Percutaneous Coronary Intervention Using Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Unprotected Left Main Coronary Artery Stenosis

A Meta-Analysis of Randomized Trials

Nitesh Nerlekar, MBBS, MPH; Francis J. Ha, BMedSci; Kunal P. Verma, MBBS; Martin R. Bennett, MD, PhD; James D. Cameron, MBBS, MD, MEngSc; Ian T. Meredith, MBBS, PhD; Adam J. Brown, MD, PhD

Background—Current guidelines suggest that coronary artery bypass grafting (CABG) should be the preferred revascularization method for unprotected left main coronary artery stenosis. In light of evidence from recent randomized trials, we assessed whether percutaneous coronary intervention (PCI) using drug-eluting stents is as safe and effective as CABG for the treatment of unprotected left main coronary artery disease.

Methods and Results—Digital databases and manual searches were performed for randomized trials comparing PCI and CABG for unprotected left main coronary artery stenosis. Among 3887 potentially relevant studies, 5 met inclusion criteria. The primary safety end point was defined as the composite of all-cause death, myocardial infarction, or stroke. Secondary end points included a clinical effectiveness composite, which was defined as all-cause death, myocardial infarction, stroke, or repeat revascularization. Summary estimates were obtained using random-effects modeling. In total, 4594 patients were included in the analysis. There was no significant difference in the primary safety end point between the revascularization strategies (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.79–1.17; P=0.73). However, when compared with CABG, PCI was less effective (OR, 1.36; 95% CI, 1.18–1.58; P=0.001) because of significantly higher rates of repeat revascularization (OR, 1.85; 95% CI, 1.53–2.23; P<0.001). The incidence of all-cause death (OR, 1.03; 95% CI, 0.78–1.35; P=0.61), myocardial infarction (OR, 1.46; 95% CI, 0.88–2.45; P=0.08), and stroke (OR, 0.88; 95% CI, 0.39–1.97; P=0.53) did not differ between PCI and CABG.

Conclusions—PCI using drug-eluting stents and CABG are equally safe methods of revascularization for patients at low surgical risk with significant unprotected left main coronary artery stenosis. However, CABG is associated with significantly lower rates of repeat revascularization. (Circ Cardiovasc Interv. 2016;9:e004729. DOI: 10.1161/CIRCINTERVENTIONS.116.004729.)

Key Words: coronary angiography ■ coronary artery bypass ■ drug-eluting stent ■ meta-analysis ■ percutaneous coronary intervention

A round 5% of patients undergoing coronary angiography are found to have significant unprotected left main coronary artery (ULMCA) stenosis. Patients with ULMCA stenosis are typically advised to undergo revascularization because this has been shown to improve prognosis when compared with optimal medical therapy. Historically, coronary artery bypass grafting (CABG) has been considered the preferred method for revascularization based on a wealth of data demonstrating the safety and durability of surgery. This has been reflected in current international guidelines, where CABG carries a class I recommendation for ULMCA disease. Percutaneous coronary intervention (PCI) is becoming increasingly used as an alternative method of ULMCA revascularization. The development of drug-eluting stents (DES) has significantly reduced repeat revascularization rates after PCI, whereas advances in technique permit treatment of more complex coronary anatomies including the distal ULMCA bifurcation. Clinical trials comparing PCI and CABG for ULMCA stenosis have shown that subsequent major adverse cardiovascular event rates between treatment strategies were similar. However, these trials were limited in their ability to definitely answer whether individual clinical end points were...
WHAT IS KNOWN

• There is continued debate on the optimal revascularization strategy for patients with significant left main coronary artery stenosis.
• Previous meta-analyses comparing percutaneous coronary intervention and coronary artery bypass grafting have demonstrated equivalence between revascularization strategies but are influenced by inclusion of observational data.

WHAT THE STUDY ADDS

• This meta-analysis is limited to randomized trials at the longest reported follow-up duration and demonstrates no difference in clinical safety outcomes between percutaneous coronary intervention using drug-eluting stents and coronary artery bypass grafting in patients at low surgical risk.
• However, coronary artery bypass grafting may be a more clinically effective revascularization strategy because percutaneous coronary intervention is associated with significantly higher rates of repeat revascularization at long-term follow-up.

significantly different between revascularization strategies. Previous meta-analyses have been influenced by the inclusion of observational studies,\(^{5,7}\) whereas results of additional multicenter randomized trials are now available.\(^{8,9}\) We, therefore, performed an updated systematic review and meta-analysis of randomized trials to evaluate clinical outcomes with PCI using DES compared with CABG in patients with significant ULMCA stenosis.

Methods

Data Sources and Search Strategy
A digital literature search was performed through the MEDLINE, EMBASE, and PubMed databases for the period January 1, 2000, to October 31, 2016. Keywords using Medical Subject Heading (MeSH), where available, included percutaneous coronary intervention, drug-eluting stent, coronary artery bypass, coronary artery disease, and left main. The search was not limited by language. Reference lists of eligible articles and previous meta-analyses were reviewed for further potential citations, along with a manual search through presentations and abstracts of major international conferences. The study protocol was prospectively registered with the PROSPERO international register (CRD42016050141) and fully adhered to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).\(^{1,2}\) An example search strategy is presented in Table I in the Data Supplement.

