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Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients With Left Main Coronary Artery Stenosis

A Systematic Review and Meta-analysis

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IMPORTANCE In patients with left main coronary artery (LMCA) stenosis, coronary artery bypass grafting (CABG) has been the standard therapy for several decades. However, some studies suggest that percutaneous coronary intervention (PCI) with drug-eluting stents may be an acceptable alternative.

OBJECTIVE To compare the long-term safety of PCI with drug-eluting stent vs CABG in patients with LMCA stenosis.

DATA SOURCES PubMed, Scopus, EMBASE, Web of Knowledge, and ScienceDirect databases were searched from December 18, 2001, to February 1, 2017. Inclusion criteria were randomized clinical trial, patients with LMCA stenosis, PCI vs CABG, exclusive use of drug-eluting stents, and clinical follow-up of 3 or more years.

DATA EXTRACTION AND SYNTHESIS Trial-level hazard ratios (HRs) and 95% CIs were pooled by fixed-effect and random-effects models with inverse variance weighting. Time-to-event individual patient data for the primary end point were reconstructed. Sensitivity analyses according to drug-eluting stent generation and coronary artery disease complexity were performed.

MAIN OUTCOMES AND MEASURES The primary end point was a composite of all-cause death, myocardial infarction, or stroke at long-term follow-up. Secondary end points included repeat revascularization and a composite of all-cause death, myocardial infarction, stroke, or repeat revascularization at long-term follow-up.

RESULTS A total of 4 randomized clinical trials were pooled; 4394 patients were included in the analysis. Of these, 3371 (76.7%) were men; pooled mean age was 65.4 years. According to Grading of Recommendations, Assessment, Development and Evaluation, evidence quality with respect to the primary composite end point was high. Percutaneous coronary intervention and CABG were associated with a comparable risk of all-cause death, myocardial infarction, or stroke both by fixed-effect (HR, 1.06; 95% CI, 0.90-1.24; $P = .48$) and random-effects (HR, 1.06; 95% CI, 0.85-1.32; $P = .60$) analysis. Sensitivity analyses according to low to intermediate Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score (random-effects: HR, 1.02; 95% CI, 0.74-1.41; $P = .89$) and drug-eluting stent generation (first generation: HR, 0.90; 95% CI, 0.68-1.20; $P = .49$; second generation: HR, 1.19; 95% CI, 0.82-1.73; $P = .36$) were consistent. Kaplan-Meier curve reconstruction did not show significant variations over time between the techniques, with a 5-year incidence of all-cause death, myocardial infarction, or stroke of 18.3% (319 events) in patients treated with PCI and 16.9% (292 events) in patients treated with CABG. However, repeat revascularization after PCI was increased (HR, 1.70; 95% CI, 1.42-2.05; $P < .001$). Other individual secondary end points did not differ significantly between groups. Finally, pooled estimates of trials with LMCA stenosis tended overall to differ significantly from those of trials with multivessel coronary artery disease without left main LMCA stenosis.

CONCLUSIONS AND RELEVANCE Percutaneous coronary intervention and CABG show comparable safety in patients with LMCA stenosis and low to intermediate–complexity coronary artery disease. However, repeat revascularization is more common after PCI.

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Viewpoint and Editor's Note
Supplemental content

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Compared with other sites, stenosis of the left main coronary artery (LMCA) is associated with a higher risk of mortality and myocardial injury owing to the larger amount of subtended myocardium.[1,2] Coronary artery bypass grafting (CABG) has been the standard of care for LMCA stenosis for many years, but due to significant advances in device technology, increased operators' expertise, and availability of improved antithrombotic therapy, percutaneous coronary intervention (PCI) has emerged as a valid alternative technique in a significant proportion of patients.[1-4]

Current European and American guidelines recommend both CABG and PCI for the treatment of LMCA stenosis in patients with overall low to intermediate complexity of coronary artery disease (CAD).[5,6] Recently, however, primary analyses of 2 randomized clinical trials comparing PCI with CABG for LMCA disease (Evaluation of Xience vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization [EXCEL][7] and Nordic-Baltic-British Left Main Revascularisation [NOBLE][8]) were reported. These large-scale trials leveraged stenting with second-generation drug-eluting stent (DES) (Xience; Abbott Vascular) and contemporary surgical techniques, showing somewhat conflicting treatment effects.

Previous meta-analyses did not include the EXCEL and NOBLE trials,[9-11] pooled both observational and randomized investigations,[9-11] combined patients receiving bare-metal stents and DESs,[9-12] assessed short-term and midterm outcomes,[9] used odds ratios or risk ratios for long-term outcomes,[10-12] and did not provide reconstruction of outcomes over time.[9-12] Against this background, we carried out an updated meta-analysis of randomized clinical trials comparing DES-based PCI with CABG at long-term follow-up in patients with LMCA disease.

Key Points

Question Does percutaneous coronary intervention with drug-eluting stenting and coronary artery bypass grafting provide similar long-term safety and efficacy in patients presenting with significant coronary artery disease involving the left main coronary artery?

Findings In this systematic review and meta-analysis including 4394 patients, the 2 revascularization techniques provided similar long-term outcomes in terms of death, myocardial infarction, and stroke. Coronary artery bypass grafting was associated with a significant reduction in the risk of repeat revascularization.

Meaning Although patients undergoing coronary artery bypass grafting benefit from a lower risk of repeat revascularization, if a patient wishes to avoid the morbidity associated with surgical revascularization, percutaneous coronary intervention is a safe and effective alternative.

