Systematic Review

Percutaneous coronary intervention versus coronary bypass surgery for unprotected left main disease: a meta-analysis of randomized controlled trials

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Background: This meta-analysis of randomized controlled trials (RCTs) was aimed at comparing coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) for the treatment of unprotected left main coronary disease.

Methods: All RCTs randomizing patients to any type of PCI with stents *vs.* CABG for left main disease (LMD) were included. Primary outcome was a composite of follow-up death/myocardial infarction/stroke/repeat revascularization. Secondary outcomes were peri-procedural mortality and the individual components of the primary outcome. Incidence rate ratio (IRR) or odds ratio (OR) and 95% confidence intervals (CIs) were pooled using a generic inverse variance method with random effects model. Subgroup analyses were done based on: (I) type of PCI [bare metal stents (BMS) *vs.* drug-eluting stents (DES)] and; (II) mean SYNTAX score tertiles. Leave one-out analysis and meta-regression were performed.

Results: Six trials were included (4,700 patients; 2,349 PCI and 2,351 CABG). Follow-up ranged from 2.33 to 5 years. PCI was associated with higher risk of follow-up death/myocardial infarction/stroke/repeat revascularization (IRR =1.328, 95% CI, 1.114–1.582, P=0.002) and of repeated revascularization (IRR =1.754, 95% CI, 1.470–2.093, P<0.001). The risk of peri-procedural mortality (OR =0.866, 95% CI, 0.460–1.628, P=0.654), follow-up mortality (IRR =0.947, 95% CI, 0.711–1.262, P=0.712), myocardial infarction (IRR =1.342, 95% CI, 0.827–2.179, P=0.234) and stroke (IRR =0.800, 95% CI, 0.374–1.710, P=0.565) were similar between groups. No differences were found between DES and BMS subgroups. The risk of follow-up death/myocardial infarction/stroke/repeat revascularization with PCI was higher in all SYNTAX tertiles, with a progressive increase from the 1st to the 3rd tertile. At meta-regression, higher mean SYNTAX score was associated with higher risk for the primary outcome in the PCI group (beta =0.02, P=0.05), whereas no association was found with female gender, mean age, or diabetes.

Conclusions: CABG remains the therapy of choice for the treatment of unprotected LMD, especially for patients with a high SYNTAX score.

Keywords: Percutaneous coronary intervention (PCI); coronary artery bypass grafting (CABG); left main disease (LMD)

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Introduction

The best option for the treatment of patients with disease of the left main coronary artery is controversial.

Traditionally, left main disease (LMD) has been considered an indication for surgery (1). However, last year the publications of the NOBLE and EXCEL trials, which respectively denied and supported the non-inferiority of percutaneous coronary intervention (PCI) compared to coronary artery bypass grafting (CABG) for LMD, have fueled the debate, adding uncertainty with respect to what the optimal strategy of revascularization for the treatment for patients with unprotected LMD should be.

Herein we perform a meta-analysis of the randomized trials that compare the two treatment options. We also evaluate the effect of the evolution in stent types and SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score on outcomes.

Methods

This meta-analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (*Table S1*) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (2,3).

Data sources and searches

PubMed, EMBASE and the Cochrane Central Register of Controlled Trials were searched from inception to November 2016, without language restrictions. Search terms were "left main" AND ("coronary artery bypass" OR CABG OR "bypass surgery" OR "coronary bypass") AND ("percutaneous coronary intervention" OR "PCI" OR "stent"). Reference lists of the identified articles and relevant reviews and meta-analyses were screened by 2 reviewers (A Di Franco, LB Ohmes) to identify any additional relevant studies (i.e., backward snowballing).

Study selection

Investigators examined references at the title/abstract level, with divergences resolved by consensus, and then, if any potentially pertinent title/abstract was found, the complete article was retrieved. All articles with random allocation to treatment, comparing CABG to PCI with stents for unprotected LMD, were included.

Data extraction and quality assessment

Baseline data including SYNTAX score (4), procedural outcome, and follow-up time were independently abstracted by two investigators (A Di Franco, LB Ohmes). Outcomes were analyzed according to the intention-to-treat principle. Outcomes were adjudicated according to the original authors' definitions. Risk of bias among included trials was appraised by two independent investigators (LB Ohmes and M Rahouma) based on the "risk of bias assessment tool" provided by the Cochrane collaboration (5), in which 7 domains were assessed for each randomized controlled trial (RCT): random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and presence of other bias. The presence of a possible source of bias in each domain was assessed, and a final judgment of low, unclear, or high risk of bias was assigned.

