Left Main Coronary Artery Stenosis

A Meta-Analysis of Drug-Eluting Stents Versus Coronary Artery Bypass Grafting

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CME Objective for This Article: At the completion of this article the learner should be able to:
1. Discuss the relationship between late stent thrombosis and MACCE in patients undergoing PCI with DES for unprotected left main stenosis;
2. Decrease target vessel revascularization rates in patients with diabetes or high SYNTAX scores by considering CABG over PCI;
3. Tailor the discussion of PCI vs. CABG to each patient’s risk profile so as to manage the long-term risk of MI or stroke.

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Left Main Coronary Artery Stenosis
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Objectives The goal of this study was to provide a systematic review comparing the long-term outcomes of percutaneous coronary intervention (PCI) with drug-eluting stents (DES) versus coronary artery bypass graft surgery (CABG) for unprotected left main coronary artery (UPLM) stenosis.

Background One-year outcomes from randomized controlled trials, observational studies, and pooled analyses have demonstrated the safety and efficacy of PCI of the UPLM when compared with CABG. However, there remain concerns over the sustainability of PCI with DES at longer follow-up.

Methods Studies published between January 2000 and December 2012 of PCI versus CABG for UPLM stenosis were identified using an electronic search and reviewed using meta-analytical techniques.

Results Twenty-four studies comprising 14,203 patients were included in the analysis. There was no significant difference for all-cause mortality between PCI or CABG at 1 year (odds ratio [OR]: 0.792, 95% confidence interval [CI]: 0.53 to 1.19), 2 years (OR: 0.920, 95% CI: 0.67 to 1.26), 3 years (OR: 0.94, 95% CI: 0.60 to 1.48), 4 years (OR: 0.84, 95% CI: 0.53 to 1.33), and 5 years (OR: 0.79, 95% CI: 0.57 to 1.08). The need for target vessel revascularization (TVR) was significantly higher in patients undergoing PCI at all time points. The occurrence of stroke, however, was significantly less frequent in patients treated with PCI. The occurrence of nonfatal myocardial infarction showed a statistically significant trend towards a lower incidence in CABG patients at 1 year (OR: 1.62, 95% CI: 1.05 to 2.50), 2 years (OR: 1.60, 95% CI: 1.09 to 2.35), and 3 years (OR: 2.06, 95% CI: 1.36 to 3.1). There was no significant difference in combined major adverse cardiovascular and cerebrovascular events between the 2 groups.

Conclusions Our findings suggest that PCI with DES is a safe and durable alternative to CABG for the revascularization of UPLM stenosis in select patients at long-term follow-up. (J Am Coll Cardiol Intv 2013;6:1219–30) © 2013 by the American College of Cardiology Foundation

In recent years, 12-month outcomes after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) of the unprotected left main coronary artery (UPLM) have consistently been shown to be noninferior to coronary artery bypass graft surgery (CABG) (1,2). This has been reflected in the current American College of Cardiology/American Heart Association guidelines, with PCI of the UPLM being upgraded from a Class III indication in 2006 to a Class IIb indication in 2009 and to a Class IIa indication in 2011, when anatomy is favorable for PCI and surgical risk is high (3). Longer follow-up of the landmark SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (4), however, has raised concerns over the durability and safety of PCI over CABG in high-risk lesions after early success. At 5 years (4), the difference between surgery and stenting in the SYNTAX trial showed a trend in favor of CABG for all-cause death (9.2% vs. 14.6%, p = 0.006), cardiac death (4.0% vs. 9.2%, p < 0.001), and myocardial infarction (MI) (3.3% vs. 10.6%, p < 0.001). The 21 composite endpoint of death/stroke/MI was similarly less frequent in patients undergoing CABG (14% vs. 22%, p < 0.001). Also observed was a slow catch-up for stroke risk, with the difference in stroke that was initially significant and in favor of PCI (1) (0.6% vs. 2.2%) being no longer present (3.0% vs. 3.4%, p = 0.66) at 5 years. Outcomes in the left main coronary artery subset at follow-up did not show this trend; nonetheless, the study was underpowered for subset analyses. Similar to in the SYNTAX trial, the early advantages of PCI over CABG has been shown to progressively shift to CABG over time in certain other coronary interventions (5). There are also concerns over the long-term safety of DES, with reference to increased MI and death driven primarily by late and very late stent thrombosis. We therefore undertook a systematic review to compare the temporal and long-term outcomes of CABG versus PCI with DES for UPLM stenosis (UPLMS).