Methods

We conducted a frequentist, pairwise meta-analysis in accordance with PRISMA and Cochrane Collaboration recommendations.[13,14] The PRISMA checklist is reported in eTable 1 in the Supplement. PubMed, Scopus, EMBASE, Web of Knowledge, and ScienceDirect databases were searched from December 18, 2001, to February 1, 2017. Three of us (R.C., A.H.F., and J.W.) performed the search independently. After removal of duplicates, full-text screening was performed with resolution of divergences by consensus (D.G., R.C., A.H.F., and J.W.). Other details on the literature search, data extraction, and feasibility assessment are provided in the eMethods in the Supplement. The meta-analysis was approved by Deutsches Herzzentrum München.

Eligibility Criteria

We included investigations fulfilling all of the following criteria: (1) randomized clinical trial, (2) LMCA stenosis, (3) PCI vs CABG, (4) exclusive use of DESs, and (5) follow-up of 3 or more years. Trials reporting follow-up of less than 3 years were excluded to allow focus on long-term outcomes and limit the influence of early nonsignificant differences.[15]

End Points

The primary end point was a composite of all-cause death, myocardial infarction, or stroke at the longest available follow-up. The secondary end points were repeat revascularization, individual components of the primary end point, cardiac death, stent or graft occlusion, and a composite of all-cause death, myocardial infarction, stroke, or repeat revascularization at the longest available follow-up.

Statistical Analysis

Fixed-effect and random-effects models with inverse variance weighting using trial-level log hazard ratios (HRs) and corresponding SEs were applied.[16,17] Trial-level and pooled estimates are reported as HR and 95% CI; risk distribution is presented by forest plots with weighting according to random-effects models.[18] We assessed heterogeneity across trials using between-study variance τ^2 and I^2 statistics.[14,16,19] I^2 values less than 25% defined low heterogeneity; 25% to 50%, moderate heterogeneity; and greater than 50%, high heterogeneity.[14] Formal testing for uniform effect size across trials with significance set at $P = .10$ was performed.[16] Data from patients with Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) (Taxus; Boston Scientific) scores[20] of 1 to 22 (low CAD complexity), 23 to 32 (intermediate), and 33 or above (high) in the Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT) and EXCEL trials[7,21] were synthesized by fixed-effect models. Testing for differences between the subgroups with significance set at $P < .05$ was performed.[16] Individual patient data reconstruction was performed by extreme-magnification digitization of high-quality Kaplan-Meier curves. Retrieved spatial information, numbers at risk, and events for each time interval were used to run a validated algorithm.[22] Reconstructed individual patient data were used for time-to-first-event Kaplan-Meier analyses to describe distribution of events over time and define cumulative incidence at 5-year follow-up. In a 1-stage, individual patient data meta-analysis, a shared frailty model accounting for clustering of patients across

the original trials with semiparametric penalized likelihood estimation of the hazard function was fitted to obtain the combined HR.[23] All analyses were performed with R, version 3.3.1 (R Foundation).

Sensitivity and Subgroup Analyses

With respect to the primary end point, several analyses were conducted: (1) inspection of individual trial influence by removing each trial independently using a random-effects model,[24] (2) selection of patients with low to intermediate CAD complexity (SYNTAX score 1-32),[21] (3) comparison according to DES generation,[25] and (4) reconstruction of individual patient data, Kaplan-Meier analysis, and estimation of HR by a shared frailty model.[26,27] We assessed the influence of individual trials by influence analyses for each of the secondary end points and explored the effect of DES generation on repeat revascularization and the secondary composite end point.

Finally, the SYNTAX trial has suggested that outcomes of patients undergoing PCI differ depending on the presence or absence of LMCA stenosis.[26] However, this trial had no power to detect differences between the 2 patterns of CAD, and no additional randomized trials have tested such a hypothesis. In a supplementary analysis, we compared safety outcomes between patients with and without LMCA stenosis.

Bias Assessment

Trial-level qualitative assessment was performed using the 7-domain Cochrane Collaboration tool.[14] The risk of bias was classified as high, unclear, or low.[14] We assessed the reliability of the results for each outcome according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[27]

Results

Characteristics of the Included Studies

After removal of duplicates and merging of data from independent searches, we identified 6569 reports (eFigure 1 in the Supplement). Search results are reported in eTable 2 in the Supplement. After screening at the title and abstract level, 14 potentially eligible trials were identified. After full-text assessment, 4 randomized clinical trials[7,8,21,26,28-31] were included in the primary analysis. The LMCA stenosis cohort of the SYNTAX trial[26,28-30,32] was included in the primary analysis. The 3-vessel disease cohort of the SYNTAX trial[32] and 2 randomized clinical trials[33,34] of patients with multivessel CAD (MV-CAD) without LMCA involvement were included for supplementary analyses. The list of trials included for primary and secondary analyses is reported in eAppendix 1 in the Supplement.

All but 1 of the included studies were prospective, multicenter, open-label, and reporting 5-year follow-up; the EXCEL trial[7] had a 3-year follow-up. A total of 4394 patients (PCI, 2197; CABG, 2197) were included in the primary analysis. Of these, 3371 (76.7%) were men; pooled mean age was 65.4 years. Trial design and main characteristics of the patients are summarized in the **Table** and eTables 3-5 in the Supplement. Inclusion and exclusion criteria of each trial are listed in eTable 6 in the Supplement.

Primary End Point

Percutaneous coronary intervention and CABG showed comparable outcomes (**Figure 1**B) both by fixed-effect (HR, 1.06; 95% CI, 0.90-1.24; $P = .48$) and by random-effects (HR, 1.06; 95% CI, 0.85-1.32, $P = .60$) models. The EXCEL trial[7] had the highest relative weight (35.9%). There was a moderate degree of heterogeneity ($I^2 = 42.5\%$, $P = .16$). Kaplan-Meier analysis did not show significant differences between treatments over time (Figure 1A), with a cumulative incidence of 18.3% (319 events) in the PCI group and 16.9% (292 events) in the CABG group at 5-year follow-up. Within the first 2 years, PCI exhibited a numeric advantage over CABG; however, from 3 to 5 years, CABG showed a nonsignificant advantage over PCI. Risk estimation by a shared frailty model showed similar safety of the techniques (HR, 1.05; 95% CI, 0.90-1.23; $P = .53$).