Outcomes

The primary outcome was a composite of follow-up death/myocardial infarction/stroke/repeat revascularization at the longest available follow-up. The secondary outcomes were peri-procedural mortality, and the individual components of the primary outcome.

For the primary outcome, two different subgroup analyses were conducted based on: (I) type of stents used in the PCI group [bare metal stents (BMS) *vs.* drug-eluting stents (DES)]; and (II) tertiles of mean SYNTAX score. The cut-offs for 1st and 2nd tertiles were 22.80 and 25.05, respectively.

Data synthesis and analysis

This pairwise meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V 3.0 (2006 Biostat, Inc, Englewood, NJ, USA). Review Manager (RevMan) 5.3 was used for risk of bias assessment (6).

Relative effect estimates were calculated as log incidence rate ratios (IRRs) or odds ratio (OR) with 95% confidence intervals (95% CIs). We pooled late outcomes as natural logarithm of the IRR to account for potentially different follow-up durations between different treatments. We estimated the IRR through different means depending on the available study data. When hazard ratios (HRs) were

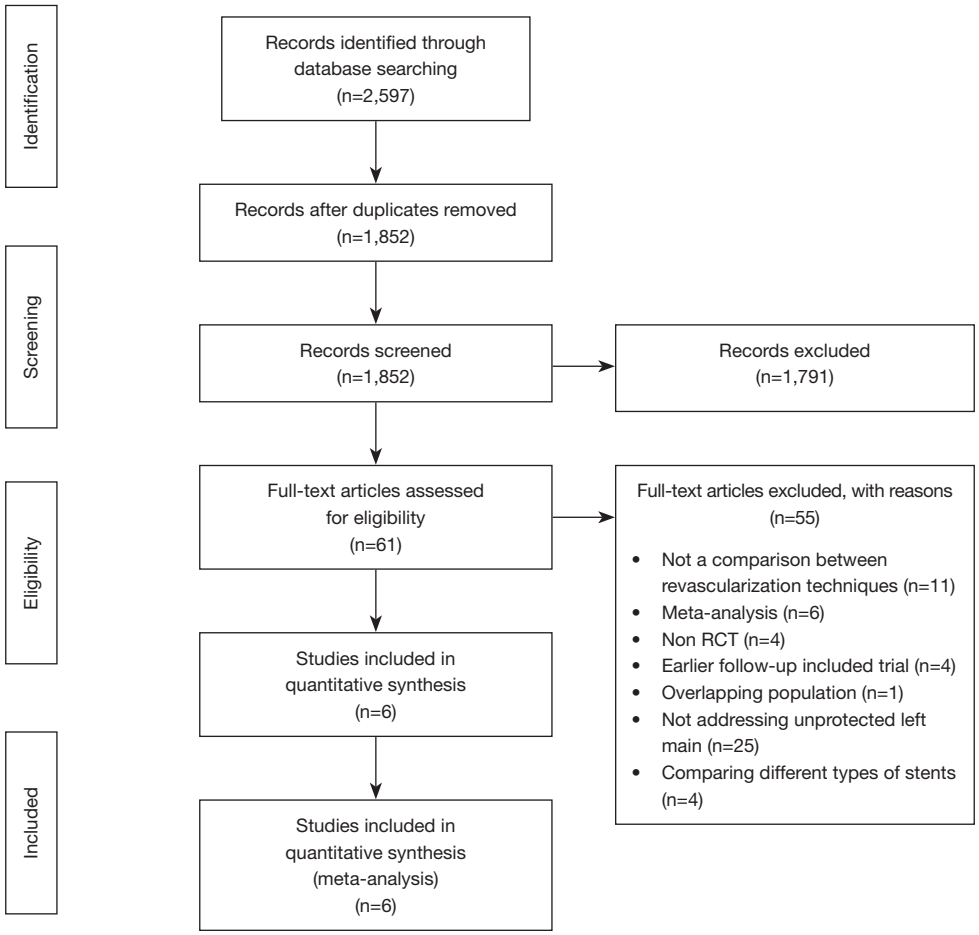

Figure 1 PRISMA flowchart of our meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

reported, we took the natural logarithm of the HR with standard error (SE) calculated from the 95% CI or log rank P value (7). When Kaplan Meier (K-M) curves were present, event rates were estimated from the curves using GetData Graph Digitizer software 2.26 (http://getdata-graph-digitizer.com/) and in case of absence of K-M curves, we used the reported event rates to calculate the IRR, as previously described (8,9).