Methods

Study selection. We conducted a systematic review of the published data on CABG versus PCI with DES for UPLM stenosis following QUOROM (Quality of Reporting of
Meta-Analyses) (6) and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines (7). The authors performed data collection from 3 online databases: Medline (PubMed), Cochrane Collaboration of Clinical Trials, and Google Scholar. The searches were limited by date and extended from January 2000 to December 2012.

The primary search term used was “left main.” A secondary search was carried out combining the term “left main” with “CABG,” “PCI,” and “DES.” For the Cochrane database, the search terms were limited by the term “clinical trial.” We subsequently limited the search parameters to the English language. The primary search term was also used in various combinations with the secondary search terms to retrieve relevant papers. We screened citations at the title and abstract level, and retrieved papers as full reports if they were clinical studies; we then compared PCI of the left main coronary artery to CABG and provided information on the outcomes. The full text of all potential papers were reviewed in detail. The bibliographies of retained studies was used to seek additional relevant studies.

**Inclusion criteria.** Studies were included if the following criteria applied: 1) comparative trials (randomized controlled trials [RCTs] and nonrandomized) of CABG versus PCI with DES stent placement; 2) unprotected left main stenosis of >50% narrowing; 3) minimum of 30 patients in the PCI arm with at least 75% receiving DES; and 4) a minimum follow-up of 1 year or more. When 2 similar studies were reported from the same institution or author, the most recent publication was included in the analysis. The 30-patient threshold was selected to comprehensively identify all available evidence on the use of DES versus CABG for the UPLMS. The penetration rate of DES use in the U.S. PCI population has been estimated to be around 76.9% (8). We therefore included reports with 75% to 100% DES use but studies with <75% DES use were excluded.

**Exclusion criteria.** Studies were excluded if any of the following criteria applied: 1) duplicate publication; 2) lack of minimum of 1-year follow-up; 3) outcomes of interest were not clearly reported or were impossible to extract or calculate from the published results; and 4) single-arm studies.

**Data extraction.** The primary studies were reviewed multiple times by both G.A. and E.P. to establish familiarity with the findings. The items for data extraction, the data extraction sheet, and the methodology for event count extraction were then standardized before data collection. Information collected included first author, year and journal of publication, study design, inclusion/exclusion criteria, definition of primary and secondary endpoints, number of subjects included, subjects undergoing PCI and CABG, percentage of DES used, study population demographics, left main stenosis location (ostial, mid-shaft, or distal), number of diseased vessels, stenting technique used to treat bifurcation lesions, type of CABG (on pump vs. off pump), left internal mammary artery graft used (single vs. double), follow-up time period, rates of angiographic follow-up, antiplatelet regimen used, and primary and secondary outcomes. Ignoring variable definitions, event counts for the primary (death, MI, stroke, and percutaneous coronary intervention [TVR]) and secondary outcomes (combined major adverse cardiovascular and cerebrovascular events [MACCE]) were extracted as reported by the individual studies. There was no disagreement between the 2 reviewers (G.A. and E.P.).

**Study endpoints.** The primary endpoints were all-cause mortality, TVR, stroke, and MI at all available time points. Secondary endpoints were cardiac mortality and combined MACCE: a composite of all-cause mortality, nonfatal MI, and stroke.

**Statistical analysis.** A forest plot with combined odds ratio (OR) estimates and 95% confidence intervals (CIs) was constructed using the random effects model of DerSimonian and Laird (9). Statistical significance for OR was set at \( p < 0.05 \) (2-tailed) provided the CI did not cross 1. Heterogeneity, which was anticipated to be significant, was assessed by a Q-statistic and I^2 test. Significant heterogeneity was considered present for \( \text{p} < 0.10 \) and/or an I^2 \( \geq 50\% \). Sensitivity analysis was performed by performing: 1) a separate analysis on adjusted outcomes (RCTs, propensity-matched, propensity score–adjusted, or multivariate-adjusted data); and 2) analysis on the basis of the SYNTAX scores. An assumption of fixed proportional hazards was made for this analysis. Data analysis was performed using Meta-analyst version 1.0 (10) and Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, New Jersey) (11).

We conducted a random effects meta-regression analysis using the method of moments to investigate the impact of various study characteristics in the PCI arm on the study estimates of ORs. The natural logarithm of the OR was the dependent variable, and the number of participants, the percentage of smokers, diabetic patients, distal left main disease, isolated left main disease, left main and 3-vessel disease, and intravascular ultrasound (IVUS) use were entered as explanatory factors. The probability of obtaining a spurious explanation for variable treatment effects is high when a small number of studies are used, and we therefore chose to perform the regression analysis on outcomes that
were reported by at least 90% of the studies. The studies were grouped into early (1 to 2 years) and late (3, 4, and 5 years) follow-up.