Influence analysis showed that heterogeneity was mainly due to the NOBLE trial[8] (Figure 1B), which was the only trial favoring CABG (omitting NOBLE: HR, 0.96; 95% CI, 0.80-1.15; $P = .66$; $I^2 = 0\%$). After including only patients with SYNTAX scores of 1 to 32, the results remained consistent (Figure 1B) (random effects: HR, 1.02; 95% CI, 0.74-1.41; $P = .89$). The grouping of trials according to DES generation did not show significant differences (Figure 1B), with comparable pooled estimates (first-generation: HR, 0.90; 95% CI, 0.68-1.20; $P = .49$; second-generation: HR, 1.19; 95% CI, 0.82-1.73; $P = .36$). Effect size was uniform within the first-generation DES group ($I^2 = 0\%$, $P = .95$), while the second-generation DES group showed high heterogeneity ($I^2 = 71.4\%$, $P = .06$) as an expression of the contrasting results of the EXCEL and NOBLE trials.[7,8]

The comparison between trials of patients with LMCA stenosis and those of patients with MV-CAD without LMCA stenosis showed a significant difference regardless of the model applied (fixed effect: $P = .01$; random effects: $P = .04$) (**Figure 2**). Descriptive data of trials including patients with MV-CAD are reported in eTables 7-11 in the Supplement. After pooling all trials regardless of the anatomic pattern, at long-term follow-up, PCI was associated with a significantly increased risk (random effects: HR, 1.21; 95% CI, 1.02-1.45; $P = .03$).

Secondary End Points

With respect to repeat revascularization (**Figure 3**A), PCI was associated with a significantly higher risk compared with CABG (HR, 1.70; 95% CI, 1.42-2.05; $P < .001$). A total of 313 events occurred in the PCI group and 184 events occurred in the CABG group. Effect size was consistent across trials ($I^2 = 0\%$, $P = .87$). The grouping of trials according to DES generation did not significantly change the results (Figure 3B). The second-generation DES (HR, 1.63; 95% CI, 1.29-2.06; $P < .001$) and first-generation DES (HR, 1.83; 95% CI, 1.37-2.45; $P < .001$) groups showed a similar risk of repeat revascularization ($P = .54$). At influence analysis, removal of each trial independently produced trivial changes (Figure 3C).

Table. Main Characteristics of the Included Trials

Source	No. of Patients Randomized, PCI vs CABG	Centers, No.	Region	Enrollment Period	Design	Primary End Point	Follow-up, y[a]	Registration[b]
LMCA stenosis								
SYNTAX (LMCA cohort)[26,28-30]	357 vs 348	85	The Netherlands, United States, Germany, United Kingdom, France, Italy, Sweden, Belgium, Hungary, Poland, Austria, Denmark, Latvia, Finland, Spain, Portugal	March 2005-April 2007	Noninferiority	All-cause death, myocardial infarction, stroke, or repeat revascularization	5	NCT00114972
PRECOMBAT[21]	300 vs 300	13	South Korea	April 2004-August 2009	Noninferiority	All-cause death, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization	5	NCT00422968
EXCEL[7]	948 vs 957	126	United States, United Kingdom, Canada, France, Italy, Germany, Spain, the Netherlands, Hungary, Switzerland, Poland, Latvia, Portugal, Argentina, Brazil, Australia, South Korea	September 2010-March 2014	Noninferiority	All-cause death, myocardial infarction, or stroke[c]	3	NCT01205776
NOBLE[8]	598 vs 603	36	United Kingdom, Sweden, Denmark, Latvia, Estonia, Finland, Germany	December 2008-January 2015	Noninferiority	All-cause death, nonprocedural myocardial infarction, stroke, or repeat revascularization	5	NCT01496651

Abbreviations: CABG, coronary artery bypass grafting; EXCEL, Evaluation of Xience vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; LMCA, left main coronary artery; NOBLE, Nordic-Baltic-British Left Main Revascularisation; PCI, percutaneous coronary intervention; PRECOMBAT, Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

[a] Longest follow-up at Kaplan-Meier analysis.

[b] Registration numbers in http://www.clinicaltrials.gov database.

[c] In the EXCEL trial,[7] the composite of all-cause death, myocardial infarction, stroke, or repeat revascularization was defined as a secondary end point.

Regarding the secondary composite end point of all-cause death, myocardial infarction, stroke, or repeat revascularization (eFigure 2, upper left in the Supplement), PCI was associated with an increased risk compared with CABG (HR, 1.27; 95% CI, 1.11-1.44; $P < .001$) without significant heterogeneity across included trials ($I^2 = 0\%$, $P = .58$). Influence analysis showed consistent results (eFigure 2, lower left in the Supplement). First- and second-generation DES groups were associated with a similar risk increase (eFigure 2, right in the Supplement).