Study Selection
Study characteristics for inclusion were as follows: (1) randomized controlled clinical trial, (2) involvement of left main coronary artery, (3) comparison of clinical outcomes between CABG and PCI using DES, and (4) fully published status. Only studies that specified outcomes in treatment of left main coronary artery disease and evaluated PCI involving DES platforms were included. Studies that did not specify clinical outcomes in the treatment of ULMCA specifically or used bare-metal stents or a combination of bare-metal stents and DES were excluded. Studies arising from observational registry data or that evaluated only angiographic outcomes without assessment of clinical outcomes at follow-up were also excluded. We evaluated clinical outcomes for each trial, with preference for the longest reported follow-up. The study characteristics are presented in Table II in the Data Supplement.

Data Items and Collection Process
Data items to be collected were specified before the literature search. Two investigators (N.N. and F.J.H.) independently conducted the literature search and performed data extraction for study design, baseline demographics, angiographic characteristics, and clinical outcomes. Extracted data were verified by the senior author (A.J.B.), with any discrepancies resolved by consensus. Risk of bias within individual articles was assessed according to the Cochrane Collaboration Assessment for risk of bias in included studies (Table III in the Data Supplement).

Clinical End Points
The primary end point of this study was clinical safety, defined as a composite of all-cause death, myocardial infarction (MI), or stroke. Secondary end points included an effectiveness/safety composite (henceforth called effectiveness end point), which was defined as all-cause death, MI, stroke, or repeat revascularization. Other secondary end points included all individual components of the effectiveness composite. Although the definition of MI varied slightly between trials, all required an elevation in cardiac biomarkers (either creatine kinase MB or troponin). However, the thresholds used for MI diagnosis and timing of definitions varied between trials. Periprocedural MI was included in 4 trials,\(^{9,11,13}\) whereas 1 trial only assessed nonprocedural MI.\(^{7}\) Stroke was generally defined as the rapid or sudden onset of new neurological deficit persisting for >24 hours with no apparent nonvascular cause. Repeat revascularization was preferentially defined as ischemia-driven revascularization by either PCI or CABG. If these data were not reported, then data on any repeat revascularization were taken. Comprehensive details of individual trial end points and trial definitions are presented in Tables IV and V in the Data Supplement.

Statistical Analysis
Data were analyzed by random-effects modeling for the primary end point and for analysis of individual secondary end points. We also performed additional analyses for both the primary and secondary effectiveness composites in studies reporting 1-year outcomes. Sensitivity analyses were performed to assess differences between early- and newer-generation DES, by duration of clinical follow-up (≤36 versus >36 months), by patients with and without diabetes mellitus, and by complexity of coronary artery disease as defined by the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) score (<22 versus ≥22). Summary statistics are reported as pooled odds ratios (ORs) with 95% confidence intervals (CIs). Statistical heterogeneity was quantified with the \(I^2\) statistic. Heterogeneity was quantified as low, moderate, or high based on \(I^2\) values of 25%, 50%, and 75%, respectively.\(^{14}\) Publication bias was visually assessed by funnel plots. A 2-sided \(P\) value of <0.05 was considered significant. Statistical analyses were performed using Stata MP 14.0 (Stata Corp LP, College Station, TX) and the metan suite of commands.

Results
A total of 3887 citations were reviewed and screened, with 27 studies identified for potential inclusion and further evaluation. Of these articles, 22 studies were excluded because they either did not specifically report clinical outcomes in ULMCA disease (13 studies) or reported clinical outcomes at an earlier time point (3 studies). Other reasons for study exclusion are provided in the PRISMA study flow chart (Figure 1).
Five randomized trials met the predefined inclusion criteria and were included in the final quantitative analysis. The multicenter randomized controlled trials included were PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease)\(^12\) (60-month follow-up), SYNTAX\(^13\) (60-month follow-up), NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis)\(^8\) (60-month follow-up), EXCEL\(^9\) (36-month follow-up), and 1 trial with 12-month clinical follow-up.\(^11\) Overall, 4594 patients were included in the analysis with 2297 patients (50.0%) undergoing PCI using DES. The prevalence of isolated ULMCA stenosis ranged from 10% to 29%, with between 55% and 80% of patients having a distal bifurcation ULMCA lesion. Three trials compared PCI using early-generation DES with CABG,\(^11-13\) with 2 trials using newer-generation DES.\(^8,9\) The baseline clinical, angiographic, and procedural characteristics for the included studies are presented in Table 1.

**Primary Safety End Point**

Four studies reported the incidence of the primary safety end point, the composite of all-cause death, MI, and stroke. The summary OR for these studies was 0.97 (95% CI, 0.79–1.17; \(P=0.73\)), demonstrating no significant difference in safety outcomes between PCI and CABG for the treatment of ULMCA stenosis (Figure 2). Clinical event rates for each trial in the analysis are presented in Table 2. There was no evidence of statistical heterogeneity between studies (\(I^2=0\%\)). The equipoise between revascularization strategies was also present in those studies reporting 1-year outcomes (OR, 0.73; 95% CI, 0.48–1.12; \(P=0.16\); \(I^2=0\%\); Figure I in the Data Supplement). In sensitivity analyses, again there remained no difference between PCI and CABG in terms of safety when the analysis was stratified by DES type (\(P_{interaction}=0.45\); Figure II in the Data Supplement), nor by clinical follow-up duration (\(P_{interaction}=0.69\); Figure III in the Data Supplement). Further sensitivity analysis was performed for the 2 studies reporting data of patients with diabetes mellitus,\(^9,13\) again demonstrating no difference in outcomes (\(P_{interaction}=0.84\); Table VI in the Data Supplement). Two studies reported SYNTAX score–specific outcomes. This demonstrated that in patients with anatomic more complex disease (SYNTAX \(\geq 22\)), the safety composite rates were significantly higher in patients undergoing PCI using DES (OR, 1.64; 95% CI, 1.22–2.20; \(P_{interaction}=0.006\); Table VI in the Data Supplement).