**Results**

By using the search key words, 5,796 reports were identified, of which 188 relevant publications were identified at the abstract and title level. By applying the inclusion and exclusion criteria, 24 reports were selected for the meta-analysis (1,2) (Online Refs. e1–e22). These included 3 randomized comparisons (1,2) (Online Ref. e11) and 21 nonrandomized comparisons (Online Refs. e1–e10,e12–e22). Of the 21 nonrandomized comparisons, 16 studies provided adjusted estimates by either propensity matching or propensity score or multivariate adjustment to account for selection bias (Online Refs. e2–e6,e9,e10,e12–e19,e22). All the studies included in the analysis were published between 2006 and 2012. Analysis was performed on 14,203 patients, of whom 7,055 (49.7%) underwent PCI with stenting and 7,148 (50.3%) underwent CABG. The study characteristics and overall patient demographics are shown in Tables 1 and 2, respectively. All the studies provided enough details on the primary endpoints of all-cause mortality, stroke, and TVR. Nonfatal MI was variably reported by the primary

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**Table 1. Characteristics of Included Studies**

<table>
<thead>
<tr>
<th>First Author/Study (Ref. #)</th>
<th>Year</th>
<th>N</th>
<th>DES</th>
<th>CABG</th>
<th>DM</th>
<th>Distal LM</th>
<th>EuroSCORE (PCI)</th>
<th>EuroSCORE (CABG)</th>
<th>SYNTAX (PCI)</th>
<th>SYNTAX (CABG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morice et al. (1)</td>
<td>2008</td>
<td>705</td>
<td>357</td>
<td>348</td>
<td>25%</td>
<td>56%</td>
<td>3.9 ± 2.6</td>
<td>3.9 ± 2.9</td>
<td>296 ± 13.5</td>
<td>302 ± 12.7</td>
</tr>
<tr>
<td>Boudriot et al. (2)</td>
<td>2011</td>
<td>201</td>
<td>101</td>
<td>100</td>
<td>36%</td>
<td>74%</td>
<td>2.4 (1.5–3.7)</td>
<td>2.6 (1.7–4.9)</td>
<td>24 (19–29)</td>
<td>23 (14.8–28)</td>
</tr>
<tr>
<td>Shimizu et al. (e1)</td>
<td>2010</td>
<td>152</td>
<td>63</td>
<td>89</td>
<td>47%</td>
<td>—</td>
<td>2.7 (1.9–5.1)</td>
<td>4.9 (2.4–11.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cheffo et al. (e2)</td>
<td>2006</td>
<td>249</td>
<td>107</td>
<td>142</td>
<td>21%</td>
<td>81%</td>
<td>4.4 ± 3.6</td>
<td>4.3 ± 3.4</td>
<td>28.8 ± 10.4</td>
<td>29.4 ± 5.74</td>
</tr>
<tr>
<td>CUSTOMIZE (e3)</td>
<td>2011</td>
<td>583</td>
<td>222</td>
<td>361</td>
<td>39%</td>
<td>52%</td>
<td>6.3 ± 3.0</td>
<td>5.6 ± 2.5</td>
<td>26.0 ± 10.8</td>
<td>33.6 ± 13.0</td>
</tr>
<tr>
<td>Ghenin et al. (e4)</td>
<td>2009</td>
<td>211</td>
<td>105</td>
<td>106</td>
<td>27%</td>
<td>74%</td>
<td>8 (6–9)</td>
<td>7 (6–8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Makikallio et al. (e5)</td>
<td>2008</td>
<td>287</td>
<td>49</td>
<td>238</td>
<td>17%</td>
<td>80%</td>
<td>7.7 ± 7.5</td>
<td>5.2 ± 4.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rittger et al. (e6)</td>
<td>2011</td>
<td>287</td>
<td>95</td>
<td>192</td>
<td>36%</td>
<td>64%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>San Martin et al. (e7)</td>
<td>2012</td>
<td>371</td>
<td>129</td>
<td>242</td>
<td>34%</td>