Analyses of all-cause death, cardiac death, myocardial infarction, and stroke are shown in **Figure 4** and eFigure 3 in the Supplement. There was a comparable risk of death between PCI and CABG in both all-cause (random effects: HR, 1.04; 95% CI, 0.81-1.33; $P = .77$) and cardiac (random effects: HR, 1.00; 95% CI, 0.72-1.39; $P = .99$), with mild heterogeneity and limited influence of individual trials. Although the risk of myocardial infarction was comparable between techniques (random effects: HR, 1.48; 95% CI, 0.85-2.58; $P = .17$), high heterogeneity was detected ($I^2 = 67.4\%$, $P = .03$) as a result of the risk increase in the PCI arm of the NOBLE trial[8] (omitting NOBLE: HR, 1.13; 95% CI, 0.76-1.67; $P = .54$; $I^2 = 27.3\%$) and the comparable incidence between treatments observed in the EXCEL trial[7] (omitting EXCEL: HR, 1.95; 95% CI, 1.26-3.02; $P = .003$; $I^2 = 0.6\%$). The risk of stroke was comparable between PCI and CABG (random effects: HR, 0.87; 95% CI, 0.39-1.92; $P = .72$), with a high degree of heterogeneity ($I^2 = 62.7\%$, $P = .045$) mainly as a consequence of the increased incidence observed after PCI in the NOBLE trial[8] (omitting NOBLE: HR, 0.63; 95% CI, 0.37-1.09; $P = .10$; $I^2 = 9.1\%$). Stent or graft occlusion was documented less frequently in patients treated with PCI compared with CABG (eFigure 4 in the Supplement), with differences according to the model used and detection of substantial heterogeneity ($I^2 = 87.6\%$, $P < .001$) mainly introduced by the EXCEL trial,[7] where stent occlusion was less frequent than graft occlusion (omitting EXCEL: HR, 0.85; 95% CI, 0.45-1.64; $P = .64$; $I^2 = 31.0\%$).

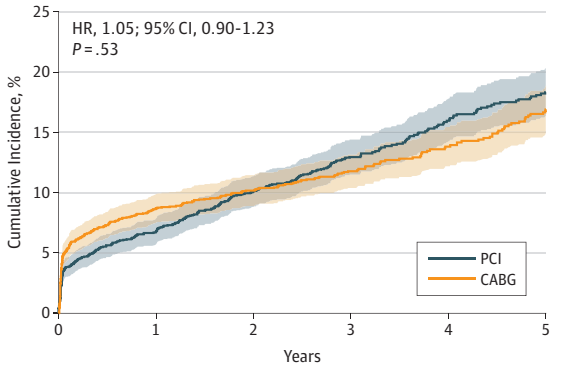
The comparison between trials of patients with LMCA stenosis and those of patients with MV-CAD without LMCA stenosis showed mixed results according to the model applied. Overall, there was a significant difference between the 2 groups of trials for the outcomes of all-cause death and myocardial infarction (eFigure 5 in the Supplement). Conversely, the 2 groups of trials seemed to be uniform in terms of stroke. Pooled estimates described a significant risk increase in all-cause death (random effects: HR, 1.21; 95% CI, 1.01-1.46; $P = .04$) and myocardial infarction (random effects: HR, 1.77; 95% CI, 1.20-2.59; $P = .004$) associated with PCI compared with CABG. Stroke showed a numerically reduced incidence after PCI compared with CABG (random effects: HR, 0.78; 95% CI, 0.49-1.26; $P = .31$).

Qualitative Review

Qualitative assessment of the trials showed an overall low risk of bias (eFigure 6 in the Supplement). According to GRADE, evidence quality with respect to the primary composite end

