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

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- **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.¹ Patients with ULMCA stenosis are typically advised to undergo revascularization because this has been shown to improve prognosis when compared with optimal medical therapy.² 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.³ This has been reflected in current international guidelines, where CABG carries a class I recommendation for ULMCA disease.^{4,5} 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

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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,^{6,7} 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).¹⁰ 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 allcause 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.8 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), SYNTAX¹³ (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), EXCEL⁹ (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 (P=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; P=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

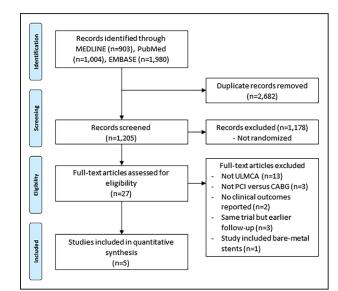


Figure 1. Study flow chart. Flow diagram illustrating the study selection process for the systematic review and meta-analysis. CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention; and ULMCA, unprotected left main coronary artery.

analysis was stratified by DES type ($P_{\text{interaction}}$ =0.45; Figure II in the Data Supplement), nor by clinical follow-up duration ($P_{\text{interaction}}$ =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 ($P_{\text{interaction}}$ =0.84; Table VI in the Data Supplement). Two studies reported SYNTAX score–specific outcomes. This demonstrated that in patients with anatomically more complex disease (SYNTAX ≥22), the safety composite rates were significantly higher in patients undergoing PCI using DES (OR, 1.64; 95% CI, 1.22–2.20; $P_{\text{interaction}}$ =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 ($l^2=0\%$). 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 $(P_{\text{interaction between early- and newer-generation DES}=0.85;$ 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 followup ($P_{\text{interaction}}$ =0.38; Figure III in the Data Supplement), and no difference observed in patients with diabetes mellitus $(P_{\text{interaction}}=0.51; \text{Table VI in the Data Supplement}).$

Individual Clinical End Points

All five trials individually reported the incidence of allcause 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

	Boudriot et al11	PRECOMBAT ¹²	SYNTAX ¹³	NOBLE ⁸	EXCEL ⁹
Sample, n	100/100	300/300	357/348	592/592 66/66	948/957
Age, y	66/69	62/63	65/66		66/66
Male sex, %	72/77	76/77	72/76	80/76	76/78
Diabetes mellitus, %	40/33	34/30	24/26	15/15	30/28
Hypertension, %	82/82	54/51	67/62	65/66	75/74
Hyperlipidemia, %	68/64	42/40 81/75		82/78	72/69
CRF, %	NR	1/0 1/2		NR	18/15
Current smoker, %	35/28	30/28 18/24		19/22	24/21
Previous CVA, %	3/6	NR 5/4		NR	6/7
Previous MI, %	19/14	4/7 29/25		NR	18/17
ACS, %	NR	47/54 31/29		18/17	39/39
LVEF, %	65/65	62/61	NR	60/60	57/57
BMI, kg/m ²	27/27	25/25	28/28	28/28	29/29
EuroSCORE	2.4/2.6	2.6/2.8	3.9/3.9	2/2	NR
LMCA only, %	28/29	9/11	12/14	NR	17/18
LMCA+SVD, %	35/27	17/18	19/20	NR	31/31
LMCA+DVD, %	26/28	34/30	31/31	NR	35/32
LMCA+TVD, %	11/17	41/41 38/35		NR	17/19
SYNTAX score, mean	24/23	24/26	30/30	23/22	21/21
Distal LMCA involvement, %	74/69	67/62	56/52	81/81	NR
DES type	SES	SES	PES	BES*	EES
No. of stents†	NR	2.7±1.4	NR	1 (IQR, 1–2)	2.4±1.5
Stent length†, mm	NR	60±42	NR	NR	49±36
Bifurcation: FKB, %	100	70	NR	55	NR
IVUS guided, %	NR	91	NR	75‡	77
No. of grafts†	NR	2.7±0.9	NR	2.5	2.6±0.8
IMA, %	99	94	NR	NR	99
Off-pump surgery, %	46	64	NR	16	29

Table 1.	Study Patient Demographics,	Angiographic Characteristics,	and Procedural Characteristics

Data are presented as percentage treated with PCI/percentage treated with CABG unless otherwise stated.