<td>66%</td>
<td>3.9 ± 2.9</td>
<td>3.9 ± 2.9</td>
<td>296 ± 13.5</td>
<td>302 ± 12.7</td>
</tr>
<tr>
<td>Kawecki et al. (e8)</td>
<td>2012</td>
<td>145</td>
<td>34</td>
<td>111</td>
<td>28%</td>
<td>72%</td>
<td>4.7 ± 3.6</td>
<td>4.81 ± 2.67</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Luo et al. (e9)</td>
<td>2012</td>
<td>823</td>
<td>331</td>
<td>492</td>
<td>27%</td>
<td>75%</td>
<td>4 (3–6)</td>
<td>5 (4–7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Palmerini et al. (e10)</td>
<td>2007</td>
<td>259</td>
<td>98</td>
<td>161</td>
<td>28%</td>
<td>72%</td>
<td>8 (4–18)</td>
<td>7 (3–14)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PRECOMBAT (e11)</td>
<td>2011</td>
<td>600</td>
<td>300</td>
<td>300</td>
<td>32%</td>
<td>67%</td>
<td>2.6 ± 1.8</td>
<td>2.8 ± 1.9</td>
<td>24.4 ± 9.4</td>
<td>25.8 ± 10.5</td>
</tr>
<tr>
<td>Zhao et al. (e12)</td>
<td>2011</td>
<td>172</td>
<td>56</td>
<td>116</td>
<td>87%</td>
<td>13%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yi et al. (e13)</td>
<td>2012</td>
<td>512</td>
<td>243</td>
<td>269</td>
<td>36%</td>
<td>43%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kang et al. (e14)</td>
<td>2010</td>
<td>462</td>
<td>205</td>
<td>257</td>
<td>41%</td>
<td>79%</td>
<td>4.2 ± 3.9</td>
<td>5.6 ± 3.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CREDO-Kyoto 2 (e15)</td>
<td>2012</td>
<td>1,005</td>
<td>365</td>
<td>640</td>
<td>44%</td>
<td>58%</td>
<td>—</td>
<td>—</td>
<td>26.5 (21–34)</td>
<td>30 (22–40)</td>
</tr>
<tr>
<td>DELTA registry (e16)</td>
<td>2012</td>
<td>2,774</td>
<td>1,874</td>
<td>900</td>
<td>30%</td>
<td>70%</td>
<td>4.9 ± 3.6</td>
<td>5.1 ± 2.6</td>
<td>28.6 ± 14.3</td>
<td>38.9 ± 13.2</td>
</tr>
<tr>
<td>ASAN (e7)</td>
<td>2010</td>
<td>395</td>
<td>176</td>
<td>219</td>
<td>34%</td>
<td>68%</td>
<td>3.3 ± 2.7</td>
<td>4.5 ± 2.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Wu et al. (e18)</td>
<td>2010</td>
<td>376</td>
<td>131</td>
<td>245</td>
<td>28%</td>
<td>72%</td>
<td>4.2 ± 2.7</td>
<td>4.3 ± 2.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chang et al. (e19)</td>
<td>2012</td>
<td>865</td>
<td>556</td>
<td>309</td>
<td>35%</td>
<td>65%</td>
<td>3.8 ± 2.5</td>
<td>4.2 ± 2.3</td>
<td>25.3 ± 10.2</td>
<td>34.5 ± 14.1</td>
</tr>
<tr>
<td>Qin et al. (e20)</td>
<td>2012</td>
<td>515</td>
<td>233</td>
<td>282</td>
<td>26%</td>
<td>68%</td>
<td>3.7 ± 2.3</td>
<td>4.5 ± 2.6</td>
<td>24.1 ± 10.5</td>
<td>34.5 ± 12.0</td>
</tr>
<tr>
<td>Park registry (e21)</td>
<td>2011</td>
<td>810</td>
<td>475</td>
<td>335</td>
<td>38%</td>
<td>65%</td>
<td>3.1 ± 2.2</td>
<td>3.7 ± 2.1</td>
<td>22.5 ± 9.9</td>
<td>37.8 ± 11.9</td>
</tr>
<tr>
<td>MAIN-COMPARE (e22)</td>
<td>2008</td>
<td>1,474</td>
<td>784</td>
<td>690</td>
<td>34%</td>
<td>57%</td>
<td>—</td>
<td>24.8 ± 10.9</td>
<td>38.7 ± 13.3</td>
<td>—</td>
</tr>
<tr>
<td>Capodanno et al. (e23)</td>
<td>2011</td>
<td>556</td>
<td>285</td>
<td>271</td>
<td>52%</td>
<td>—</td>
<td>20.1 ± 6.3</td>
<td>22.8 ± 6.1</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Table 2. Overall Patient Demographics**

