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Meta-Analysis of Randomized Controlled Trials of Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease

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Few randomized controlled trials (RCTs) and observational studies had shown acceptable short-term efficacy and safety of percutaneous coronary intervention (PCI) with drug-eluting stents (DES) compared with coronary artery bypass grafting (CABG) in selected patients with left main coronary artery disease (LMCAD). We aimed to evaluate long-term outcomes of PCI using DES compared with CABG in patients with LMCAD. On November 1, 2016, we searched available databases for published RCTs directly comparing DES PCI with CABG in patients with LMCAD. Odds ratios (ORs) were used as the metric of choice for treatment effects using a random-effects model. I-squared index was used to assess heterogeneity across trials. Prespecified end points were all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, and repeat revascularization at maximal available follow-up. We identified 5 RCTs including a total of 4,595 patients, with a median follow-up of 60 months. The risk of all-cause mortality (OR 1.01; 95% confidence interval [CI] 0.76 to 1.34) and cardiovascular mortality (OR 1.02; 95% CI 0.73 to 1.42) were comparable between PCI with DES and CABG. Similarly, there were no statistically significant differences between PCI with DES and CABG for MI (OR 1.45; 95% CI 0.87 to 2.40) and stroke (OR 0.87; 95% CI 0.38 to 1.98). Conversely, repeat revascularization was significantly higher with PCI compared with CABG (OR 1.82; 95% CI 1.51 to 2.21). In conclusion, in patients with LMCAD, PCI with DES appears to be a viable alternative to CABG at long-term follow-up, with similar risks of ischemic adverse events (mortality, MI, and stroke) but a higher risk of repeat revascularization. **(Am J Cardiol 2017;119:1942−1948)**

Left main coronary artery disease (LMCAD) is present in 4% to 9% of patients who underwent coronary angiography[1,2] and is frequently associated with multivessel disease.[3] In the past decades, coronary artery bypass graft surgery (CABG) was considered the standard-of-care treatment for LMCAD due to mortality benefit over medical therapy[4] and the high risk of restenosis and adverse outcomes associated with percutaneous coronary intervention (PCI).[5] However, recent technologic and procedural advances have paved the way for PCI as a viable alternative to CABG for revascularization of LMCAD.[6−10] The synergy between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial suggested clinical equipoise between PCI using DES and CABG[11] which led to 2012 American College of Cardiology/American Heart Association guidelines upgrade for PCI with DES to a class IIa level B in patients with favorable anatomy and high surgical risk.[12] Recently, 2 large noninferiority randomized controlled trials (RCTs) comparing PCI using newer generation DES with CABG for LMCAD have reported contrasting long-term results, thus adding to the continuing debate.[13,14] Therefore, we conducted this updated meta-analysis to compare long-term safety and efficacy of PCI using DES with CABG for the treatment of LMCAD.

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See page 1946 for disclosure information.

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Methods

We carried out a literature search using MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science, and Cochrane databases, of all studies published from January 1, 2000, to November 1, 2016, reporting direct comparisons between PCI using DES and CABG for LMCAD. We used the Mesh search headings "Left main," "Left main coronary artery," "PCI," "DES," and "CABG" in different combinations.

The following criteria were applied for study inclusion: (1) RCTs comparing PCI with DES and CABG published in peer-reviewed journals, (2) median follow-up of at least 1 year, and (3) reporting at least 1 clinical end point based on revascularization approach. Exclusion criteria were (1) nonrandomized study design and (2) use of bare metal stent in the PCI arm. The review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

Two reviewers (AG and KT) independently screened study reports for eligibility, assessed risk of bias, and collected data from each eligible study using predetermined forms. Any disparities between the 2 investigators were discussed with a third investigator (SA) until consensus was reached. From eligible RCTs, we collected information on study characteristics (study design, year and journal of publication, inclusion and exclusion criteria, data source, sample size, follow-up period, and primary and secondary end point definitions), baseline patient characteristics, mean SYNTAX and EuroScore, percentage of distal LMCAD lesion, and event rate of primary and secondary end points.

Prespecified end points of interest were all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, and repeat revascularization (either PCI or CABG) at maximal available follow-up.

Meta-analyses were conducted according to recommendations from the Cochrane Collaboration using the Review Manager, version 5.3, Nordic Cochrane Centre, Copenhagen, Denmark.[16] For each clinical end point, pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using random-effects models with Mantel-Haenszel method. p value of <0.05 was assigned as the measure of statistical significance. Heterogeneity between studies was calculated using I^2 statistic. Heterogeneity was considered significant in case of I^2 $>50\%$. Forest plots were generated to show the relative effect size of PCI versus CABG for each clinical outcome. In case of significant heterogeneity, sensitivity analyses were performed by excluding individual studies to test the influence of single trials.