**Secondary Effectiveness End Point**

Four trials reported the incidence of the secondary effectiveness composite end point, which included all-cause death, MI, stroke, or repeat revascularization. The summary OR was 1.36 (95% CI, 1.18–1.58; \(P<0.001\)) in favor of CABG (Figure 3), with again no evidence of statistical heterogeneity (\(I^2=0\%\)). However, in the 3 trials reporting 1-year data, there was no significant difference between PCI and CABG in terms of effectiveness (OR, 1.14; 95% CI, 0.86–1.49; \(P=0.33\); \(I^2=0\%\)). In sensitivity analyses performed at longest clinical follow-up, PCI continued to have a significantly higher risk of events, regardless of DES generation used (\(P_{interaction between early- and newer-generation DES}=0.85\); Figure II in the Data Supplement). Analysis by trial duration confirmed the benefit of CABG, with no demonstrable differences between studies that reported outcomes at \(\leq 36\) and >36-month follow-up (\(P_{interaction}=0.38\); Figure III in the Data Supplement), and no difference observed in patients with diabetes mellitus (\(P_{interaction}=0.51\); Table VI in the Data Supplement).

**Individual Clinical End Points**

All five trials individually reported the incidence of all-cause death, MI, and repeat revascularization (Figure 4). The incidence of all-cause death was not significantly different between revascularization strategies (OR, 1.03; 95% CI, 0.78–1.35; \(P=0.61\); \(I^2=23.7\%\)). Similar outcomes between PCI and CABG were also observed for the incidence of MI (OR, 1.46; 95% CI, 0.88–2.45; \(P=0.08\); \(I^2=58.1\%\)). However, CABG was associated with a significant reduction in the risk of repeat revascularization (OR, 1.85; 95% CI, 1.53–2.23; \(P<0.001\); \(I^2=0\%\)). Four studies reported the incidence of stroke, with again no difference observed in this outcome between revascularization strategies (OR, 0.88; 95% CI, 0.39–1.97; \(P=0.53\); \(I^2=62.5\%\)).

**Publication Bias**

There was no visually observed publication bias either in the trials included in the primary safety outcome, nor the secondary effectiveness outcome (Figure IV in the Data Supplement). However, the small number of trials included in the analysis does limit the interpretation of funnel plots.

**Discussion**

To our knowledge, this is the largest meta-analysis of randomized trials investigating whether PCI using DES is as effective as CABG for the treatment of ULMCA stenosis. Our major
finding is to demonstrate that rates of the safety composite were similar between PCI using DES and CABG for revascularization of significant ULMCA stenosis in patients at low surgical risk. In addition, we find that CABG is associated with a reduction in rates of the effectiveness composite, although this benefit was not apparent within the first year. In terms of individual clinical end points, there was no difference in the rates of all-cause death, MI, or stroke between PCI using DES and CABG. However, CABG was associated with significantly lower rates of repeat revascularization. These results are important for informing treatment decisions made by multidisciplinary teams worldwide.

Revascularization of ULMCA stenosis is frequently performed for prognostic gain because CABG has been shown...
in randomized trials to improve survival when compared with optimal medical therapy. Thus, it is imperative when considering alternate revascularization strategies, such as PCI, that the treatment offered does not confer deleterious outcomes. In our study, we demonstrate that there is no difference in the composite outcome of all-cause mortality, MI, or stroke between PCI using DES and CABG. Importantly, the rates of the individual end points of the composite also remain similar between groups, and this equipoise appears regardless of trial follow-up duration. These data imply that PCI using DES for ULMCA disease is not harmful and should be considered an acceptable revascularization option. However, this does not mean that undertaking PCI for ULMCA intervention is not without risk, and suboptimal PCI results may have profound implications for the patient. Previous studies have emphasized that short- and long-term clinical outcomes can be improved when ULMCA PCI procedures are performed in high-volume centers by experienced operators. Ultimately, the decision on which revascularization strategy should be used rests with the patient, who should be fully informed of the risks and potential benefits of each treatment option by a multidisciplinary heart team that understands the local expertise available.

