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What is This?
Unprotected left main coronary stenting as alternative therapy to coronary bypass surgery in high surgical risk acute coronary syndrome patients

Hany D. Abdelmalak, Hesham R. Omar, Devanand Mangar and Enrico M. Camporesi

Abstract: Acute coronary syndrome has a high mortality rate that dramatically increases in the presence of left main coronary artery (LMCA) disease. Over the past decades, coronary artery bypass graft (CABG) surgery has been commonly accepted as the standard of care for patients with LMCA stenosis and is still considered the first-line treatment in current practice guidelines. Percutaneous coronary intervention (PCI) of protected and unprotected LMCA has gained popularity and is increasingly utilized with comparable outcomes to CABG in randomized controlled trials. In-stent restenosis and the need for revascularization provide the main obstacle to LMCA revascularization. The advent of better PCI equipment, stents, ablative devices, intravascular ultrasound, hemodynamic support devices and antithrombotic agents have ignited a renewed interest in the practice of LMCA PCI, especially for high surgical risk patients who are neither candidates nor agreeable to CABG surgery. Herein, we review the studies comparing unprotected LMCA stenting with CABG surgery in regard to 3 main endpoints: mortality, major adverse events and the incidence of repeat revascularization.

Keywords: left main coronary artery disease, left main stenting, left main stenosis
right coronary artery (RCA). Over the past decade, stenting of the LMCA has been increasingly utilized in certain high surgical risk patients averted the need for CABG surgery. However most studies were performed with small samples, in single centers, and after short-term follow up. The main concern with unprotected LMCA stenting is the peri-procedural complications including dissection, thrombosis, in-stent restenosis (ISR) and the need for revascularization. The increased elastic and smooth muscle fiber within LMCA makes recoil and restenosis a feared problem after balloon angioplasty. However, the recent advances in PCI equipment, drug eluting stents (DESs), ablative devices, intravascular ultrasound (IVUS) and hemodynamic support devices, in addition to the evolution of dual antiplatelet therapy (DAPT), have spread optimism to accept LMCA percutaneous revascularization as a reasonable alternative for CABG surgery.

Studies reported 0–4% in-hospital mortality for LMCA stenting [Agostoni et al. 2005; Chieffo et al. 2005; Valgimigli et al. 2005; Silvestri et al. 2000; Takagi et al. 2002], which is comparable with the 3.5% postoperative mortality in LMCA disease treated with CABG surgery [Keogh, 2002]. However, due to the estimated 22% incidence of ISR reported in PCI-treated patients [Park et al. 1998], LMCA disease is primarily managed by CABG. Three single-center observational studies [Chieffo et al. 2006; Lee et al. 2006; Palmerini et al. 2006] and a small-scale randomized trial [Buszman et al. 2008] have concluded that there is no statistically significant difference in the intermediate term mortality between LMCA stenting and CABG for LMCA disease. The catheter-based reperfusion of unprotected left main stenosis during an acute MI, the ULTMA (Unprotected Left Main Trunk Intervention Multi-center Assessment) registry found that patients with LMCA disease who underwent stenting were sicker than their CABG counterparts, which might explain the better long-term results with CABG surgery [Marso et al. 1999].

The work by Wu and colleagues confirmed the same findings [Wu et al. 2008]. The outcome of the SYNTAX (SYNergy between PCI with TAXus and cardiac surgery) trial, the first randomized controlled trial with all-comers design that compared CABG with PCI using DESs for LMCA and three-vessel coronary artery disease (CAD) [Morice et al. 2010], demonstrated comparable safety and efficacy with both approaches but with a trade-off for higher incidence of repeat revascularization at 1-year in the PCI group. However, in subgroup analysis according to the number of additionally affected vessels and the complexity of lesions (SYNTAX score) the sample was unacceptably small. A few months later, a randomized study on 201 patients concluded that DESs were inferior to CABG with regard to freedom from major adverse cardiovascular events (MACE) and repeat revascularization but with no significant difference in death or MI [Boudriot et al. 2011]. Other comparative studies showed a trend towards favorable early outcome of PCI in comparison with CABG and agreed with the associated increased incidence of revascularization. The complexity of coronary anatomy is a main obstacle for LMCA PCI. Although it is reasonable that CABG surgery is more effective for patients with more complex coronary anatomy, this needs to be supported by randomized trials. In some centers, PCI has now become a feasible alternative for patients with LMCA disease who are neither candidates nor agreeable to CABG surgery. Herein, we review the literature in regard to the main outcomes of unprotected LMCA stenting compared with CABG surgery for patients with LMCA disease.