IRRs were pooled using the generic inverse variance method with random model. As per guidelines, we reported heterogeneity as: low (I^2=0–25%), moderate (I^2=26–50%) and high (I^2>50%) (5). In all comparisons, the CABG group was used as reference.

For the primary outcome, leave-one-out analysis and funnel plot with trim and fill method to assess for publication bias were performed. Visual inspection and Egger's test were used to assess for funnel asymmetry (10). Meta-regression was used to assess any association between the primary outcome and female gender, mean age, diabetes and mean SYNTAX score.

Results

Among 2,597 potentially relevant articles, 6 met the inclusion criteria and were included in the final analysis (11-16). A PRISMA flow chart of study selection is shown in *Figure 1*. An overview of the included articles is shown in *Tables 1,2*. Risk of bias assessment for each trial is shown in *Figure S1*.

In total, 4,700 patients were included (2,349 PCI and 2,351 CABG). Follow-up ranged from 2.33 to 5 years.

Primary outcome

PCI was associated with higher risk of follow-up death/myocardial infarction/stroke/repeat revascularization (IRR

Table 1 Characteristics of individual studies

Trial/year	Study period	Primary endpoints*	Secondary endpoints	CABG (n)	PCI (n)	Stents used	Mean/median follow-up
Boudriot 2011 (15)	2003–2009	MACE	Individual components of MACE	100	101	SES, PES	36.5 (IQR: 24.4–60.9) months
PRECOMBAT (14)	2004–2009	MACCE	Individual components of MACCE	300	300	SES	5 years
LE MANS (13)	2001–2004	Change in LVEF	30-day and 1-year MAE and MACCE, length of hospitalization, exercise tolerance; survival and MACCE and target vessel failure and revascularization	53	52	DES, BMS	28±9.9 months
NOBLE (12)	2008–2015	MACCE	NR	592	592	BES	37.2 (IQR: 24.0–60.0) months
SYNTAX (11)	2009–2014	MACCE	NR	348	357	TAXUS Express	5 years
EXCEL (16)	2010–2014	Death, stroke or MI (3 years)	Primary endpoints at (30 days); revascularization (3 years)	957	948	EES	36 months

*, MACCE was defined as (all cause death, stroke, myocardial infarction, and repeat revascularization); MACE was defined as (death, Q-wave myocardial infarction, or target lesion revascularization), MAE all-cause mortality, acute myocardial infarction, repeated revascularization, acute heart failure, or low output syndrome requiring intravenous inotropic agents and/or intra-aortic balloon pump support, post procedural complications leading to reintervention, stroke, arrhythmia, major bleeding requiring additional blood transfusion, and infections compromising post-procedural rehabilitation. BES, biolimus-eluting stent; BMS, bare metal stent; DES, drug eluting stent, EES, everolimus-eluting stent; IQR, inter-quartile range; MACCE, major adverse cardiac or cerebrovascular event; MACE, major adverse cardiovascular events; MAE, major adverse events; MI, myocardial infarction; NR, not reported; PES, paclitaxel-eluting stents; SES, sirolimus eluting stents.