Results

As reported in Figure 1, the initial search identified 981 publications; 384 studies were screened at abstract level. After full-text review, 5 studies were selected for inclusion in the final meta-analysis. These included 4 RCTs[9,13,14,17] and 1 prespecified subgroup analysis of an RCT,[18] including a total of 4,595 patients—2,297 randomly allocated to PCI with DES and 2,298 randomly allocated to CABG; 1 RCT was excluded from the analysis due to use of bare metal stent in majority of the patients randomized to PCI arm.[19,20] Of the 5 studies, 3 reported outcomes at 5 years,[14,17,18] 1 reported outcomes at 3 years,[13] and 1 reported outcomes at 1 year,[9] for a mean (median) follow-up of 45.6 months (60).

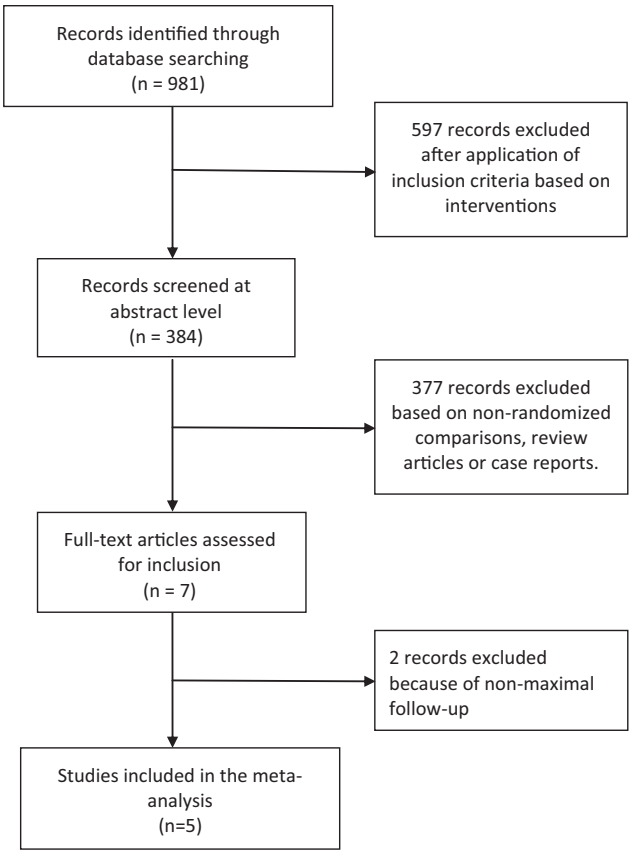

Figure 1. Search and screening flow.

Baseline characteristics of included studies and subject demographics are listed in Table 1. Mean age of patients was 66 years, and 76% were men. PCI was performed using first-generation DES (paclitaxel or sirolimus-eluting stents) in 36% of patients who underwent PCI and new-generation DES (everolimus or biolimus-eluting stents) in 64% of patients who underwent PCI. A left internal mammary artery graft was used in 96% of patients who underwent CABG, and off-pump technique use ranged from 15% to 64% in different studies. The studies were well balanced in terms of SYNTAX score and logistic EuroSCORE which ranged from 21% to 30% and 2% to 3.9%, respectively. Of the available data, complete revascularization was achieved in 81% and 83% of patients who underwent PCI and CABG, respectively.

All included studies reported all-cause mortality, MI, and repeat revascularization,[9,13,14,17,18] whereas stroke and cardiovascular mortality were reported in 4 of the 5 studies.[13,14,17,18]

PCI with DES and CABG had similar risks of all-cause mortality (OR 1.01; 95% CI 0.76 to 1.34) (Figure 2) and cardiovascular mortality (OR 1.02; 95% CI 0.73 to 1.42) (Figure 3), with no evidence of heterogeneity across studies. Similarly, there were no statistically significant differences between PCI with DES and CABG for MI (OR 1.45; 95% CI 0.87 to 2.40) (Figure 4) and stroke (OR 0.87; 95% CI 0.38 to