<table>
<thead>
<tr>
<th></th>
<th>PCI (n = 7,065)</th>
<th>CABG (n = 7,148)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>63.9 ± 9.1</td>
<td>66.9 ± 7.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>5,576 (79.03)</td>
<td>5,458 (76.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2,415 (34.2)</td>
<td>2,582 (36.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4,812 (68.2)</td>
<td>4,725 (66.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3,383 (47.9)</td>
<td>2,926 (40.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>2,536 (35.9)</td>
<td>2,435 (34.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>415 (5.8)</td>
<td>352 (4.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Prior MI</td>
<td>763 (10.8)</td>
<td>976 (13.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>1,364 (19.3)</td>
<td>644 (9.09)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). MI = myocardial infarction; other abbreviations as in Table 1.
studies. The definition of primary and secondary endpoints by the individual studies was variable (Online Table 1). The time-point analysis involved 14 studies on 1-year outcomes (1,2) (Online Refs. e2–e8,e11,e14,e15,e18,e21), 10 on 2-year outcomes (1) (Online Refs. e1,e9–e12,e14,e15,e18,e21), 6 on 3-year outcomes (Online Refs. e14,e15,e18,e20,e23,e24), 4 on 4-year outcomes (Online Refs. e16,e18,e22,e25), and 6 on 5-year outcomes (4) (Online Refs. e13,e17,e19,e26,e27).

There was no significant difference in the incidence of all-cause mortality (Fig. 1) between PCI and CABG at 1 year (OR: 0.792, 95% CI: 0.53 to 1.19), 2 years (OR: 0.920, 95% CI: 0.67 to 1.26), 3 years (OR: 0.94, 95% CI: 0.60 to 1.48), 4 years (OR: 0.84, 95% CI: 0.53 to 1.33), and 5 years (OR: 0.79, 95% CI: 0.57 to 1.08).

The need for TVR (Fig. 2) was significantly higher in patients undergoing PCI at 1 year (OR: 3.92, 95% CI: 2.87 to 5.34), 2 years (OR: 3.67, 95% CI: 2.61 to 5.18), 3 years (OR: 3.45, 95% CI: 2.23 to 5.35), 4 years (OR: 2.73, 95% CI: 1.86 to 4.03), and 5 years (OR: 3.77, 95% CI: 2.43 to 5.87).

The occurrence of stroke (Fig. 3) was significantly less frequent in patients undergoing PCI at 1 year (OR: 0.54, 95% CI: 0.31 to 0.94), 2 years (OR: 0.56, 95% CI: 0.36 to 0.86), 3 years (OR: 0.56, 95% CI: 0.32 to 0.98), 4 years (OR: 0.57, 95% CI: 0.38 to 0.86), and 5 years (OR: 0.27, 95% CI: 0.13 to 0.55).

There was a statistically significant trend towards a higher incidence of nonfatal MI (Fig. 4) in PCI patients at 1 year (OR: 1.62, 95% CI: 1.05 to 2.50), 2 years (OR: 1.60, 95% CI: 1.09 to 2.35), and 3 years (OR: 2.06, 95% CI: 1.36 to 3.1). The occurrence of nonfatal MI was similar between the 2 groups at 4 years (OR: 1.12, 95% CI: 0.75 to 1.68), and 5 years (OR: 1.38, 95% CI: 0.71 to 2.70).

MACCE at follow-up (Fig. 5) was not significantly different between the 2 groups at 1 year (OR: 0.93, 95% CI: 0.66 to 1.34), 2 years (OR: 1.01, 95% CI: 0.74 to 1.38), 3 years (OR: 1.15, 95% CI: 0.81 to 1.63), and 4 years (OR: 0.83, 95% CI: 0.61 to 1.11). MACCE at 5 years was significantly lower in the PCI group (OR: 0.64, 95% CI: 0.51 to 0.80).

There was no significant difference in the incidence of cardiac mortality between PCI and CABG at 1 year (OR: 1.19, 95% CI: 0.59 to 2.39), 2 years (OR: 1.02, 95% CI: 0.54 to 1.89), 3 years (OR: 1.08, 95% CI: 0.37 to 3.11), 4 years (OR: 1.11, 95% CI: 0.81-1.52), and 5 years (OR: 0.95, 95% CI: 0.36 to 2.50).

We explored the robustness of our findings in sensitivity analysis by: 1) performing an analysis on adjusted estimates derived from studies on the basis of randomization, propensity matching, propensity score adjustment, or multivariate adjustment; and 2) analysis on the basis of the SYNTAX scores.

In the subgroup analysis (Table 3) of studies reporting on adjusted outcomes, there was no difference in all-cause mortality and MACCE between the 2 groups as reported in the primary analysis. TVR was higher in the PCI arm despite adjustments for confounding factors. Adjusted data for stroke and MI were underreported and therefore could not be adequately analyzed. The analysis was severely restricted with loss of over two-thirds of the study.
population for these 2 analyses, thereby limiting the reliability of these results.