Table 2 Demographics of the included populations

Trial/year	Age (mean ± SD) (year)	Female (%)	Diabetics (%)	Renal impairment (%)	COPD (%)	EuroSCORE (mean ± SD/ median & IQR)	Mean SYNTAX score
Boudriot 2011 (15)	CABG =69 [63–73], PCI =66 [62–73]	CABG =23, PCI =28	CABG =33, PCI =40	NR	NR	CABG =2.6 (1.7–4.9), PCI =2.4 (1.5–3.7)	CABG =23.0 (14.8–28.0), PCI =24.0 (19.0–29.0)
PRECOMBAT (14)	NR	CABG =23, PCI =23.6	CABG =30, PCI =34	NR	NR	NR	CABG =25.8±10.5, PCI =24.4±9.4
LE MANS (13)	CABG =61.3±8.4, PCI =60.6±10.5	CABG =27, PCI =40	CABG =17, PCI =19	NR	NR	CABG =3.5±2.3, PCI =3.3±2.3	CABG =24.7±6.8, PCI =25.2±8.7
NOBLE (12)	CABG =66.2±9.4, PCI =66.2±9.9	CABG =24.0, PCI =20.0	CABG =15.0, PCI =15.0	NR	NR	CABG =2 [2–4], PCI =2 [2–4]	CABG =22.4±8.0, PCI =22.5±7.5
SYNTAX (11)	CABG =65.6±10.1, PCI =65.4±9.8	CABG =24.4, PCI =28.0	CABG =25.6, PCI =23.8	CABG =2.3, PCI =1.4	NR	CABG =3.9±2.9, PCI =3.9±2.8	CABG =37.8+13.3, PCI =31.6+12.3
EXCEL (16)	CABG =65.9±9.5, PCI =66.0±9.6	CABG =22.5, PCI =23.8	CABG =28.0, PCI =30.2	CABG =15.4, PCI =17.6	CABG =8.5, PCI =6.9	NR	CABG =20.5+6.1, PCI =20.6+6.2

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; IQR, inter-quartile range; SD, standard deviation; NR, not reported; PCI, percutaneous coronary intervention.

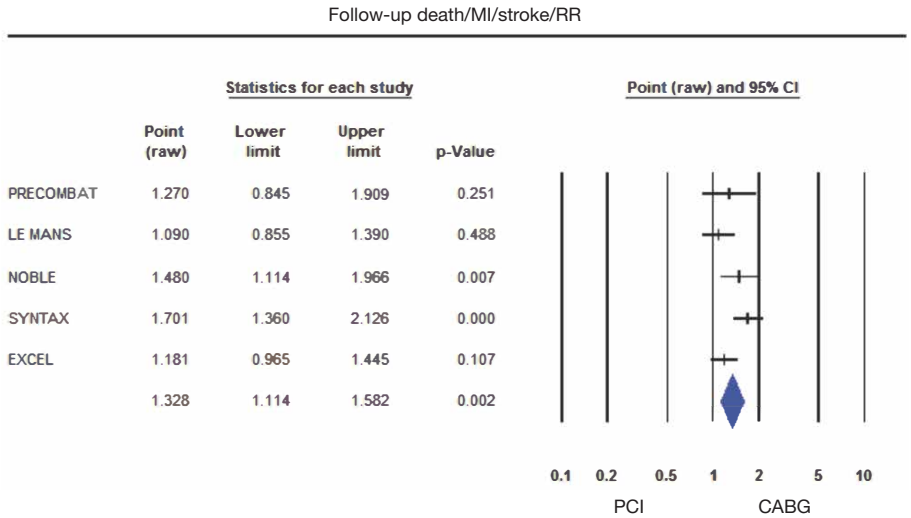

Figure 2 Forest plot for the composite of follow-up death/myocardial infarction/stroke/repeated revascularization (incidence rate ratio). CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR repeated revascularization.

=1.328, 95% CI, 1.114–1.582, P=0.002) (*Figure 2*).

Leave-one-out analysis and funnel plot with trim and fill method for the primary outcome are shown in *Figure S2*. Egger's test intercept was 0.277 (95% CI, –11.22–11.77, P=0.944).

At meta-regression, higher mean SYNTAX score was associated with higher risk of the primary outcome in the PCI group (beta =0.02, P=0.05). No association was found with female gender (beta =–0.01, P=0.70), mean age (beta =0.05, P=0.31), and diabetes (beta =–0.02, P=0.36) (*Figure S3*). At subgroup analysis based on stents category, PCI was associated with higher risk of the primary outcome both in the BMS (IRR =1.548, 95% CI, 1.184–2.023, P=0.001) and DES (IRR =1.218, 95% CI, 1.038–1.430, P=0.016) subgroups. At subgroup analysis based on tertiles of mean SYNTAX category, PCI was associated with progressively higher risk of the primary outcome in the 1st and 3rd SYNTAX tertile subgroups (IRR =1.292, 95% CI, 1.040–1.604, P=0.021 and IRR =1.548, 95% CI, 1.184–2.023, P=0.001) (*Figure 3*, *Table S2*).