Although we find no difference in the primary safety outcome in our study, we did observe that PCI was associated with significantly higher rates of repeat revascularization (14.2% versus 8.3%). This drove the secondary outcome of clinical effectiveness in favor of CABG. Previous trials comparing PCI using DES with CABG in multivessel coronary artery disease have shown similar findings, with repeat revascularization rates often more than doubled after PCI. The beneficial

Table 2. Summary and Individual Trial Clinical Event Rates

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Boudriot et al</th>
<th>PRECOMBAT</th>
<th>SYNTAX</th>
<th>NOBLE</th>
<th>EXCEL</th>
</tr>
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<tbody>
<tr>
<td>Safety end point</td>
<td>13.7/14.1/14.1</td>
<td>5.0/8.9</td>
<td>8.4/9.6</td>
<td>19.0/20.8</td>
<td>NR</td>
<td>15.4/14.7</td>
</tr>
<tr>
<td>Effectiveness end point</td>
<td>23.3/18.2</td>
<td>NR</td>
<td>17.5/14.3</td>
<td>36.9/31.0</td>
<td>29.0/19.0</td>
<td>23.1/19.1</td>
</tr>
<tr>
<td>All-cause death</td>
<td>7.4/7.0</td>
<td>2.0/5.0</td>
<td>5.7/7.9</td>
<td>12.8/14.6</td>
<td>12.0/9.0</td>
<td>8.2/5.9</td>
</tr>
<tr>
<td>MI</td>
<td>6.0/4.8</td>
<td>3.0/3.0</td>
<td>2.0/1.7</td>
<td>8.2/4.8</td>
<td>7.0/2.0</td>
<td>8.0/8.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.0/2.2</td>
<td>NR</td>
<td>0.7/0.7</td>
<td>1.5/4.3</td>
<td>5.0/2.0</td>
<td>2.3/2.9</td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td>14.2/8.3</td>
<td>14.0/5.9</td>
<td>13.0/7.3</td>
<td>26.7/15.5</td>
<td>16/10</td>
<td>12.9/7.6</td>
</tr>
</tbody>
</table>

Data are presented as percentage treated with PCI/percentage treated with CABG. CABG indicates coronary artery bypass grafting; MI, myocardial infarction; NOBLE, Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis; NR, not recorded; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery.
The effect of CABG in reducing the need for repeat intervention is multifactorial. Graft occlusion, in stark contrast to stent thrombosis, does not necessarily result in clinical symptoms, as the subtended myocardium may be partly supplied through the native vessel. The high use of internal mammary grafts also plays an important role in reducing the need for future revascularization because this conduit almost seems protected from the development of atherosclerosis. Although refinements in DES technology continue to reduce rates of target lesion failure, it is unlikely to ever match the long-term patency rates of an adequately harvested internal mammary graft.

One interventional technique that has proven itself in reducing the need for repeat intervention during DES implantation is use of intravascular ultrasound (IVUS). Although IVUS-guided PCI was frequent (91%) in PRECOMBAT, only 47% of patients underwent pre-PCI IVUS in NOBLE. Use of IVUS during PCI allows for robust measurement of reference vessel dimensions and assessment of lesion characteristics, acting to inform on stent selection and interventional strategy. Stent expansion can also be assessed after implantation, guiding operators on the need for aggressive balloon post-dilatation. Previous studies have shown that DES underexpansion is one of the strongest predictors of restenosis and stent thrombosis. Thus, methods that act to minimize underexpansion are of paramount importance. Meta-analyses have found that IVUS-guided PCI is associated with significantly lower rates of ischemia-driven target lesion revascularization, principally because of larger postinterventional luminal dimension. Although similar gains in stent expansion can be achieved using optical coherence tomography, achieving the blood-free field required for optimal OCT image acquisition can be challenging in ULMCA intervention. Accordingly, operators should give due consideration to IVUS guidance when considering PCI using DES for ULMCA stenosis particularly to reduce the risk of repeat revascularization.

Finally, it is important to appreciate that our results may not necessarily be generalizable to all patients under consideration for ULMCA revascularization. The majority of patients included in the randomized trials presented either with stable angina or with clinically adjudicated unstable angina and the absence of biomarkers indicating myocardial injury. In addition, the predicted operative mortality risk for the cohort was low, as evidenced by the EuroScore values reported by the included trials (2.0%–3.9%). Thus, choice of revascularization strategy is not solely dependent on anatomy and is affected by many other factors including clinical presentation and presence of adverse medical comorbidities. This is most evident in patient presenting with ST-segment elevation MI, where PCI may be preferable as it has the advantage of providing more rapid revascularization, particularly when complicated by cardiogenic shock or ventricular arrhythmias.

**Study Limitations**

There are some limitations to our analysis that should be considered. First, follow-up data between trials was variable, with 1 trial having follow-up at 12 months, 1 having midterm follow-up at 36 months, and 3 having long-term follow-up at 60 months. Because the benefits of CABG may accumulate over time, the reported pooled results may not adequately estimate a true long-term effect between interventions. Second, the definition of repeat revascularization slightly differed between trials. Ischemia-driven target lesion

### Figure 3.

Risk estimates for secondary effectiveness end point for percutaneous coronary intervention vs coronary artery bypass grafting (CABG). Forest plot displays summary odds ratio (OR) and 95% confidence intervals (CI) for combined outcome of all-cause death, myocardial infarction (MI), stroke, or repeat revascularization. DES indicates drug-eluting stent.
revascularization rates were not reported in all trials, which made it difficult to assess the durability of DES results. Third, the included randomized studies used a variety of DES platforms with differing stent designs. Thus, the pooled event rates, including repeat revascularization, may not accurately reflect the performance of any one particular DES. Fourth, ORs were chosen to represent differences in clinical outcomes and have potential to overestimate effect size, particularly when the risk of events is high or when the OR departs from unity. However, the overall clinical event rates and ORs reported were modest and are unlikely to have significantly misrepresented differences between revascularization strategies. Finally, we did not have access to patient-level data and have, therefore, been unable to assess the effect of specific patient or procedural characteristics that may influence clinical end points.