Three studies stratified outcomes on the basis of the angiographic SYNTAX score. In pooled analyses of these 3 studies, the 3-year mortality (Fig. 6), MI, and MACCE were not significantly different with PCI compared with those of CABG for the low and intermediate SYNTAX scores. In patients with a high SYNTAX score, PCI was unfavorable for mortality (OR: 1.62, 95% CI: 1.11 to 2.36, \( P = 0.55, I^2 = 0.00 \)), MI (OR: 2.53, 95% CI: 1.32 to 4.85, \( P = 0.83, I^2 = 0.00 \)), and MACCE (OR: 1.44, 95% CI: 1.01 to 2.06, \( P = 1.95, I^2 = 0.00 \)). TVR was higher in all 3 subgroups. Stroke was not significantly different between PCI and CABG for any of the 3 subgroups.

The meta-regression analysis demonstrated an inverse relationship between percentage of diabetic patients and studies, the 3-year mortality (Fig. 6), MI, and MACCE were not significantly different with PCI compared with those of CABG for the low and intermediate SYNTAX scores. In patients with a high SYNTAX score, PCI was unfavorable for mortality (OR: 1.62, 95% CI: 1.11 to 2.36, \( P = 0.55, I^2 = 0.00 \)), MI (OR: 2.53, 95% CI: 1.32 to 4.85, \( P = 0.83, I^2 = 0.00 \)), and MACCE (OR: 1.44, 95% CI: 1.01 to 2.06, \( P = 1.95, I^2 = 0.00 \)). TVR was higher in all 3 subgroups. Stroke was not significantly different between PCI and CABG for any of the 3 subgroups.

The meta-regression analysis demonstrated an inverse relationship between percentage of diabetic patients and
odds of TVR with PCI with DES at long-term follow-up (Fig. 7), that is, diabetic patients were more prone to TVR when treated by PCI with DES at long-term follow-up ($p = 0.015$). Meta-regression analysis did not disclose any other statistically significant relationship.

**Discussion**

Our review of over 24 studies, including 3 RCTs and a total of 14,203 patients, is the largest meta-analysis on this topic on long-term follow-up, to our knowledge. Our findings suggest that in select patients, PCI is a safe and durable alternative to CABG at short- and long-term follow-up.

Previous meta-analyses on the same topic have been limited to a 1-year follow-up (12,13) or have combined short and longer lengths of follow-up (14). Contrasting PCI and CABG outcomes at 1 year, though important, is not a fair assessment because it adversely affects CABG by negating its potential long-term advantage. With current medical therapy and advances in both fields, a follow-up of at least 5 years would be necessary to detect significant outcome differences.

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**Figure 4. Forest Plot of MI in PCI Versus CABG patients for UPLMS**

Forest plot showing the odds ratios for myocardial infarction (MI) in PCI versus CABG patients for UPLMS after 1, 2, 3, 4, and 5 years. Years are indicated by the numbers on the left. Abbreviations as in Figure 1.

**Figure 5. Forest Plot of MACCE in PCI Versus CABG Patients for UPLMS**

Forest plot showing the odds ratios for major adverse cardiovascular and cerebrovascular events (MACCE) in PCI versus CABG patients for UPLMS after 1, 2, 3, 4, and 5 years. Years are indicated by the numbers on the left. Abbreviations as in Figure 1.
differences. Similarly, given the potential for treatment effect sizes to diverge over time, combining short and longer lengths of follow-up may be misleading. Analyzing outcomes over varied follow-ups separately, therefore, appears worthwhile. Importantly our meta-analysis involves close to 4,000 patients at each separate time point and is more worthwhile. Importantly our meta-analysis involves close to 4,000 patients at each separate time point and is more inclusive of the DES data that are currently available.

The absence of a survival benefit with CABG even at 5 years from the index procedure, a time period in which a portion of the benefit from CABG may have accrued, suggests that the increased rate of TVR in the PCI arm is not translating into increased mortality as compared with CABG. In other words, there is a similar short- and long-term risk of mortality between the 2 procedures. In our analysis, first-generation DES were predominantly used. First-generation DES are associated with increased risk of very late stent thrombosis occurring >1 year after stent implantation (15). Despite this increased risk, our analysis shows an equivalence of PCI with DES as compared with CABG for the outcome of mortality up to 5 years.