**Review of literature**

We reviewed the literature for studies that compared the outcome of CABG versus PCI in treating LMCA disease. The review is based on data published in scientific journals indexed by the PubMed and Medline databases using the following keywords: ‘unprotected left main stenting’, ‘left main stenosis’ and ‘CABG versus stenting for left main disease’. Articles in English were included up to August 2011. A total of 18 studies were found and data for three main endpoints were compiled: major adverse cardiovascular and cerebrovascular events (MACCE); long-term mortality; and target vessel revascularization (TVR).

**Incidence of revascularization in both groups**

It is clear that most studies agreed that TVR was significantly higher in patients with LMCA disease treated with PCI. ISR has been the major contributing factor to the inferiority of PCI in treating LMCA disease. Incidence of restenosis at 6 months has been found to reach 25.7% [Colombo et al. 2004] and is mainly observed in patients with distal bifurcated LMCA disease, which has a prevalence of 36.9% [Das and Meredith, 2007; Giannoglou et al 2006]. TVR is six-fold higher in patients with bifurcational
stentosis compared with nonbifurcational lesions [Valgimigli et al. 2006]. Distal bifurcational lesions have been associated with higher incidence of restenosis at the origin of the LCX in three major studies [Chieffo et al. 2005; Valgimigli et al. 2005; Park et al. 2005]. One study evaluated the outcome of stenting of LMCA in regard to the site of lesion and concluded a significant increase in MACE at 1 year (p = 0.014) and 2 years (p = 0.002) in the group with distal bifurcated lesions [Chen et al. 2009]. Kim and colleagues found a significantly lower angiographic restenosis and TVR with the use of DESs compared with bare metal stents (BMSs) [5.4% versus 12.1%; hazard ratio (HR) 0.40; 95% confidence interval (CI) 0.22–0.73;p = 0.003] [Kim et al. 2009]. However, a major concern since the evolution of DESs is stent thrombosis [Omar et al. 2012], which is especially important when more than one DES is used with overlapping struts increasing drug dosage and impairing re-endothelialization [Finn et al. 2005]. For this reason, the US 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 patients with unprotected LMCA stentosis.

Another factor explaining the increased incidence of revascularization in the PCI group is the significantly higher rate of follow-up angiography. In one study, 73% of patients in the PCI group versus 14.6% in the CABG group received coronary angiography, underestimating the number of patients with asymptomatic graft stenosis or occlusion [Seung et al. 2008]. Moreover, LMCA disease is frequently associated with significant calcification and other multivessel stenoses [Price et al. 2006].

Is there any mortality benefit with either approach?
The Society of Thoracic Surgeons (STS) National Database reported an in-hospital mortality of 3.9% in patients with LMCA disease undergoing CABG surgery [STS, 1999] and the Cleveland clinic foundation reported an in-hospital and 1-year mortality of 2.3% and 11.3%, respectively [Ellis et al. 1998]. These numbers were comparable with patients undergoing PCI for unprotected LMCA disease. As is clear from Table 1, most studies did not find a statistically significant difference in long-term mortality between PCI and CABG despite the complexity of patient population in the PCI group. One study showed a significant survival benefit [Wu et al. 2008] with a mortality rate (when including all patients from 1 January 2000 to 31 December 2004) of 5.93% in CABG versus 17% in PCI patients (HR 0.32, CI 0.14–0.71; p = 0.003). However, in the DES era (between 10 January 2003 and 31 December 2004), the difference in mortality between the PCI and CABG group was insignificant (HR = 0.73, p = 0.69). Interestingly, in a later study, there was a trend toward lower mortality after PCI compared with CABG with propensity score analysis (p = 0.06); however, results did not reach significance [Wu et al. 2010].

The 5-year survival after PCI or CABG for LMCA disease was evaluated by two studies [Park et al. 2010; Chieffo et al. 2010], which found no significant difference between both approaches. Mortality in the elderly patients >75 years was evaluated in three studies [Ghenim et al. 2009; Rittger et al. 2011; Palmerini et al. 2007]. After adjusting for the propensity score, patients treated with DESs had a nonsignificant trend towards better survival (HR = 0.81, 95% CI 0.37–1.81) [Palmerini et al. 2007].