**Conclusions**

PCI using DES and CABG are equally safe methods of revascularization for patients with significant ULMCA stenosis in patients at low surgical risk. However, CABG is associated with significantly lower rates of repeat revascularization. Multidisciplinary teams should be aware of these results when considering treatment options.

**Sources of Funding**

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**References**


**Figure 4.** Risk estimates for individual clinical outcomes for percutaneous coronary intervention vs coronary artery bypass grafting (CABG). Forest plot displays summary estimates for (A) all-cause death, (B) myocardial infarction (MI), (C) stroke, and (D) repeat revascularization. CI indicates confidence interval; DES, drug-eluting stent; and OR, odds ratio.
10.1016/j.jacc.2015.03.033.


10.1016/j.esmo.2015.07.008.


10.1056/NEJMoa094026.

10.1016/j.ijcard.2012.06.051.


10.1016/j.circinterventions.2011.03.007.


10.1161/HTJ.113.094026.


2005;45:995–998.


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SUPPLEMENTAL MATERIALS

Percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery stenosis: a meta-analysis of randomized trials

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Table S2. Study characteristics

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<tr>
<td>Boudriot et al.(^1)</td>
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EXCEL, Evaluation of the Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; F/U, Follow up; NOBLE, Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery.
Table S3. Cochrane Review of bias

<table>
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<tr>
<th></th>
<th>Random Sequence Generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Overall judgment</th>
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<td>Boudriot et al.</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
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</tr>
<tr>
<td>SYNTAX</td>
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<tr>
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<tr>
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<tr>
<td>Trial</td>
<td>Main inclusion criteria</td>
<td>Main exclusion criteria</td>
<td>Primary endpoint</td>
<td>Secondary endpoint</td>
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<tr>
<td>Boudriot et al.</td>
<td>Patients aged 18 to 80 years with ULMCA (stenosis ≥50%) with or without additional multi-vessel CAD</td>
<td>MI &lt;48 hours requiring immediate intervention, additional valvular heart disease requiring surgery, previous surgical treatment for coronary artery or valvular disease, severe peripheral arterial disease, significant carotid stenosis requiring treatment, renal dysfunction requiring dialysis, any disease with limited life expectancy, overt congestive heart failure, and contraindication to antiplatelet therapy</td>
<td>Freedom from composite of all-cause death, MI, and the need for repeat revascularization within 12 months</td>
<td>Each individual component of the primary endpoint</td>
<td></td>
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<tr>
<td>PRECOMBAT</td>
<td>Patients older than 18 years of age with a diagnosis of stable angina, unstable angina, silent ischemia, or non-ST-segment elevation MI.</td>
<td>Any previous PCI within 1 year, previous bypass surgery, acute MI within 1 week, ejection fraction &lt;30%, cardiogenic shock, any stroke with a persistent neurological deficit or any cerebrovascular accident within 6 months</td>
<td>MACCE as a composite of all-cause death, MI, stroke or ischemia-driven TVR after randomisation</td>
<td>Individual components of the primary endpoint; composite of all-cause death, MI, or stroke; clinically driven TVR; ST</td>
<td></td>
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<tr>
<td>SYNTAX</td>
<td>Patients with ULMCA and/or 3VD and ≥50% target vessel stenosis with MI (stable, unstable, silent)</td>
<td>Prior PCI or CABG, acute MI, concomitant cardiac valve disease requiring surgical therapy (reconstruction or replacement)</td>
<td>MACCE as a composite of all-cause death, MI, cerebrovascular accident/stroke, and repeat revascularization</td>
<td>Individual components of the primary endpoint; Quality of Life</td>
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<tr>
<td>NOBLE</td>
<td>Patients with stable, unstable angina pectoris or ACS; significant lesion of ULMCA ostium, mid-shaft and/or bifurcation with no more than three additional non-complex PCI lesions; ST-elevation MI within 24 hours; CABG clearly better treatment option (ULMCA stenosis and &gt;3, or complex additional coronary lesions); patient is too high risk for CABG</td>
<td>ST-elevation MI within 24 hours; CABG clearly better treatment option (ULMCA stenosis and &gt;3, or complex additional coronary lesions); patient is too high risk for CABG</td>
<td>Composite of all-cause death, non-procedurally related MI, stroke and repeat revascularization (PCI or CABG)</td>
<td>Individual components of the primary endpoint; composite of all-cause death, stroke or MI; definite ST/symptomatic graft occlusion; CCS angina score; NYHA functional class; duration of admission for index treatment</td>
<td></td>
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<tr>
<td>EXCEL</td>
<td>Patients ≥18 years of age with ULMCA with angiographic diameter stenosis ≥70%</td>
<td>Prior PCI of left main trunk, PCI of any other (non-left main) coronary artery lesions within one year prior to randomisation, CABG at any time; need for any concomitant cardiac surgery other than CABG; non-cardiac comorbidities with life expectancy &lt;3 years</td>
<td>Composite of all-cause death, MI, or stroke</td>
<td>Individual components of the primary endpoint; revascularization (all, ischemia-driven and non-ischemia-driven); disability following stroke event; composite of all-cause death, MI, or stroke; composite of all-cause death, MI, stroke, or ischemia-driven revascularization; ST; bleeding complications; elapsed times: randomisation to procedure, procedure to discharge, procedure to return to work and ICU days; major adverse events: composite of all-cause death, MI, stroke, TIMI major or minor bleeding, transfusion of ≥2 units of blood, major arrhythmia, unplanned coronary revascularization for ischemia, any unplanned surgery or therapeutic radiologic procedure, renal failure, sternal wound dehiscence, infection requiring antibiotics for treatment, intubation for &gt;48 hours, post-pericardiotomy syndrome</td>
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</table>