Strokes are significantly reduced in patients undergoing PCI at follow-up and do not support concerns raised by the SYNTAX trial of a late catch-up of strokes in the PCI arm (4) (Online Refs. e24,e25). Our result is also in line with that of Capodanno et al. (12), who reported an increased risk of stroke in patients undergoing CABG. The risk of stroke with CABG is therefore real and should be factored in determining the choice of therapy for an individual patient.

In our overall analysis, nonfatal MI showed a trend in mortality 1 year after PCI vs. CABG, with CABG having an increased 2.08 (0.26) relative risk compared with PCI vs. CABG with a 5-year follow-up period. The risk of stroke in patients undergoing CABG is therefore real and should be factored in determining the choice of therapy for an individual patient.
Figure 6. Forest Plots of Mortality, MI, MACCE, and TVR in PCI Versus CABG Patients for UPLMS

Forest plot showing the odds ratios for (A) mortality, (B) MI, (C) MACCE, and (D) TVR in PCI versus CABG patients for UPLMS. Groups are stratified by the SYNTAX score into low, intermediate, and high score groups. Abbreviations as in Figures 1 to 5.

Figure 7. Plot of Univariate Meta-Regression Examining the Effect of DM on the Relationship Between PCI and TVR

Plot of univariate meta-regression examining the effect of diabetes (DM) on the relationship between PCI and TVR ($p = 0.015$). Abbreviations as in Figure 1.
and observational studies of increased MI among PCI-treated patients (4,5,16). In the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (5), 1,900 diabetic patients with multivessel disease were randomized to receive either PCI with DES or CABG. Over a median follow-up of 3.8 years, MI occurred more frequently in patients undergoing PCI with DES when compared with CABG (13.9% vs. 6%, p < 0.001).

The finding of increased risk of TVR with PCI with DES than with CABG came as no surprise. Of note, the majority of patients received first-generation DES in the included studies. The TVR rates ranged from as low as 4% to as high as 29% at 1 year, 6% to 34% at 2 years, 7% to 36% at 3 years, 12% to 23% at 4 years, and 11% to 28% at 5 years. In the PRECOMBAT 2 (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) study (17) that compared the second-generation everolimus-eluting stents to the historical controls of the PRECOMBAT study on first-generation sirolimus-eluting stents, the rate of clinically driven TVR was 3.4% versus 6% over 18 months. The current second-generation stents with new stent platforms and superior polymer and drug coating have been shown to have increased benefits in other lesions in head-to-head trials and pooled analysis with first-generation DES (18,19). Therefore, with increasing use of second-generation DES, we should expect a drop in TVR in future trials. The results of the EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (20) comparing the Xience Prime stent (Abbott Vascular, Santa Clara, California) with CABG for left main disease, therefore, are eagerly awaited in this regard. Highest rates of TVR in the PCI arm were also observed in studies with more distal left main disease (Online Refs. e2,e10). This observation is well recognized and has been linked to procedural complexity and multileSIONAL stenting. In an Italian observational study on ostial and mid-shaft lesions versus bifurcation lesions in 1,111 patients with UPLMS, Palmerini et al. (21) showed that the 2-year incidence of MACCE was significantly higher in patients with distal left main–bifurcation disease. On stratifying bifurcation lesions according to the technique used, patients treated with 2 stents had a significantly higher incidence of MACCE compared with patients with ostial and mid-shaft lesions, whereas patients with bifurcation lesions treated with 1 stent had a clinical outcome similar to that of patients with ostial and mid-shaft lesions. In our analysis, we could not make the distinction between single stenting versus multiple stenting in distal lesions. In the included studies, IVUS guidance for PCI was not routinely performed. But in included studies that did use IVUS, there was a trend towards lower rates of TVR. In the PRECOMBAT trial (Online Refs. e11), the usage of IVUS was around 83%. This translated to a TVR of 6% at 1 year and 9% at 2 years. In 201 matched pairs of the overall population of the MAIN-COMPARE (revascularization for unprotected left MAIN coronary artery stenosis: COMparison of Percutaneous coronary Angioplasty versus surgical REvascularization) registry, Park et al. (22) showed a tendency of lower risk of 3-year morality with IVUS guidance compared with angiography guidance (6.0% vs. 13.6%, log rank p = 0.063; hazard ratio = 0.54; 95% CI = 0.28 to 1.03). Despite evidence (23,24) in favor of IVUS guidance to decrease stent thrombosis and restenosis, its routine clinical use has not been widely accepted. We believe that IVUS guidance during PCI of UPLMS is necessary to optimize stent expansion and ensure full lesion coverage.