Figure 1. Primary End Point of Major Adverse Cardiac and Cerebrovascular Events

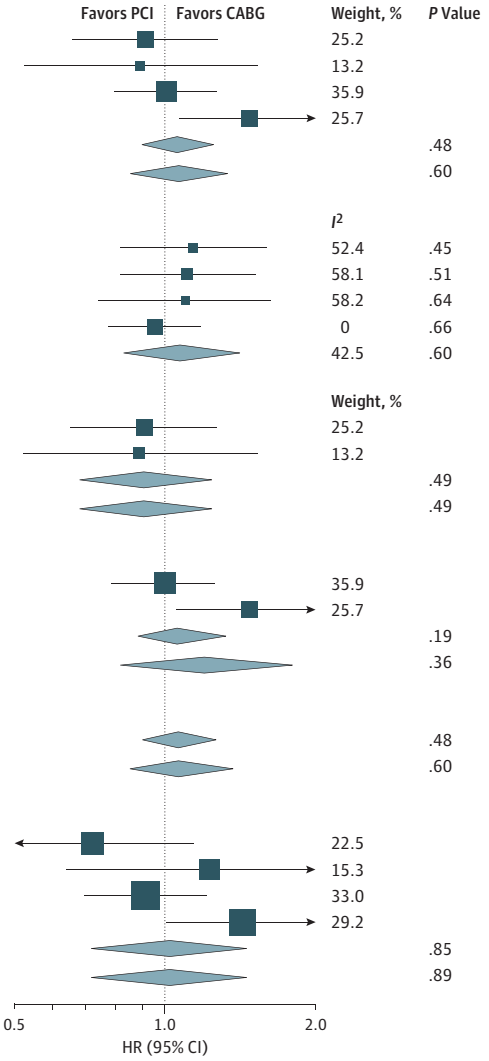
A Kaplan-Meier analysis



No. at risk

PCI	2197	1993	1817	1419	778	680
CABG	2197	1939	1772	1368	746	631

B Meta-analysis



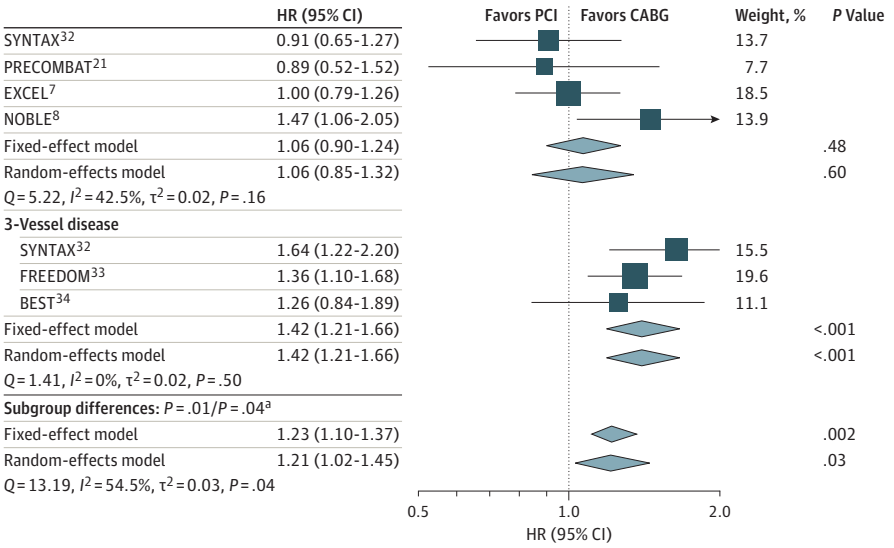
Source	HR (95% CI)	Weight, %	P Value
SYNTAX[30]	0.91 (0.65-1.27)	25.2	
PRECOMBAT[21]	0.89 (0.52-1.52)	13.2	
EXCEL[7]	1.00 (0.79-1.26)	35.9	
NOBLE[8]	1.47 (1.06-2.05)	25.7	
Fixed-effect model	1.06 (0.90-1.24)		.48
Random-effects model	1.06 (0.85-1.32)		.60
$Q = 5.22$, $I^2 = 42.5\%$, $\tau^2 = 0.02$, $P = .16$			
Influence analysis		I^2	
Omitting SYNTAX[30]	1.12 (0.84-1.49)	52.4	.45
Omitting PRECOMBAT[21]	1.09 (0.84-1.42)	58.1	.51
Omitting EXCEL[7]	1.09 (0.77-1.54)	58.2	.64
Omitting NOBLE[8]	0.96 (0.80-1.15)	0	.66
Random-effects model	1.06 (0.85-1.32)	42.5	.60
Grouped by DES			
First-generation DES		Weight, %	
SYNTAX[30]	0.91 (0.65-1.27)	25.2	
PRECOMBAT[21]	0.89 (0.52-1.52)	13.2	
Fixed-effect model	0.90 (0.68-1.20)		.49
Random-effects model	0.90 (0.68-1.20)		.49
$Q = 0.01$, $I^2 = 0\%$, $\tau^2 = 0$, $P = .95$			
Second-generation DES			
EXCEL[7]	1.00 (0.79-1.26)	35.9	
NOBLE[8]	1.47 (1.06-2.05)	25.7	
Fixed-effect model	1.14 (0.94-1.38)		.19
Random-effects model	1.19 (0.82-1.73)		.36
$Q = 3.49$, $I^2 = 71.4\%$, $\tau^2 = 0.05$, $P = .06$			
Subgroup difference: $P = 0$; $P = .19/P = .25$[a]			
Fixed-effect model	1.06 (0.90-1.24)		.48
Random-effects model	1.06 (0.85-1.32)		.60
$Q = 5.22$, $I^2 = 42.5\%$, $\tau^2 = 0.02$, $P = .16$			
SYNTAX score 1-32			
SYNTAX[30]	0.71 (0.44-1.14)	22.5	
PRECOMBAT[21]	1.23 (0.63-2.38)	15.3	
EXCEL[7]	0.89 (0.67-1.19)	33.0	
NOBLE[8]	1.44 (1.01-2.04)	29.2	
Fixed-effect model	1.02 (0.84-1.24)		.85
Random-effects model	1.02 (0.74-1.41)		.89
$Q = 7.10$, $I^2 = 57.7\%$, $\tau^2 = 0.06$, $P = .07$			

A, In Kaplan-Meier analysis, cumulative incidence across the 5 years of follow-up did not show significant difference between techniques. B, In meta-analyses, patients with coronary artery disease (CAD) involving left main coronary artery, percutaneous coronary intervention (PCI) vs coronary artery bypass grafting (CABG) had comparable risk of a composite of all-cause death, myocardial infarction, or stroke. In influence analysis, the Nordic-Baltic-British Left Main Revascularisation (NOBLE) trial[8] introduced heterogeneity. In drug-eluting stent (DES) generation, results were not significantly influenced when trials were grouped according to drug-eluting stent generation. In anatomic complexity, results also were not significantly influenced after including only patients with low to intermediate CAD complexity. EXCEL indicates Evaluation of Xience vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (Xience; Abbott Vascular); HR, hazard ratio; PRECOMBAT, Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery (Taxus; Boston Scientific).

[a] Testing for interaction by using values of fixed-effect and random-effects models, respectively.

point and repeat revascularization was high, evidence quality for death was moderate, and evidence quality for myocardial infarction, stroke, and stent or graft occlusion was low (eTable 12 in the Supplement).

Figure 2. Comparison of Trials Including Patients With Coronary Artery Disease (CAD) Involving Left Main Coronary Artery (LMCA) Stenosis vs Trials Including Patients With Multivessel CAD (MV-CAD) Without LMCA Involvement



The group of trials of patients with CAD involving the LMCA differed significantly from the group with MV-CAD without LMCA involvement. BEST indicates Bypass Surgery vs Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease; CABG, coronary artery bypass grafting; EXCEL, Evaluation of Xience vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (Xience; Abbott Vascular); FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus; HR, hazard ratio; NOBLE, Nordic-Baltic-British Left Main Revascularisation; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery (Taxus; Boston Scientific).

[a] Testing for interaction by using values for fixed-effect and random-effects models, respectively.