*3VD, Triple-vessel disease; ACS, Acute coronary syndrome; CAD, Coronary artery disease; CABG, Coronary artery bypass grafts; CCS, Canadian Cardiovascular Society; MACCE, Major adverse cardiac and cerebrovascular events; MI, Myocardial infarction; NYHA, New York Heart Association; ICU, Intensive Care Unit; PCI, Percutaneous coronary intervention; ST, Stent thrombosis; TIMI, Thrombolysis in myocardial infarction; TVR, Target vessel revascularization; ULMCA, Unprotected left main coronary artery*
### Table S5. Definition of outcomes

<table>
<thead>
<tr>
<th>Boudriot et al.</th>
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</thead>
<tbody>
<tr>
<td><strong>Major adverse cardiovascular events:</strong> all-cause death, myocardial infarction and the need for repeat revascularization within 12 months</td>
</tr>
<tr>
<td><strong>Myocardial infarction:</strong> increase in CK-MB activity &gt;3 times ULN after PCI and &gt;5 times after CABG with standard electrocardiographic criteria applied</td>
</tr>
<tr>
<td><strong>Stent thrombosis:</strong> defined in accordance with the Academic Research Consortium definitions(^6)</td>
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<tr>
<td><strong>Repeat revascularization:</strong> any revascularization by CABG or PCI within 12 months</td>
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<table>
<thead>
<tr>
<th>SYNTAX</th>
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<tr>
<td><strong>Major adverse cardiac and cerebrovascular events:</strong> all-cause death, cerebrovascular event, documented myocardial infarction, repeat revascularization (PCI and/or CABG)</td>
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<tr>
<td><strong>Cerebrovascular event:</strong> any acute event related to the impairment of the cerebral circulation that lasts more than 24 hours and results in irreversible brain damage or permanent body impairment. Strokes may be further classified as ischemic or hemorrhagic based on imaging studies. The definitive evaluation for the absence or presence of CVA was conducted and confirmed in both revascularization arms by a local neurologist.</td>
</tr>
<tr>
<td><strong>Myocardial infarction:</strong> a definitive diagnosis of MI is made based on the following:</td>
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<tr>
<td>• within the first 7 days post intervention (PCI or CABG) – either new, abnormal Q waves and 1 ratio of peak CK-MB/peak total CK&gt;10% or new, abnormal Q-waves and 1 plasma level of CK-MB 5x ULN</td>
</tr>
<tr>
<td>• 7 day after any intervention procedure (PCI or CABG) – either new, abnormal Q waves or enzyme changes defined as more than 10% of the ratio of peak CK-MB/peak total CK on one or more than one sample (if no ratio is available – one or more than 1 plasma level of CK-MB 5x upper limit for normal)</td>
</tr>
<tr>
<td><strong>Repeat revascularization:</strong> any revascularization by CABG or PCI</td>
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</table>

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<th>PRECOMBAT</th>
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<tr>
<td><strong>Myocardial infarction:</strong></td>
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<tr>
<td>• Within the first 48 hours after procedure (CABG or PCI) – the presence of new Q waves in at least 2 or more contiguous leads, or new LBBB and one plasma level of CK-MB 5x upper limit for normal</td>
</tr>
<tr>
<td>• More than 48 hours after the procedure (CABG or PCI) – typical rise and gradual fall of troponin or more rapid rise and fall of CK-MB for detecting myocardial necrosis with at least one of the following:</td>
</tr>
<tr>
<td>• Ischemic symptoms or atypical symptoms of ischemia;</td>
</tr>
<tr>
<td>• Development of pathologic Q waves on the ECG, or new LBBB; AND</td>
</tr>
<tr>
<td>• Enzyme changes defined as one or more than one plasma level of CK-MB above upper level of normal</td>
</tr>
<tr>
<td><strong>Stent thrombosis:</strong> occurrence of any of the following defined by the Academic Research Consortium Definitions(^6):</td>
</tr>
<tr>
<td>1. <strong>Definite stent thrombosis</strong> – clinical presentation of acute coronary syndrome with angiographic confirmation of thrombus or occlusion or pathologic confirmation of acute thrombosis</td>
</tr>
<tr>
<td>2. <strong>Probable stent thrombosis</strong> – Unexplained death within 30 days or target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion</td>
</tr>
<tr>
<td>3. <strong>Possible stent thrombosis</strong> – unexplained death after 30 days</td>
</tr>
</tbody>
</table>
Stent thrombosis can be Acute (≤1 day post-procedure), Sub-acute (>1 day and ≤30 days post-procedure), Late (>30 days and ≤1-year post-procedure) or Very Late (>1 year post-procedure)

Cerebrovascular accident: defined as sudden onset of vertigo, numbness, aphasia, or dysarthria to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours

Repeat coronary vascularization: any subsequent PCI procedure or CABG surgery, as determined by the patient’s physician to be clinically indicated.