Secondary outcomes

A summary of the outcomes is given in *Table 3*. No difference between PCI and CABG were found for peri-procedural mortality (OR =0.866, 95% CI, 0.460–1.628, P=0.654), follow-up mortality (IRR =0.947, 95% CI, 0.711–1.262, P=0.712), myocardial infarction (IRR =1.342, 95% CI, 0.827–2.179, P=0.234), or stroke (IRR =0.800, 95% CI, 0.374–1.710, P=0.565). PCI was associated with a higher risk of repeated revascularization (IRR =1.754, 95% CI, 1.470–2.093, P<0.001) (*Figures 4*,*5*).

Discussion

According to the current North American and European Guidelines for the treatment of unprotected LMD, CABG is a class I recommendation whereas PCI is class IIa/III recommendation, depending on the SYNTAX score (1,17). Last year, the publication of two independent randomized trials (the EXCEL and NOBLE trials) (12,16) with opposite results fueled the debate on the best therapeutic strategy for the treatment of LMD. As detailed elsewhere (18), the two studies have very important differences in design, follow-up and outcomes definitions and this is the most likely explanation for the divergence in their conclusions.

In this meta-analysis, we pooled aggregate data from 6 trials totaling 4,700 patients randomized to CABG or PCI. We found that at a mean follow-up ranging from 2.33 to 5 years, PCI was associated with a significantly higher risk of a composite of death/myocardial infarction/stroke/repeat revascularization. This difference was clearly driven by the higher need for repeat revascularization in the PCI arm. No difference in the other individual components of the composite outcome were in fact found. Of note, these findings are in accordance with recent data from Palmerini *et al.* (19), who showed that PCI, as compared to CABG for treatment of unprotected LMD, while associated with