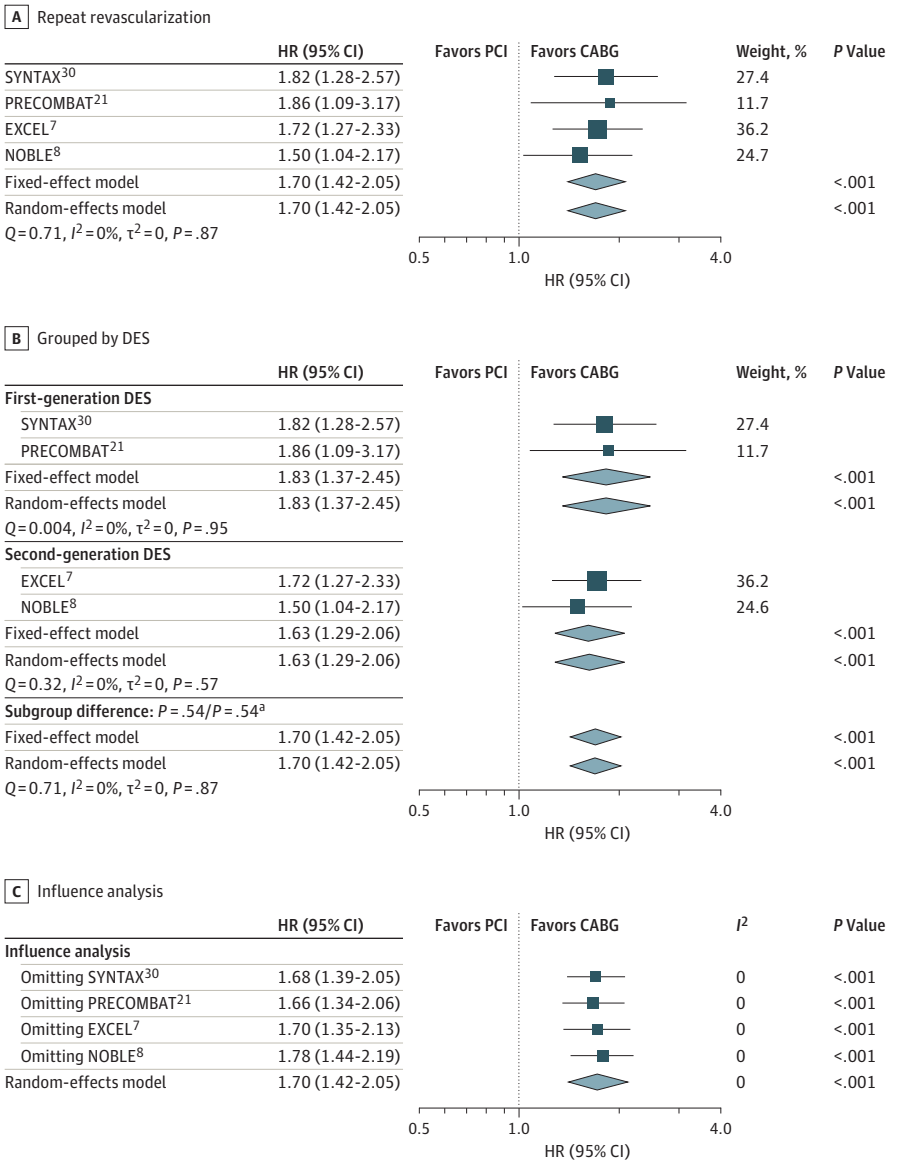
Discussion

The main finding of this meta-analysis is that, in patients with significant LMCA stenosis, both PCI with DESs and CABG are associated with a comparable risk of all-cause death, myocardial infarction, or stroke at long-term follow-up. Cumulative Kaplan-Meier curve reconstruction did not show significant differences over time, and long-term safety was acceptable with both PCI and CABG. The risk of repeat revascularization is the most important difference between techniques, with a higher risk for PCI at long-term follow-up compared with CABG.

The use of first-generation DESs has been traditionally considered one of the explanations for the differential effectiveness between PCI and CABG in early randomized trials. In this respect in the EXCEL and NOBLE trials,[7,8] patients who underwent PCI were treated with new-generation DESs. However, in our analysis, neither the risk of repeat revascularization nor the risk of the primary end point between techniques was influenced by DES generation. Considering the large amount of evidence supporting the superior antirestenotic properties of second-generation DESs compared with first-generation DESs,[25,35-37] it might be speculated that the superiority of CABG in this respect is driven by protection against the need for further revascularization in lesions outside the treated segment. In the EXCEL and NOBLE trials,[7,8] a several-fold increased risk of revascularization outside the target lesion was observed with PCI compared with CABG.

We performed a sensitivity analysis for the primary end point including only patients with low to intermediate complexity of CAD (according to the SYNTAX score[20]) without detecting significant variations in treatment effects. In the SYNTAX trial,[26] the stratification of patients with LMCA stenosis according to SYNTAX score terciles showed significant differences in the primary outcome. However, in the PRECOMBAT and EXCEL trials,[7,21] the largest number of events occurred in tercile 23 to 32 and there were no significant differences across terciles; however, in the NOBLE trial[8] the distribution of events was higher in the first tercile. These findings may reflect limitations of the anatomic SYNTAX score and support the use of tools also accounting for clinical characteristics.[39] The risk of issues arising relating to revascularization completeness, arterial grafting, and off-pump surgery is presented in eAppendix 2 in the Supplement. The risk of all-cause death and cardiac death between the techniques was similar at long-term follow-up. However, although the risks of myocardial infarction and stroke were also similar, we observed numeric variations between the techniques that are both likely attributable to heterogeneity introduced by the NOBLE trial.[8] With respect to myocardial infarction in the NOBLE trial,[8] there was a substantial risk increase with PCI. This finding can be partially explained by the definition of myocardial infarction used in the trial[8] that excluded periprocedural events, which generally are more frequent in patients undergoing CABG than PCI and sometimes large enough to be prognostically relevant over the long term. Moreover, although the incidence of periproce-

Figure 3. Secondary End Point of Repeat Revascularization



The risk of repeat revascularization was significantly higher in patients randomized to percutaneous coronary intervention (PCI). The effect was consistent across trials, and no heterogeneity was detected. Although the excess risk of repeat revascularization with PCI vs coronary artery bypass grafting (CABG) was numerically lower in second-generation drug-eluting stents (DESs) compared with first-generation DESs, testing for subgroup differences was nonsignificant and CABG continued to perform better than PCI. EXCEL indicates Evaluation of Xience vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (Xience; Abbott Vascular); HR, hazard ratio; NOBLE, Nordic-Baltic-British Left Main Revascularisation; PRECOMBAT, Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery (Taxus; Boston Scientific).