Target lesion revascularization: any repeat PCI or bypass surgery of the lesion was treated during the index procedure. A target lesion revascularization will be considered ischemia-driven if the target lesion diameter stenosis is ≥50% by QCA and any of the following occur:
- The patient had a positive functional study corresponding to the area served by the target lesion;
- Ischemic ECG changes at rest in a distribution consistent with the target vessel; or
- Ischemic symptoms referable to the target lesion

Target vessel revascularization: Any PCI of the target vessel or bypass surgery of the target vessel. The target vessel consists of the target lesion(s) plus any additional lesions in the main epicardial coronary artery or branches containing the target lesion (LAD, LCX or RCA)

Thrombocytopenia: Nadir platelet count <100,000 cells/mm³ in a patient with a baseline platelet count >100,000 cells/mm³. Further divided into mild (50,000 - <100,000 cells/mm³), moderate (20,000 - <50,000 cells/mm³), or severe (<20,000 cells/mm³, or requiring platelet transfusion)

NOBLE

Cardiac death: any death due to a suspected cardiac cause (MI, low-output heart failure, fatal arrhythmia), unwitnessed death and death of unknown cause. All procedure-related deaths, including those related to concomitant treatment, were classified as cardiac death.

Non-procedure-related myocardial infarction: a rise in biochemical markers exceeding the decision limit for myocardial infarction (99th percentile including <10% CV) with at least one of the following:
1. Ischemic symptoms
2. ECG changes indicative of ischemia (ST segment elevation or depression)
3. Development of a pathologic Q-wave with no relation to a PCI procedure

Procedural myocardial infarction: diagnosis of procedural MI for both PCI and CABG patients was based on CK-MB elevations when available. Patients needed to have stable angina pectoris as the clinical indication OR a normal baseline CK-MB, TnI, TnT, or highly-sensitive TnT, to be assessable for procedural MI. Diagnosis required a CK-MB value above 10 x URL or ULN to establish the diagnosis. The diagnosis could also be placed by the combination of a CK-MB value above 5 x URL or ULN, AND one or more of the following:
1. New pathological Q waves in at least 2 contiguous leads or new persistent non-rate-related LBBB
2. Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow
3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Repeat revascularization: any new PCI or CABG operation performed during follow-up. If an index revascularization was attempted or successful, any subsequent revascularization was counted as repeat revascularization.

Target lesion revascularization: repeat revascularization by PCI of any target segment treated during the index procedure. A target lesion segment was defined as a stented or balloon treated segment and its 5 mm margin

Definite stent thrombosis: defined in accordance with the Academic Research Consortium definitions

Symptomatic graft occlusion: diagnosis of symptomatic graft occlusion required it to be detected during a clinically indicated coronary angiography
**Stroke**: Ischemic or hemorrhagic cerebrovascular event verified by CT or MRI brain

**EXCEL**

**Post-procedure myocardial infarction**: defined as the occurrence within 7 hours after either PCI or CABG of either:
- CK-MB >10x URL OR
- CK-MB >5x URL plus
  - New pathological Q-waves in at least two contiguous leads or new persistent non-rate-related LBBB, or
  - Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

**Spontaneous myocardial infarction**: defined as the occurrence >72 hours after any PCI or CABG of:
- The rise and/or fall of cardiac biomarkers (CK-MB or troponin) >1x URL PLUS
  - ECG changes indicative of new ischemia [ST-segment elevation or depression, in the absence of other causes of ST-segment changes such as left ventricular hypertrophy or bundle branch block] or
  - Development of pathological Q waves (≥0.04 seconds in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads) of the ECG, or
  - Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

**Stroke**: the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumour, or infection). A vascular neurologist or stroke specialist determined whether a stroke had occurred and determined the stroke severity using the NIHSS TIA/stroke questionnaire. Available neuroimaging studies was considered to support the clinical impression and to determine if there was a demonstrable lesion compatible with an acute stroke. Strokes were classified as ischemic, hemorrhagic, or unknown. Four criteria must be fulfilled to diagnose stroke:

1. Rapid onset of a focal/global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia/aphasia, hemianopia, amaurosis fugax, other new neurological sign(s)/symptom(s) consistent with stroke; and

2. Duration of a focal/global neurological deficit ≥24 hours or <24 hours if any of the following conditions exist:
   a. At least one of the following therapeutic interventions:
      i. Pharmacologic (i.e., thrombolytic drug administration)
      ii. Non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty)
   b. Available brain imaging clearly documents a new hemorrhage or infarct
   c. The neurological deficit results in death

3. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, other metabolic abnormality, peripheral lesion, or drug side effect). Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
4. Confirmation of the diagnosis by a neurology or neurosurgical specialist and at least one of the following:
   a. Brain imaging procedure (at least one of the following):
      i. CT scan
      ii. MRI scan
      iii. Cerebral vessel angiography
   b. Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)