ACS indicates acute coronary syndrome; BES, biolimus-eluting stent; BMI, body mass index; CABG, coronary artery bypass grafting; CRF, chronic renal failure; CVA, cerebrovascular accident; DES, drug-eluting stent; DVD, double-vessel disease; EES, everolimus-eluting stent; EXCEL, Evaluation of the Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FKB, final kissing balloon; IMA, internal mammary artery; IQR, interquartile range; IVUS, intravascular ultrasound; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction (presented as median or mean); 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; PES, paclitaxel-eluting stent; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SES, sirolimus-eluting stent; SVD, single-vessel disease; SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery; and TVD, triple-vessel disease.

*BES was the recommended study stent but other Conformité Européene-marked DES could be used at the operators' discretion. †Per-patient level analysis.

⁺Postimplantation IVUS evaluation only.

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

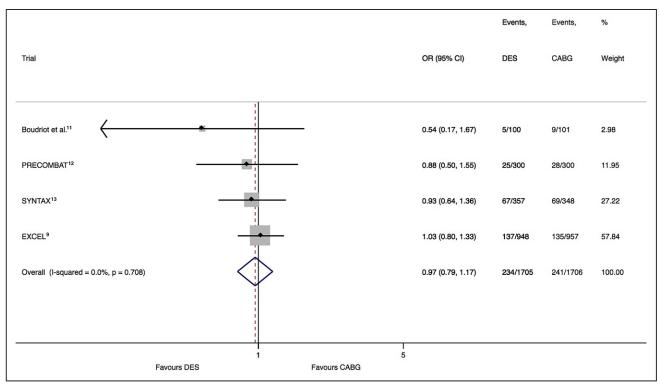


Figure 2. Risk estimates for primary safety end point for percutaneous coronary intervention vs coronary artery bypass grafting (CABG). Forest plot displays summary odds ratio (OR) and 95% confidence intervals (CI) for combined outcome of all-cause death, myocardial infarction (MI), or stroke. DES indicates drug-eluting stent.

in randomized trials to improve survival when compared with optimal medical therapy.¹⁵ 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.¹⁶ 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.¹⁷

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.^{18,19} The beneficial

	Overall	Boudriot et al11	PRECOMBAT ¹²	SYNTAX ¹³	NOBLE ⁸	EXCEL ⁹
Safety end point	13.7/14.1	5.0/8.9	8.4/9.6	19.0/20.8	NR	15.4/14.7
Effectiveness end point	23.3/18.2	NR	17.5/14.3	36.9/31.0	29.0/19.0	23.1/19.1
All-cause death	7.4/7.0	2.0/5.0	5.7/7.9	12.8/14.6	12.0/9.0	8.2/5.9
МІ	6.0/4.8	3.0/3.0	2.0/1.7	8.2/4.8	7.0/2.0	8.0/8.3
Stroke	2.0/2.2	NR	0.7/0.7	1.5/4.3	5.0/2.0	2.3/2.9
Repeat revascularization	14.2/8.3	14.0/5.9	13.0/7.3	26.7/15.5	16/10	12.9/7.6

Table 2. Summary and Individual Trial Clinical Event Rates

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.

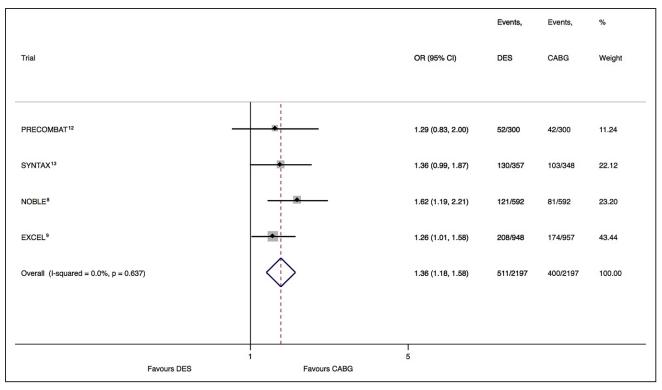


Figure 3. Risk estimates for secondary effectiveness end point for percutaneous coronary intervention vs coronary artery bypass grafting (CABG). Forest plot displays summary odds ratio (OR) and 95% confidence intervals (CI) for combined outcome of all-cause death, myo-cardial infarction (MI), stroke, or repeat revascularization. DES indicates drug-eluting stent.