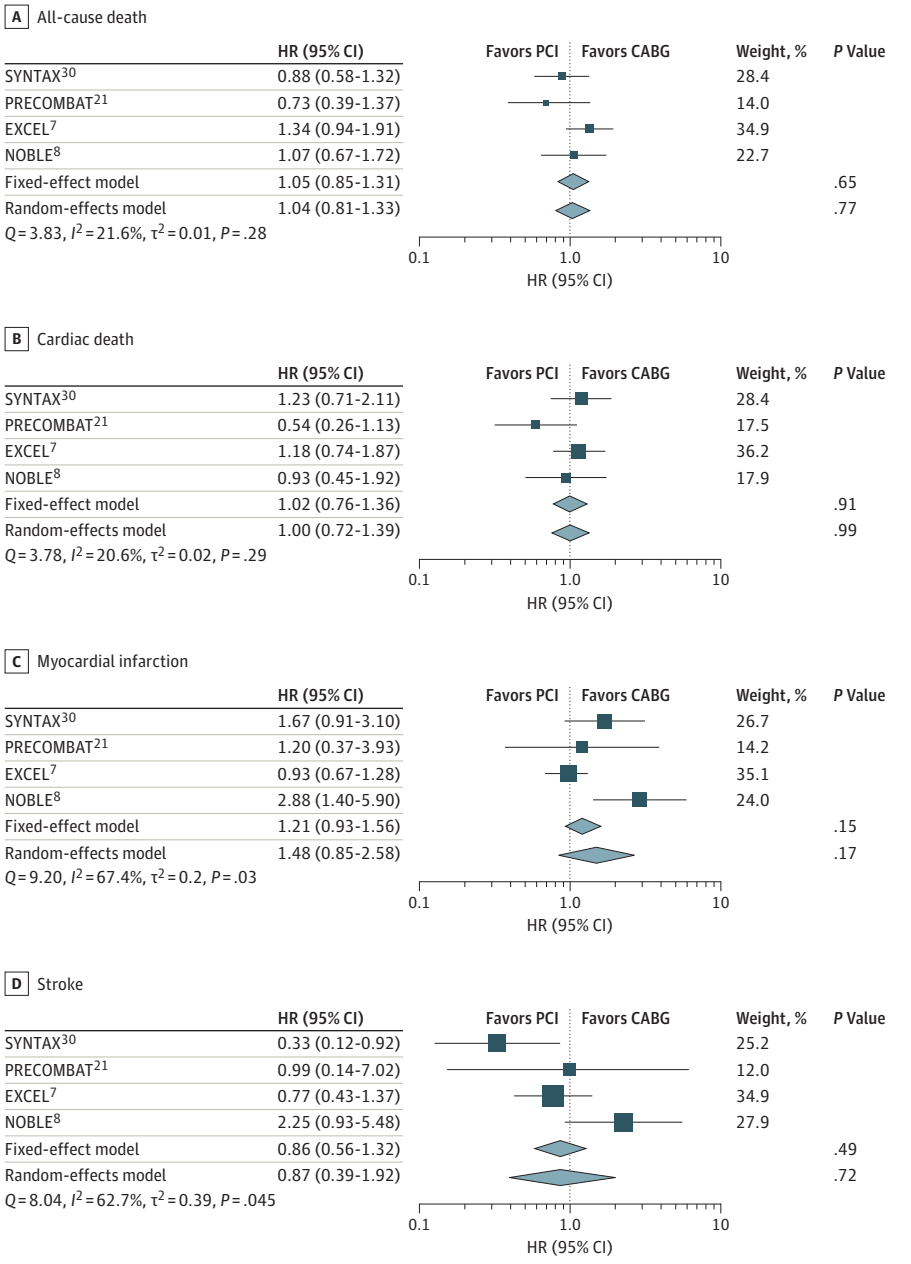
[a] Testing for interaction by using values for fixed-effect and random-effects models, respectively.

dural myocardial infarction between PCI and CABG in the NOBLE trial[8] seemed comparable, data were collected in only approximately half of the patients. However, as observed in the SYNTAX trial,[30] a numeric increase in myocardial infarction may be partially explained by a possible superior protection of grafts against ischemic events due to CAD progression in nontarget lesions and a possible increase in periprocedural events in the higher number of patients requiring repeat revascularization after PCI. Similarly, with respect to stroke, the risk between techniques was reduced or comparable in all but the NOBLE trial,[8] in which an unexpected numeric increase in events occurred after PCI.

The reason for the heterogeneity introduced by the NOBLE trial[8] is unclear. The main clinical, angiographic, and procedural characteristics of patients enrolled in the NOBLE trial[8] were overall comparable to or even more favorable for PCI (eg, 15% patients with diabetes, 91.7% completeness of revascularization, and 74% poststenting intravascular ultrasonography) than in other trials.