Table 1
Characteristics of included studies and patient demographics

	Number of Patients		Mean Age (years)	Male	DM	ACS (PCI/CABG)	Mean SYNTAX score (PCI/CABG)	Mean logistic euroscore (PCI/CABG)	Distal LMCA (PCI/CABG)	LM+TVD (PCI/CABG) (%)	Primary composite endpoint	Maximum available follow-up (years)
	PCI	CABG										
EXCEL[13] (2016)	948	957	66	77%	29%	39%/39%	20.6/20.5	-/-	82%/79%	17%/19%	Death/MI/stroke	3
NOBLE[14] (2016)	592	592	66	78%	15%	18%/17%	22.5/22.4	2/2	81%/81%	-/-	Death/MI/repeat revascularization/stroke	5
PRECOMBAT[17] (2015)	300	300	63	76%	32%	47%/54%	24.4/25.8	2.6/2.8	67%/62%	41%/41%	Death/MI/stoke/TVR	5
SYNTAX[18] (2014)	357	348	66	74%	25%	29%/30%	29.6/30.2	3.9/3.8	56%/52%	38%/35%	Death/stroke/MI/repeat revascularization	5
Budriot et al[9] (2011)	100	101	67.5	74%	36%	-/-	24/23	2.4/2.6	74%/69%	11%/17%	Death/MI/repeat revascularization	1

ACS = acute coronary syndrome; CABG = coronary artery bypass surgery; DES = drug eluting stent; DM = diabetes mellitus; EXCEL = effectiveness of XIENCE versus coronary artery bypass surgery for effectiveness of left main revascularization; LMCA = left main coronary artery; MI = myocardial Infarction; NOBLE = Nordic-Baltic-British Revascularization; PCI = percutaneous coronary intervention; PRECOMBAT = 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; TVD = triple vessel disease; TVR = target vessel revascularization.

1.98) (Figure 5) but with significant heterogeneity ($I^2 = 57\%$ and $I^2 = 64\%$, respectively). Conversely, the risk of repeat revascularization was significantly higher with PCI with DES compared with CABG (OR 1.82; 95% CI 1.51 to 2.21) (Figure 6), with no evidence of heterogeneity across trials.

We performed sensitivity analyses for the end points of MI and stroke to explore the observed heterogeneity. The heterogeneity for MI was no longer evident after excluding the Nordic-Baltic-British Left Main Revascularization Study (NOBLE) trial, with similar risk between PCI and CABG (OR 1.07; 95% CI 0.81 to 1.42; $I^2 = 0\%$) (Supplementary Figure 1). Similarly, there was no heterogeneity for stroke after excluding the NOBLE trial, with similar risk between PCI versus CABG (OR 0.62; 95% CI 0.35 to 1.10; $I^2 = 12\%$) (Supplementary Figure 2).

Discussion

This updated meta-analysis of randomized trials comparing myocardial revascularization strategies for LMCAD shows that at long-term follow-up, patients who underwent PCI with DES have similar risks of ischemic adverse events (i.e., all-cause mortality, cardiovascular mortality, MI, and stroke) but a higher risk of repeat revascularization compared with those treated with CABG.

Our findings consolidate the results of previous studies comparing PCI with DES and CABG for revascularization of LMCAD.[9–11,17,18] Five-year outcomes of the large Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT)[17] and SYNTAX[18] randomized trials showed no significant difference in mortality risk between PCI with DES and CABG in all-comer populations with LMCAD. Conversely, a prospective, observational study from Japan showed a higher cumulative mortality risk among patients who underwent PCI with DES compared with CABG after 5-year follow-up,[21] a finding that was no longer significant after adjustment for cardiovascular confounders. More recently, results of the large-scale noninferiority randomized Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial have been reported.[13] In this study, among 1,905 patients with LMCAD and low or intermediate anatomical complexity, PCI using everolimus-eluting stents was found to be noninferior to CABG with respect to the composite of death, MI, or stroke at 3-year follow-up. This was in contrast to the findings of the NOBLE randomized trial, which failed to show noninferiority between PCI and CABG in LMCAD for the composite of all-cause mortality, nonprocedural MI, any repeat coronary revascularization, and stroke while suggesting improved outcomes with CABG at 5 years of follow-up.[14]

We performed the present analysis in an attempt to reconcile these contrasting findings. Our results indicate a clinical equipoise between PCI and CABG with respect to ischemic adverse events during long-term follow-up. As it relates to mortality, our findings reinforce the message of available randomized trials—that consistently indicated similar risks of all-cause and cardiovascular mortality between LMCAD patients treated with PCI and CABG—by

