followed by provisional stenting for a 71-year-old man. (A and B) baseline angiograms; (C) debulking due to a difficulty in the advancement of the wire into the left anterior descending artery; (D) successful wiring; (E and F) final angiograms after provisional stenting with three 2.5–33mm, 3.0–23mm and 3.5–18mm Cypher® sirolimus-eluting stents (Cordis Corp, Johnson & Johnson, Warren, NJ, USA).
for LMCA stenosis. Old age, MI, cardiogenic shock and decreased left ventricular ejection fraction are common clinical conditions requiring elective or provisional hemodynamic support. Among the hemodynamic support devices, which include intraaortic balloon pumps, percutaneous hemodynamic support devices or left ventricular assist devices, the intraaortic balloon pump has most frequently been used. Although there is no doubt that provisional use of an intraaortic balloon pump in patients with hemodynamic compromise is necessary for a successful procedure, from the literature, the prevalence of planned use of balloon pump varies considerably. A study recently suggested the role of intraaortic balloon pump support from 219 elective LMCA interventions [64]. They used a prophylactic balloon pump for a broad range of patients with distal LMCA bifurcation lesions, a low ejection fraction of less than 40%, use of debulking devices, unstable angina and critical right coronary artery disease. In that study, interestingly, although the patients receiving elective intraaortic balloon pump support had a more complex clinical risk profile, the rate of procedural complications was lower than those not receiving its support (1.4 vs 9.3%; p = 0.032). Therefore, at least, its elective use needs to be positively considered for patients with a high-risk condition such as multivessel disease, complex LMCA anatomy, low ejection fraction or unstable presentations. Hopefully, the new support devices, such as TandemHeart® (CardiacAssist, Pittsburgh, PA, USA) or the Impella Recover LP 2.5 System (Impella® CardioSystems, Aachen, Germany) may improve the feasibility of implementing these devices and improve complication rates.

- **Antithrombotics**

Although the reported incidence of stent thrombosis in DES treatment for LMCA lesions was very low [65], fear of stent thrombosis remains a major concern preventing more generalized use of DES. Therefore, careful administration of antiplatelet agents is a very important treatment to prevent the occurrence of stent thrombosis. In fact, premature discontinuation of clopidogrel was strongly associated with stent thrombosis in several studies [32,66]. Therefore, as generally recommended, dual antiplatelet therapy including aspirin and clopidogrel (or ticlopidine) should be maintained to 1 year. If the patients appear to be 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 [66]. After stopping clopidogrel between 31 to 180 days, the risk of cardiac death or MI was 4.20 (p = 0.009) compared with stopping between 181 to 36 days. Furthermore, in some institutions in Asian countries, adjunctive administration of cilostazol has been used for the purpose of reducing thrombotic complications [67].

Aggressive use of antithrombotics should also be considered for complex lesion anatomy or unstable coronary conditions. For example, as shown in previous studies, use of a glycoprotein IIb/IIIa inhibitor may play a role in reducing procedure-related thrombotic complications including death or MI [68]. However, the additive role of the glycoprotein IIb/IIIa inhibitor, cilostazol, low-molecular-weight heparin, direct thrombin inhibitors or other new drugs in DES treatment for LMCA lesions needs to be investigated in future studies. Until evidence is accumulated, an aggressive combination of antithrombotic drugs before, during or after the procedure should be considered to avoid thrombotic complications for high-risk patients. Although what constitutes high risk is not well delineated, off-label use of DES, such as diabetes mellitus, multiple stenting, long DES, chronic renal failure, or presentation with MI is a good index of high-risk procedure [69].

**Future perspective**

Current studies, although limited by nonrandomized study design, small sample size and short-term follow-up, have shown the procedural and mid-term safety and effectiveness of DES to be promising compared with treatment with BMS or CABG. With these attempts, in our opinion, PCI with DES will progressively increase and can be recommended as a 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 for the percutaneous approach, we are still optimistic as further studies on novel procedural techniques, new dedicated stent platforms and optimal pharmacotherapies may improve outcomes. Furthermore, we hope that with the upcoming randomized clinical trials comparing PCI to CABG for unprotected LMCA stenosis, more confidence in the long-term safety, durability and efficacy of PCI will occur in the near future.
Executive summary

**Long-term mortality after drug-eluting stent placement for unprotected left main coronary artery stenosis**
- Comparable incidence compared with bare-metal stent (BMS) treatment.
- Requires longer follow-up study.

**Risk of stent thrombosis after drug-eluting stent treatment**
- Comparable incidence compared with BMS in current studies.
- Reported incidence of less than 2% in elective procedure.

**Risk stratification model for prediction of poor prognosis**
- Good prediction of long-term mortality with EuroSCORE, which is representative of clinical risks.
- Long-term prediction with angiographic SYNTAX score.

**Repeat revascularization after drug-eluting stent treatment**
- Very low incidence (<5%) for ostial or shaft left main coronary artery lesions.
- Relatively higher risk for left main coronary artery bifurcation lesions.
- Lower revascularization rate with use of simple stenting compared with complex stenting, for bifurcation lesions.

**Drug-eluting stents compared with bypass surgery**
- Comparable long-term mortality or myocardial infarction between the two treatments.
- Higher or comparable risk of revascularization with use of drug-eluting stents.

**Technical considerations**
- Preference for provisional stenting for left main coronary artery bifurcation lesions with normal left circumflex artery.
- Strong recommendation for intravascular ultrasound during stenting.
- Dual antiplatelet therapy with aspirin and clopidogrel for at least 1 year.
- Mechanical support device for hemodynamic instability or complex lesions.
- Selective use of debulking atherecotomy or rotablator device for lesion preparation.

### Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

### Bibliography

**Papers of special note have been highlighted as:**
- of interest


2. Landmark study making coronary artery bypass graft (CABG) surgery the standard therapy for unprotected left main coronary artery (LMCA) stenosis.


6. First study showing the feasibility of drug-eluting stents for unprotected LMCA stenosis.


16* First randomized study comparing the outcomes of drug-eluting stents versus CABG.


* The largest registry comparing the outcomes of stenting versus CABG for unprotected LMCA stenosis in a nation-based registry.


Randomized study comparing outcomes of the two current drug-eluting stents.