Percutaneous coronary intervention presents a higher risk of a composite end point of major adverse cardiac and cerebrovascular events, including repeat revascularization, compared with CABG as a consequence of the significant excess in repeat revascularization. Trial design should take into account the prominent impact of repeat revascularization in driving differences in this end point. Moreover, it is likely inadvisable in this setting to combine safety end points (ie, all-cause death, myocardial infarction, or stroke) with an efficacy end point (ie, repeat revascularization). In patients with LMCA stenosis undergoing PCI or CABG, the importance of end point and estimator selection has been recently highlighted in the Drug-Eluting Stent for Left Main Coronary Artery Disease registry.[40]

Figure 4. Secondary End Points of All-Cause Death, Cardiac Death, Myocardial Infarction, and Stroke



The risk of all-cause death (A) and cardiac death (B) was comparable between patients randomized to percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). The risk of myocardial infarction (C) tended to be higher in patients randomized to PCI, but the difference was nonsignificant compared with the risk in patients assigned to CABG and was mainly driven by the Nordic-Baltic-British Left Main Revascularisation (NOBLE) trial.[8] The risk of stroke (D) was numerically lower in patients randomized to PCI, but the difference was nonsignificant and attenuated by the NOBLE trial.[8] EXCEL indicates Evaluation of Xience vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (Xience; Abbott Vascular); HR, hazard ratio; PRECOMBAT, Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery (Taxus; Boston Scientific).

After assessing the evidence according to GRADE, we found high-quality evidence both with respect to the primary composite end point and repeat revascularization and moderate quality of evidence for death. However, evidence quality for myocardial infarction, stroke, and stent or graft occlusion was low, and caution must be exercised in interpreting the observations in relationship to these end points. Qualitative assessment of trials according to the Cochrane Collaboration tool showed an overall low risk of bias. Nevertheless, differences in patient characteristics and study definitions may have contributed to the variations in treatment effects seen.

Finally, we undertook additional analyses including randomized clinical trials comparing PCI with CABG in patients with MV-CAD without LMCA involvement to provide a comprehensive overview of long-term safety of PCI vs CABG. We observed significant between-group differences in the primary end point, with a higher risk of events with PCI compared with CABG in patients with MV-CAD and a borderline increased risk for all-cause death and myocardial infarction. These findings support the considerable influence of the pattern of CAD on treatment effects. Beyond unmeasured clinical differences between patients with the 2 CAD patterns, the difference in treatment effects may be related to several complementary factors, such as the larger reference vessel diameter of diseased coronary segments in the LMCA stenosis subset and the more diffuse extent of CAD in the MV-CAD sub-

set. Against this, the similar pooled risks of stroke in the LMCA stenosis and MV-CAD groups are likely explained by the close relationship of events with procedural invasiveness rather than CAD disease pattern.

In aggregate, these findings suggest that, in patients with significant stenosis of the LMCA and predominantly low to intermediate CAD complexity, both PCI and CABG are valid approaches to revascularization. Patient preference should be taken into consideration regarding the risks of periprocedural complications of surgery and long-term repeat revascularization after PCI. Patients with low surgical risk may benefit from CABG owing to more sustained effectiveness as evidenced by the reduced incidence of repeat revascularization. However, if a patient is not a good candidate for surgery or wishes to avoid the morbidity associated with surgical revascularization, PCI is a safe and effective alternative.

Limitations

Our study has some limitations. First, the absence of individual patient data and partial disclosure of results in original publications did not permit us to stratify patients according to every SYNTAX score tercile, perform additional subgroup analyses, and explore the impact of technical aspects of PCI procedures both in terms of the number of stents implanted to treat LMCA bifurcation (1 or 2 stents) and technique performed (eg, culotte, V-stenting, T and protrusion, crush, and double kissing crush).[41] In addition, although the use of intravascular imaging guidance has been associated with higher event-free survival after LMCA stenting,[42] data on this issue are not uniformly available across trials. Second, in this meta-analysis, the SYNTAX trial[26,28-30,32] was considered as 2 cohorts. However, the randomization process was stratified according to the presence or absence of LMCA stenosis. Third, in the PRECOMBAT trial,[21] the composite end point included ischemia-driven target vessel revascularization instead of repeat revascularization as in the other trials. Fourth, in the NOBLE trial[8] during early enrollment, 11% of patients in the PCI group received first-generation DESs. Fifth, available follow-up in the EXCEL trial[7] was 3 years, while data from the other trials were from 5-year analyses. Although the effect on pooled estimate of possible effect size variation is expected to be limited, the results of the EXCEL trial[7] at 5 years may significantly change. In addition, fewer than half of the patients enrolled in the NOBLE trial[8] reached the 5-year follow-up, which reduces the precision of estimated cumulative incidences. Finally, the absence of significant differences between PCI and CABG in terms of all-cause death, myocardial infarction, or stroke may be due to lack of statistical power. All of the included trials have a noninferiority design—some with large margins and computations made for composite end point, including also repeat revascularization. Even after pooling the data, the total number of patients was not large enough for superiority testing.

Conclusions

In patients undergoing revascularization of LMCA stenosis, the PCI and CABG techniques are associated with a comparable risk of a composite of all-cause death, myocardial infarction, or stroke at long-term follow-up. However, patients treated with PCI present a higher risk of repeat revascularization compared with those who undergo CABG. Evidence quality with respect to both of these end points was high. Risk of death—both all-cause and cardiac—was comparable between the 2 strategies, and only numeric differences in myocardial infarction and stroke were observed. The group of trials including patients with CAD involving LMCA stenosis tended to show diverging results from the group of trials including patients with MV-CAD without LMCA stenosis. In aggregate, these findings suggest that, in patients with significant stenosis of the LMCA and overall low to intermediate CAD complexity, both PCI and CABG are valid approaches to revascularization.

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