Ischemia-driven revascularization:

A coronary revascularization procedure may be either a CABG or PCI. The coronary segments revascularized will be sub-classified as:

- Target lesion: a lesion revascularized in the index procedure (or during a planned or provisional staged procedure)
- Target vessel: the target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself
- Target vessel non-target lesion: the target vessel non-target lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by QCA
- Non-target vessel: for the purposes of this trial, the only possible non-target vessel would be the RCA and its major branches that were not treated by either PCI or CABG at the index procedure (unless either the LAD or LCX is occluded at baseline and no attempt was made to revascularize these territories by either PCI or CABG)

All revascularization events will be adjudicated as either ischemia-driven or non-ischemia-driven. Revascularization will be considered ischemia-driven if the diameter stenosis of the revascularized coronary segment is ≥50% by QCA and any of the following criteria for ischemia are met:

- A positive functional study corresponding to the area served by the target lesion; or
- Ischemic ECG changes at rest in a distribution consistent with the target vessel; or
- Typical ischemic symptoms referable to the target lesion; or
- IVUS of the target lesion with a MLA of ≤4 mm² for non-left main lesions or ≤6 mm² for left main lesions. If the lesions are de novo (i.e., not restenotic), the plaque burden must also be ≥60%; or FFR of the target lesion ≤0.80

CABG, Coronary artery bypass grafts; CK, Creatine-kinase; CK-MB, Creatine-kinase MB; CT, Computed tomography; CVA, Cerebrovascular accident; ECG, Electrocardiogram; FFR, Fractional flow reserve; IVUS, Intravascular ultrasound; LAD, Left anterior descending; LBBB, Left bundle branch block; LCX, Left circumflex artery; MLA, Minimal Lumen area; MRI, Magnetic Resonance Imaging; MI, Myocardial Infarction; NIHSS, National Institutes of Health Strokes Scale; PCI, Percutaneous coronary intervention; QCA, Quantitative coronary angiography; RCA, Right coronary artery; TIA, Transient ischemic attack; TnI, Troponin-I; TnT, Troponin-T; ULN, Upper limit of normal; URL, Upper reference limit
Table S6. Sensitivity analysis

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<tr>
<th>Studies included</th>
<th>Outcome</th>
<th>Subgroup</th>
<th>OR</th>
<th>95% CI</th>
<th>(I^2)</th>
<th>p-value</th>
<th>P-interaction</th>
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<td>SYNTAX EXCEL</td>
<td>Death, MI, stroke</td>
<td>Diabetics</td>
<td>0.92</td>
<td>0.60-1.42</td>
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<td>Non-Diabetic</td>
<td>0.99</td>
<td>0.76-1.28</td>
<td>0%</td>
<td>0.99</td>
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<tr>
<td>PRECOMBAT SYNTAX</td>
<td>Death, MI, stroke, revascularization</td>
<td>Diabetics</td>
<td>1.46</td>
<td>0.90-2.36</td>
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<td>0.18</td>
<td>0.51</td>
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<td>Non-Diabetics</td>
<td>1.20</td>
<td>0.88-1.64</td>
<td>0%</td>
<td>0.16</td>
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<td>PRECOMBAT EXCEL</td>
<td>Death, MI, stroke</td>
<td>Syntax &lt;22</td>
<td>0.78</td>
<td>0.50-1.21</td>
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<td>68%</td>
<td>0.002</td>
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Table displays results stratified by Diabetic group and SYNTAX score with at least 2 studies reporting outcomes. Results are pooled OR by random-effects modelling.

*MI, myocardial infarction; OR, odds ratio*
**Figure S1. Risk estimates at 1-year follow up**

Forest plot displays summary odds ratio (OR) and 95% confidence intervals (CI) for A) Safety endpoint of all-cause death, MI and stroke; and B) Efficacy-safety endpoint of all-cause death, MI, stroke and repeat revascularization.

CABG, coronary artery bypass grafting, DES, drug-eluting stent; MI, myocardial infarction,
**Figure S2. Risk estimates by stent generation**

Forest plot displays summary estimates (odds ratios and 95% confidence intervals) of studies using early generation DES vs. new generation DES compared to CABG. A) Safety endpoint of death, MI or stroke. B) Efficacy-safety endpoint of death, MI, stroke or revascularization. p-value for interaction is displayed as heterogeneity between groups.

**CABG, Coronary artery bypass grafts; DES, Drug eluting stent;**
Figure S3: Risk estimates by follow-up duration

Forest plot displays summary estimates (odds ratios and 95% confidence intervals) of studies by short-term (12-months), mid-term (36-months) and long-term (60-months) follow-up. A) Safety endpoint of all-cause death, MI or stroke. B) Efficacy-safety endpoint of all-cause death, MI, stroke or revascularization. P-value for interaction is displayed as heterogeneity between groups.

CABG, Coronary artery bypass grafts; DES, Drug eluting stent;
Figure S4. Funnel plot for visual estimation of publication bias

A) Safety endpoint of all-cause death, MI, stroke. B) Efficacy-safety endpoint of all-cause death, MI, stroke or revascularization.
References


Christiansen EH. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *The Lancet*.  