Predictors of mortality were determined by several studies. Kim and colleagues demonstrated that high surgical risk represented by high EuroSCORE or Parsonnet score were independent predictors of death or myocardial infarction after PCI for unprotected LMCA disease [Kim et al. 2008]. Brener and colleagues showed two predictors of mortality at 3 years to be a high Euroscore (HR 1.33, 95% CI 1.16–1.54; p < 0.001) and diabetes mellitus (HR 1.96, 95% CI 1.24–3.09; p = 0.004) [Brener et al. 2008]. In one study, the predictors of mortality at 2 years were: peripheral vascular disease, left ventricular ejection fraction and acute coronary syndrome (ACS) [Palmerini et al. 2007]. Reduced left ventricular systolic function was the most significant independent predictor of mortality in another study (HR 14.9, 95% CI 5.5–40.0, p < 0.001) [Mäkikallio et al. 2008].

MACCE and major adverse events
Three studies demonstrated a significant benefit for CABG over PCI in LMCA disease with regards to MACCE [Kang et al. 2010; Serruys et al. 2009; White et al. 2008]. The increase in MACCE was essentially driven by an increase in revascularization rate. Other studies failed to show any benefit...
### Table 1. A compilation of the three major outcomes from studies utilizing PCI versus CABG for treatment of LMCA disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>N (PCI arm)</th>
<th>Stent type</th>
<th>MACCE</th>
<th>Long-term mortality</th>
<th>Revascularization</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. [2006]</td>
<td>50</td>
<td>DES</td>
<td>At 30 days, 17% in CABG versus 2% in PCI, (p &lt; 0.01). MACCE-free survival at 6 months and 1 year was 83% and 75% in the CABG group versus 89% and 83% in the PCI group, (p = 0.2)</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.18)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.22)</td>
<td>DES is not associated with increased immediate or medium-term complications compared with CABG.</td>
</tr>
<tr>
<td>Sanmartin et al. [2007]</td>
<td>96</td>
<td>DES</td>
<td>At 30 days 2.1% in PCI and 9% in CABG, (p = 0.03). However, at 1 year, 10.4% in PCI and 11.4% in CABG, (p = 0.5) (NS)</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.37)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.02)</td>
<td>PCI provided similar clinical results at midterm compared with CABG.</td>
</tr>
<tr>
<td>Palmerini et al. [2007]</td>
<td>98</td>
<td>DES</td>
<td>Incidence of 2-year MI was 6% in CABG and 4% in DES, (p = 0.11)</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.74)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.0001)</td>
<td>No mortality difference between CABG and PCI. TLR higher in PCI group.</td>
</tr>
<tr>
<td>Wu et al. [2008]</td>
<td>135</td>
<td>DES and BMS</td>
<td>At 2 years, 5.93% in CABG versus 17% in PCI, (p = 0.005)</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.37)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.02)</td>
<td>CABG is associated with lower risk of long-term death and repeat revascularization compared with PCI.</td>
</tr>
<tr>
<td>White et al. [2008]</td>
<td>120</td>
<td>DES*</td>
<td>MACCE higher in PCI group. HR 1.83, CI 1.01 → 3.32, (p = 0.05)</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.74)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.0001)</td>
<td>Propensity-adjusted risk of mortality does not differ between PCI- and CABG-treated groups.</td>
</tr>
<tr>
<td>Buszman et al. [2008]</td>
<td>52</td>
<td>DES and BMS</td>
<td>PCI had lower 30-day risk of MAE (p &lt; 0.006) and MACCE (p = 0.03) and shorter hospitalization (p &lt; 0.0007) but total MACCE-free 1-year survival was comparable</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.37)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.02)</td>
<td>PCI group had a favorable early outcome in comparison with CABG group. After 2 years, MACCE-free survival was similar, with trend towards better survival with PCI.</td>
</tr>
<tr>
<td>Makikallio et al. [2008]</td>
<td>49</td>
<td>DES</td>
<td>4% in PCI versus 11% in CABG, (p = 0.136)</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.37)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.02)</td>
<td>PCI for selected LMCA disease patients results in short- and midterm outcomes comparable with CABG.</td>
</tr>
<tr>
<td>Brener et al. [2008]</td>
<td>97</td>
<td>DES and BMS**</td>
<td>3-year mortality 15% in CABG versus 20% in PCI, (p = 0.14)</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.37)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.02)</td>
<td>PCI had 3-year survival similar to CABG.</td>
</tr>
<tr>
<td>Serruys et al. [2009]</td>
<td>903</td>
<td>PES</td>