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.²⁰ Although refinements in DES technology continues 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).²¹ 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.22 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.23 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,²⁴ principally because of larger postinterventional luminal dimension.²⁵ Although similar gains in stent expansion can be achieved using optical coherence tomography,²⁶ 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.²⁷

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

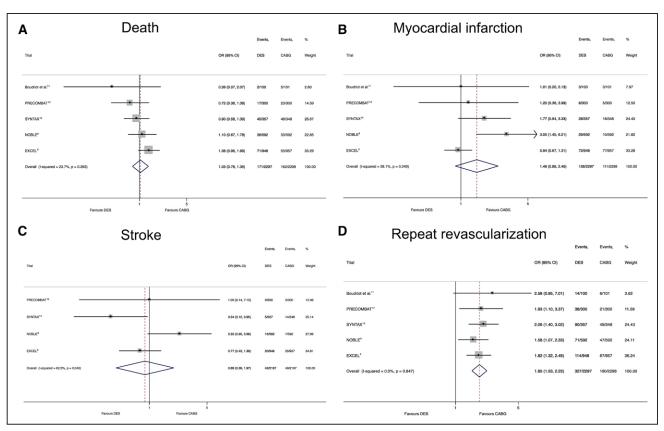


Figure 4. Risk estimates for individual clinical outcomes for percutaneous coronary intervention vs coronary artery bypass grafting (CABG). Forest plot displays summary estimates for (**A**) all-cause death, (**B**) myocardial infarction (MI), (**C**) stroke, and (**D**) repeat revascularization. Cl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

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.²⁸ 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.

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References

Disclosures

- Fajadet J, Chieffo A. Current management of left main coronary artery disease. Eur Heart J. 2012;33:36–50b. doi: 10.1093/eurheartj/ehr426.
- Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Longterm CASS experience. *Circulation*. 1995;91:2335–2344.
- Taggart DP, Kaul S, Boden WE, Ferguson TB Jr, Guyton RA, Mack MJ, Sergeant PT, Shemin RJ, Smith PK, Yusuf S. Revascularization for unprotected left main stem coronary artery stenosis stenting or surgery. J Am Coll Cardiol. 2008;51:885–892. doi: 10.1016/j.jacc.2007.09.067.
- 4. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354-e471. doi: 110.1161/CIR.0b013e318277d6a0.
- Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M,

Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A; European Society of Cardiology Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; EACTS Clinical Guidelines Committee, Sousa Uva M, Achenbach S, Pepper J, Anyanwu A, Badimon L, Bauersachs J, Baumbach A, Beygui F, Bonaros N, De Carlo M, Deaton C, Dobrev D, Dunning J, Eeckhout E, Gielen S, Hasdai D, Kirchhof P, Luckraz H, Mahrholdt H, Montalescot G, Paparella D, Rastan AJ, Sanmartin M, Sergeant P, Silber S, Tamargo J, ten Berg J, Thiele H, van Geuns RJ, Wagner HO, Wassmann S, Wendler O, Zamorano JL; Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery; European Association of Percutaneous Cardiovascular Interventions. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardiothorac Surg. 2014;46:517-592. doi: 10.1093/ejcts/ezu366.

- 6. Jang JS, Choi KN, Jin HY, Seo JS, Yang TH, Kim DK, Kim DS, Urm SH, Chun JH, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Meta-analysis of three randomized trials and nine observational studies comparing drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery disease. *Am J Cardiol.* 2012;110:1411–1418. doi: 10.1016/j.amjcard.2012.06.051.
- Gargiulo G, Tamburino C, Capodanno D. Five-year outcomes of percutaneous coronary intervention versus coronary artery bypass graft surgery in patients with left main coronary artery disease: an updated meta-analysis of randomized trials and adjusted observational studies. *Int J Cardiol.* 2015;195:79–81. doi: 10.1016/j.ijcard.2015.05.136.
- 8. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IBA, Trovik T, Eskola M, Romppanen H, Kellerth T, Ravkilde J, Jensen LO, Kalinauskas G, Linder RBA, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Sørensen HT, Nielsen PH, Niemelä M, Kervinen K, Lassen JF, Maeng M, Oldroyd K, Berg G, Walsh SJ, Hanratty CG, Kumsars I, Stradins P, Steigen TK, Fröbert O, Graham ANJ, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L; 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 [published online ahead of print October 31, 2016]. Lancet. doi: 10.1016/S0140-6736(16)32052–9.
- 9. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice M-C, Lembo N, Brown WMI, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogáts G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Pagé P, Dressler O, Kosmidou I, Mehran R, Pocock SJ; Kappetein AP; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease [published online ahead of print October 31, 2016]. N Engl J Med.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151:W65–W94.
- Boudriot E, Thiele H, Walther T, Liebetrau C, Boeckstegers P, Pohl T, Reichart B, Mudra H, Beier F, Gansera B, Neumann FJ, Gick M, Zietak T, Desch S, Schuler G, Mohr FW. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol.* 2011;57:538–545. doi: 10.1016/j.jacc.2010.09.038.
- 12. Ahn JM, Roh JH, Kim YH, Park DW, Yun SC, Lee PH, Chang M, Park HW, Lee SW, Lee CW, Park SW, Choo SJ, Chung C, Lee J, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB, Park SJ. Randomized trial of stents versus by-pass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT study. J Am Coll Cardiol. 2015;65:2198–2206. doi: 10.1016/j.jacc.2015.03.033.
- 13. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or

coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation*. 2014;129:2388–2394. doi: 10.1161/CIRCULATIONAHA.113.006689.

- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. doi: 10.1136/ bmj.327.7414.557.
- Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344:563–570.
- Xu B, Redfors B, Yang Y, Qiao S, Wu Y, Chen J, Liu H, Chen J, Xu L, Zhao Y, Guan C, Gao R, Généreux P. Impact of operator experience and volume on outcomes after left main coronary artery percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2016;9:2086–2093. doi: 10.1016/j. jcin.2016.08.011.
- Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes DR Jr, Leon MB, Marco J, Bogers AJ, Kappetein AP. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. *Eur Heart J*. 2013;34:2510–2518. doi: 10.1093/eurheartj/eht059.
- Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S 3rd, Bertrand M, Fuster V; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med.* 2012;367:2375–2384. doi: 10.1056/NEJMoa1211585.
- Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961–972. doi: 10.1056/ NEJMoa0804626.
- Otsuka F, Yahagi K, Sakakura K, Virmani R. Why is the mammary artery so special and what protects it from atherosclerosis? *Ann Cardiothorac Surg.* 2013;2:519–526. doi: 10.3978/j.issn.2225-319X.2013.07.06.
- Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Kang WC, Her AY, Kim YH, Kim Y, Hur SH, Hong BK, Kwon H, Jang Y, Hong MK; IVUS-XPL Investigators. Effect of intravascular ultrasoundguided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA*. 2015;314:2155–2163. doi: 10.1001/jama.2015.15454.
- McDaniel MC, Eshtehardi P, Sawaya FJ, Douglas JS Jr, Samady H. Contemporary clinical applications of coronary intravascular ultrasound. *JACC Cardiovasc Interv.* 2011;4:1155–1167. doi: 10.1016/j. jcin.2011.07.013.
- 23. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol.* 2005;45:995–998. doi: 10.1016/j.jacc.2004.12.066.
- Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes with intravascular ultrasound-guided stent implantation: a meta-analysis of randomized trials in the era of drug-eluting stents. *Circ Cardiovasc Interv.* 2016;9:e003700. doi: 10.1161/CIRCINTERVENTIONS.116.003700.
- Jang JS, Song YJ, Kang W, Jin HY, Seo JS, Yang TH, Kim DK, Cho KI, Kim BH, Park YH, Je HG, Kim DS. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. *JACC Cardiovasc Interv.* 2014;7:233–243. doi: 10.1016/j.jcin.2013.09.013.
- 26. Ali ZA, Maehara A, Généreux P, Shlofmitz RA, Fabbiocchi F, Nazif TM, Guagliumi G, Meraj PM, Alfonso F, Samady H, Akasaka T, Carlson EB, Leesar MA, Matsumura M, Ozan MO, Mintz GS, Ben-Yehuda O; Stone GW. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial [published online ahead of print October 30, 2016]. doi: 10.1016/S0140-6736(16)31922–5.
- 27. Lee MS, Bokhoor P, Park SJ, Kim YH, Stone GW, Sheiban I, Biondi-Zoccai G, Sillano D, Tobis J, Kandzari DE. Unprotected left main coronary disease and ST-segment elevation myocardial infarction: a contemporary review and argument for percutaneous coronary intervention. JACC Cardiovasc Interv. 2010;3:791–795. doi: 10.1016/j.jcin.2010.06.005.
- Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ. 1998;316:989–991.