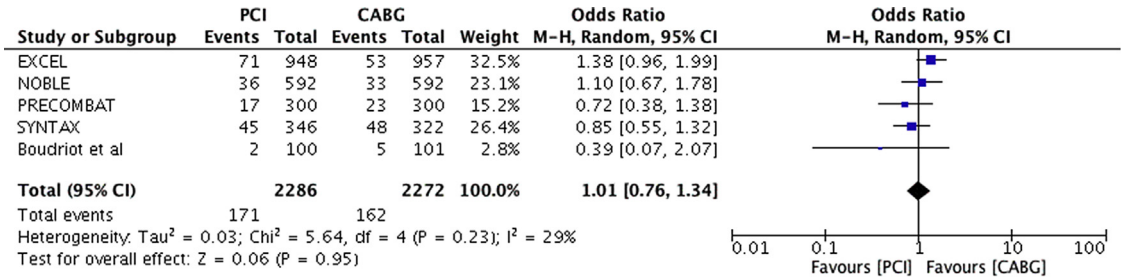

Figure 2. Risk of all-cause mortality.

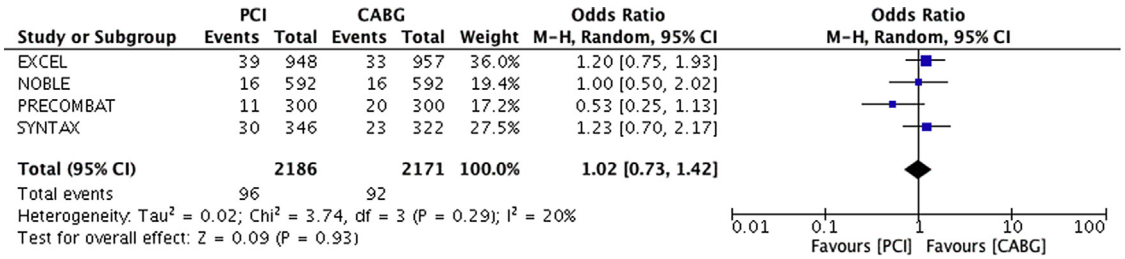

Figure 3. Risk of cardiovascular mortality.

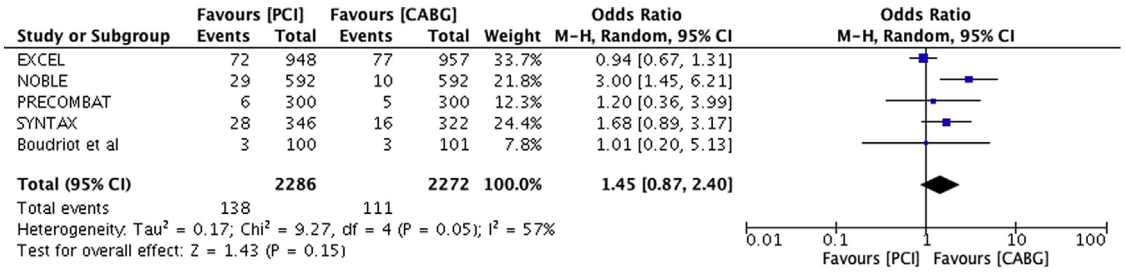

Figure 4. Risk of MI.

increasing precision of risk estimates. With respect to MI, beyond providing evidence of absence of significant differences in risk between PCI and CABG, we attempted to resolve the contrasting findings between NOBLE and other randomized trials. Specifically, although our pooled estimate crossed the equivalence line, we observed a significant degree of heterogeneity across trials that disappeared in sensitivity analyses excluding the NOBLE trial. The high prevalence of distal LM bifurcation lesions and the unexpected higher incidence of repeat revascularization due to de novo lesions among patients allocated to PCI in the NOBLE trial might explain, at least in part, the excess of MI risk in the PCI arm of this trial. Of note, repeat revascularization due to de novo lesions might be interpreted as a proxy of incomplete revascularization, which has been identified by previous studies as a key determinant of clinical outcomes with PCI compared with CABG.[22] We observed a similar phenomenon for stroke, with the NOBLE trial being responsible for the detected heterogeneity across trials. It is noteworthy that the higher risk of stroke among PCI allocated patients in the NOBLE trial counterintuitively emerged beyond the first year of follow-up. In the absence of any obvious reasons for these late stroke events, the difference may be attributed to chance. Moreover, the NOBLE trial design has been a matter of debate because the trial primary end point was changed from the original design.[14] However, we wish to underscore that we observed similar risks of all adverse ischemic events between PCI and CABG irrespective of inclusion of the NOBLE trial in our meta-analysis.