<td>17.8% in PCI versus 12.4% in CABG, (p = 0.002). Higher risk of stroke in CABG group 22% versus 0.6% in PCI, (p = 0.003)</td>
<td>Freedom from death at 1 year: 85% in CABG versus 96% in PCI, (p = 0.37)</td>
<td>Freedom from TVR at 1 year: 95% in CABG versus 87% in PCI, (p = 0.02)</td>
<td>CABG remains the gold standard of care for patients with LMCA disease due to lower rates of combined endpoint of MACCE at 1 year.</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
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<th>Revascularization</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ghenim et al. [2009]</td>
<td>105</td>
<td>DES</td>
<td>At 1 year, 13.9% in CABG versus 14.9% in PCI, $p = 0.841$ ***</td>
<td>1% in CABG versus 13.9% in PCI, $p &lt; 0.001$</td>
<td>In patients with high probability of being treated with PCI (old age, high Euroscore, high creatinine, single vessel disease), MACCE was significantly lower. Incidence of repeat revascularization was significantly higher in PCI group.</td>
<td></td>
</tr>
<tr>
<td>Wu et al. [2010]</td>
<td>131</td>
<td>DES⁣</td>
<td>27% in PCI versus 22% in CABG, $p = 0.42$</td>
<td>4.6% in PCI versus 9.4% in CABG; propensity score–adjusted HR 0.34, $p = 0.06$</td>
<td>18% in PCI versus 9% in CABG, $p = 0.02$. However, ischemic TVR was not significantly different between both groups, $p = 0.16$</td>
<td>At 4-year follow up, MACCE were similar in both PCI and CABG groups, with a trend toward lower mortality after PCI. DES were associated with a higher TVR but ischemic TVR was comparable in both groups.</td>
</tr>
<tr>
<td>Morice et al. [2010]</td>
<td>357</td>
<td>PES</td>
<td>13.7% in CABG versus 15.8% in PCI, $p = 0.44$. Stroke mortality was 4.4% in CABG versus 4.2% in PCI, $p = 0.88$</td>
<td>11.8% in PCI versus 6.5% in CABG, $p = 0.02$</td>
<td>At 1 year, all-cause mortality was 4.4% in CABG versus 4.2% in PCI, $p = 0.88$. However, ischemic TVR was not significantly different between both groups, $p = 0.16$</td>
<td>Revascularization with PCI was comparable with CABG at 1 year.</td>
</tr>
<tr>
<td>Park et al. [2010]</td>
<td>1102</td>
<td>DES and BMS ‡‡</td>
<td>HR of PCI versus CABG was 1.02 [CI 0.74 – 1.39], $p = 0.91$</td>
<td>HR of PCI versus CABG was 4.55 [CI 2.88 – 7.2], $p &lt; 0.001$</td>
<td>At 5 years, HR for PCI versus CABG was 1.02 [CI 0.74 – 1.39], $p = 0.91$</td>
<td>At 5 years, there was no significant difference in death or MAACE, but higher revascularization in PCI group.</td>
</tr>
<tr>
<td>Chieffo et al. [2010]</td>
<td>107</td>
<td>DES ‡</td>
<td>At 5 years, 32.4% in PCI versus 38.3% in CABG, Adjusted OR 1.57, $p = 0.18$</td>
<td>At 5 years, cardiac death 11.9% in CABG versus 7.5% in PCI, Adjusted OR 0.502, $p = 0.24$</td>
<td>At 5 years, cardiac death 11.9% in CABG versus 7.5% in PCI, Adjusted OR 0.502, $p = 0.24$</td>
<td>At 5 years, there was no significant difference in death or MAACE, but higher revascularization in PCI group.</td>
</tr>
<tr>
<td>Kang et al. [2010]</td>
<td>205</td>
<td>DES ††</td>
<td>35.1% in PCI versus 21.8% in CABG, $p = 0.001$</td>
<td>14.1% in PCI versus 12.1% in CABG, $p = 0.428$</td>
<td>22.4% in PCI versus 5.1% in CABG, $p = 0.0004$</td>
<td>At 5 years, there was no difference in MACCE between PCI and CABG but PCI had less composite endpoints of death, MI and/or stroke. CABG had benefit of less intervention.</td>
</tr>
<tr>
<td>Shimizu et al. [2010]</td>
<td>64</td>
<td>DES †††</td>
<td>At 2 years, MACCE-free survival 82.2% in CABG versus 62.6% in PCI, $p = 0.033$</td>
<td>At 2 years, overall survival 91.9% in PCI versus 93.4% in CABG, $p = 0.288$</td>
<td>23.4% in PCI versus 1.6% in CABG</td>
<td>PCI is safe comparable to CABG but with the added risk of increased repeat revascularization. CABG is more cost-effective and can still be the first revascularization strategy. Total hospitalization costs were lower in CABG group ($p = 0.013$).</td>
</tr>
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(Continued)
Although MACCE was greater in the PCI group (HR 1.83, 95% CI 1.01 to 3.32; \(p = 0.05\)) in the study by White and colleagues, MACCE-free survival was not different in propensity-matched individuals [White et al. 2008]. On the other hand, several studies found a significant increase in stroke risk in the CABG group. Serruys and colleagues concluded that the rate of stroke was significantly higher with CABG (2.2% versus 0.6% with PCI; \(p = 0.003\)) even after adjustment for confounding variables including carotid artery disease and other stroke risk factors [Serruys et al. 2009]. In the SYNTAX trial, stroke was also significantly higher at 1 year in the CABG arm (2.7% in CABG versus 0.3 in PCI; \(p = 0.009\)).