MACCE is a widely used endpoint in cardiovascular trials to decrease sample size and increase power (25). However, the use of MACCE is not without limitations. Despite its frequent use, there is no standardized definition for MACCE. Also, depending on the set of components used to define MACCE, widely different results and conclusions may be obtained (25). The individual components of MACCE, with the exception of mortality, are not uniformly defined across studies, thereby limiting systematic comparisons. Leonardi et al. (26) found that the definition for MI was heterogeneous, and implementation of recent consensus recommendations for defining MI was also low in a large number of contemporary RCTs in cardiovascular disease. The interpretation of MACCE can be difficult when the individual components lack a directional consistency, yet another limitation to the use of MACCE. We therefore analyzed MACCE as a secondary endpoint, contrary to other meta-analyses (13,14). Despite the trend towards increased MI among PCI-treated patients, there was no difference in MACCE, suggesting that the risk of stroke with CABG is positive. The less sensitive definition of MI (only Q-wave MI) used by the studies in the 5-year analysis likely decreased the event counts of MI and tilted the balance of MACCE in favor of PCI at 5 years in our analysis. Nevertheless, the clinical significance of interpreting MACCE in this situation is questionable with stroke and MI, 2 equally significant clinical components being affected in opposite directions.

Diabetic patients pose special challenges to percutaneous therapy of coronary artery disease. Numerous clinical studies (27–29) in the percutaneous transluminal coronary angioplasty and bare-metal stent era have shown that these patients have accelerated restenosis, a need for repeat revascularization, and an increased mortality at long-term follow-up when treated with percutaneous techniques in comparison with surgical revascularization. The heightened risk of restenosis in these patients is primarily due to an exaggerated intimal hyperplasia that causes decreased vessel lumen area. DES have been shown to lower the incidence of
restenosis when compared with percutaneous transluminal coronary angioplasty or stenting with bare-metal stents in diabetic patients (30). Despite the superiority of DES, diabetes remained a significant predictor of higher risk of repeat revascularization after PCI with DES for UPLMS as opposed to CABG at long-term follow-up (>2 years) in our analysis. At short-term (1 to 2 years) follow-up, there was no significant interaction for the outcome of TVR between PCI versus CABG and percentage of diabetic patients enrolled. There was similarly no difference in mortality at short-or long-term follow-up between the 2 treatments. Our findings are similar to 2 large multicenter trials that compared PCI with DES to surgical revascularization in patients with multivessel disease (5,31). Both studies showed comparable results between PCI with DES and CABG at short-term follow-up; however, long-term follow-up demonstrated superior results with surgical revascularization. With few exceptions, CABG should therefore remain the preferred treatment option in diabetic patients with UPLMS.

The use of the angiographic SYNTAX score for patient selection in UPLMS is conflicting. Our analysis of available data, however, supports the idea that patients with a high SYNTAX score may be better served with CABG. The correlation of a high SYNTAX score to mortality may not be perfect but likely identifies a group of patients who may not fare well with PCI. The results of the EXCEL trial (20) comparing the Xience Prime stent with CABG for left main disease in patients with low-to-intermediate SYNTAX scores, therefore, are eagerly awaited.

Study limitations. Some of the limitations of this study are those inherent to any meta-analysis: 1) inclusion of nonrandomized comparisons and very few randomized studies; 2) inclusion of nonrandomized comparisons introduced heterogeneity in our analyses of certain outcomes; 3) incomplete reporting and variable definitions of endpoints by the primary studies may have introduced reporting and detection bias; 4) incomplete reporting resulted in underpowered analyses for certain outcomes during sensitivity testing; 5) we could not adjust for confounding variables if not reported by the primary studies; and 6) publication bias is another inherent limitation of any meta-analyses.

Conclusions

From available all-comers data (RCT and real world), there is no survival benefit of CABG over PCI for UPLMS up to 5 years from the index procedure in the DES era. Furthermore, there is no difference in the safety endpoint of MACCE during follow-up. There is a persistent risk of stroke with CABG and of MI with PCI. Diabetes is a predictor of increased TVR after PCI at long-term follow-up. Patients with high angiographic SYNTAX scores may have better outcomes with CABG. However, PCI with DES is a comparable alternative to CABG for patients with low and intermediate SYNTAX scores. These results should be taken into consideration when selecting revascularization strategy for patients with severe left main stenosis.

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REFERENCES


Key Words: CABG ■ long-term follow-up ■ PCI with DES ■ SYNTAX score ■ UPLMS.

APPENDIX

For supplemental references and a table, please see the online version of this paper.

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