In line with previous evidence, our study shows higher risks of repeat revascularization with PCI using DES compared with CABG.[9–12] This may be explained, at least in part, by a small excess in restenosis with DES compared with the optimal results of arterial grafting and by the potential protective effect of arterial grafting in prevention of progression of CAD.[23] Moreover, distal LM lesions involving the left anterior descending and left circumflex coronary arteries are technically challenging and are associated with increased intra- and postprocedural complications.[24,25] In addition, our analysis included a significant number of patients who received early-generation DES which could also contribute to a higher risk of revascularization in the PCI group.[26,27] It is noteworthy, however, that a higher risk of repeat revascularization among patients treated with PCI did not translate into increased mortality or MI in our analysis. This highlights the different prognostic impact of the end point repeat revascularization compared with hard ischemic end points such as mortality, MI, and stroke.

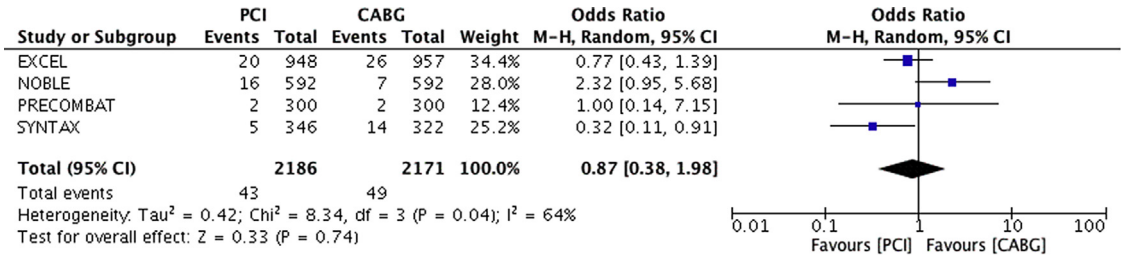

Figure 5. Risk of stroke.

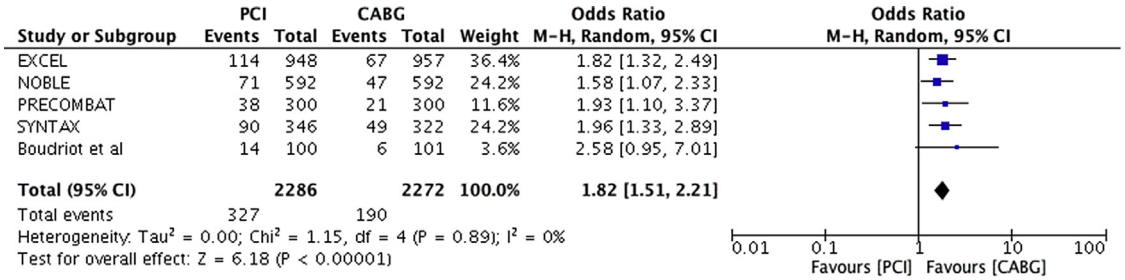

Figure 6. Risk of repeat revascularization.

The findings of our study have important clinical implications. Although previous studies have shown comparable survival and MI outcomes among PCI with DES and CABG at short-term follow-up, whether this correlation sustains at 5 years remains under-investigated.[28] Our study differs from another meta-analysis published recently, in that we further explored the heterogeneity observed by performing sensitivity analyses.[29] Additionally, instead of composite end points, we focused on independent pooling of individual end points to limit the bias associated with heterogeneous definitions of composite end points included in trials. On the basis of results of this study, PCI with DES should be considered noninferior to CABG for treating LMCAD given their equivalence in terms of all-cause and cardiovascular mortality and ischemic end points of MI and stroke, although it may result in more future need for revascularization. However, newer stent platforms, increasing utilization of imaging techniques and increasing center volumes are expected to reduce the revascularization rates. At the individual patient level, the choice of PCI or CABG requires consideration of patient preference, anatomic complexity, operative risk, and be ideally made using a heart-team approach.

This study suffers from some limitations. First, the analysis is based on aggregate data and shares the possible limitations of the included trials. Moreover, the absence of patient-level data precludes further stratified analyses or adjusted analyses to account for possible confounders. Second, a significant number of patients received early-generation DES within the trials included in our analysis. Third, current guidelines recommend use of the SYNTAX score to guide revascularization strategies in patients with LMCAD. Because of individual trial design and absence of patient-level data, we were unable to stratify results based on Syntax score.

Disclosures

Dr. Stefanini has received a research grant to the institution from Boston Scientific, Natick, Massachusetts and speaker/consultant fees from B. Braun, Bethlehem, Pennsylvania, Boston Scientific, and Edwards Lifesciences, Irvine, California. Dr. Rao is a consultant to Medtronic, Minneapolis, Minnesota and Svelte Medical, New Providence, New Jersey. The other authors report no conflicts of interest.

Supplementary data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2017.03.019.

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