Furthermore, some studies showed a statistically significant lower risk of major adverse events (MAEs) and MACCE in the PCI group at 30 days. Buszman and colleagues demonstrated a lower incidence of MAEs in the PCI group at 30 days (8% in PCI versus 28% in CABG, 95% CI 0.64–0.94; \(p = 0.006\)) and lower MACCE (2% in PCI versus 13% in CABG, 95% CI 0.79–0.99; \(p = 0.003\)) in addition to shorter hospitalization; \(p = 0.0007\) [Buszman et al. 2008]. Sanmartín and colleagues showed a decreased incidence of MACCE at 30 days in the PCI group (2.1% in PCI versus 9% in CABG; \(p = 0.03\)) [Sanmartín et al. 2007]. In another study the 30-day MACCE was 2% in the PCI group versus 17% in the CABG group in addition to longer hospitalization of the CABG group (\(p < 0.01\)) [Lee et al. 2006]. In all three studies, however, long-term MAE- and MACCE-free survival were comparable in both groups [Buszman et al. 2008; Sanmartín et al. 2007; Lee et al. 2006].

In the SYNTAX study, predictors of MACCE at 1 year were emergent revascularization, diabetes mellitus and higher Euroscore, whereas female gender was associated with significantly reduced MACCE [Morice et al. 2010]. Bifurcation involvement was determined to be a predictor of MACE in another study (HR 12.9, 95% CI 1.36–122.45; \(p = 0.0259\)) [Kim et al. 2008]. Lee and colleagues determined the predictors of MACCE to be Parsonnet score, diabetes mellitus and MI [Lee et al. 2006]. Another factor found to affect MACCE was whether CABG was performed on-pump versus off-pump. In-hospital MACCE was lower in patients with off-pump surgery (19.6%
versus 36% with on-pump CABG; \( p = 0.04 \) and this benefit was maintained at 1 year (MACCE 30.3% versus 43% with on-pump CABG; \( p = 0.15 \)) [Chieffo et al. 2006].

**Conclusion**

The review emphasizes that stenting of LMCA disease can be a therapeutic option, with promising short- and intermediate-term results, in high surgical risk patients presenting with ACS due to LMCA disease. The safety profile suggested by these observational and randomized trials suggest that PCI for LMCA disease might be an alternative to CABG surgery in patients with significant comorbidities increasing their surgical risk if the patient is willing to accept the higher incidence of repeat revascularization. Further randomized trials are mandatory to directly address the safety and long-term outcome of LMCA stenting.

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**Conflict of interest statement**

The authors declare no conflicts of interest in preparing this article.

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