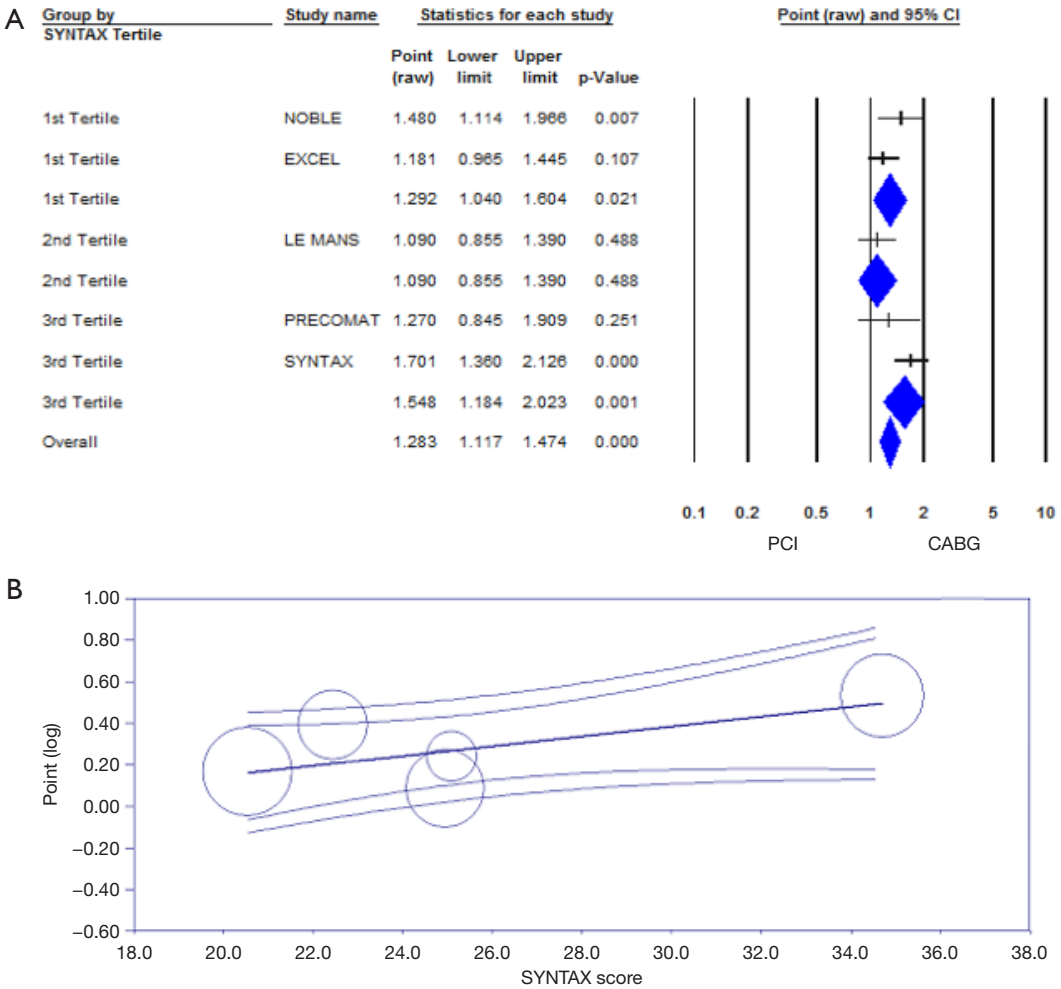

Figure 3 Effect of SYNTAX score on the primary outcome. (A) Subgroup analysis using tertiles of mean SYNTAX score; (B) meta-regression using mean SYNTAX score (beta =0.02, P=0.05). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Table 3 Outcomes summary

Variable	Number of studies	IRR/OR[¶]	95% CI	Overall effect (Z value, P value)	Heterogeneity (I^2, P value)	Tau squared
Follow-up death/MI/stroke/RR	5	1.328	1.114–1.582	3.172, P=0.002	56.311, P=0.057	0.022
Peri-procedural mortality	4	0.866[¶]	0.460–1.628	−0.448, P=0.654	31.650, P=0.222	0.135
Follow-up mortality	6	0.947	0.711–1.262	−0.369, P=0.712	33.342, P=0.186	0.040
Follow-up RR	6	1.754	1.470–2.093	6.239, P<0.001	0.000, P=0.803	0.000
Follow-up MI	6	1.342	0.827–2.179	1.191, P=0.234	52.028, P=0.064	0.160
Follow-up stroke	5	0.800	0.374–1.710	−0.576, P=0.565	55.177, P=0.063	0.364
Follow-up death/MI/stroke	6	0.980	0.725–1.324	−0.132, P=0.895	60.228, P=0.028	0.071

[¶], OR was used for operative mortality. IRR, incidence rate ratio; MI, myocardial infarction; OR, odds ratio; RR, repeated revascularization.

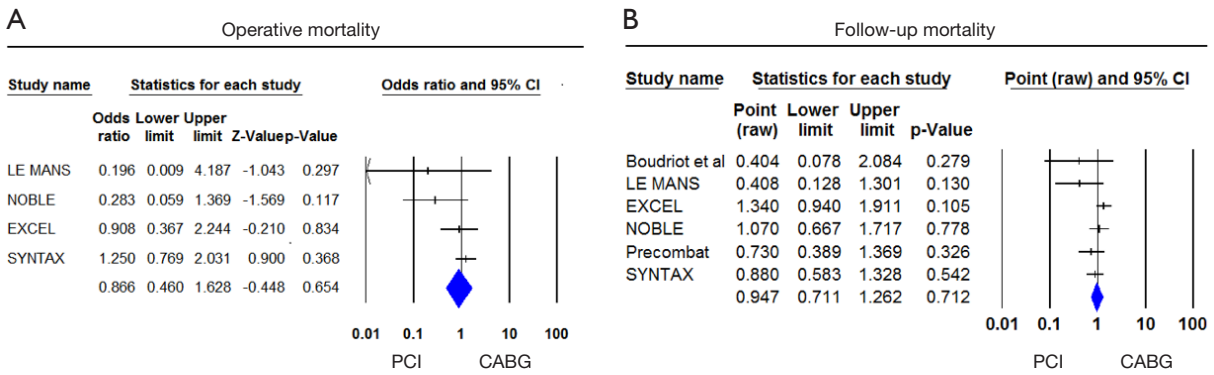

Figure 4 Mortality outcomes. (A) Peri-procedural mortality (odds ratio); and (B) follow-up mortality (incidence rate ratio). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

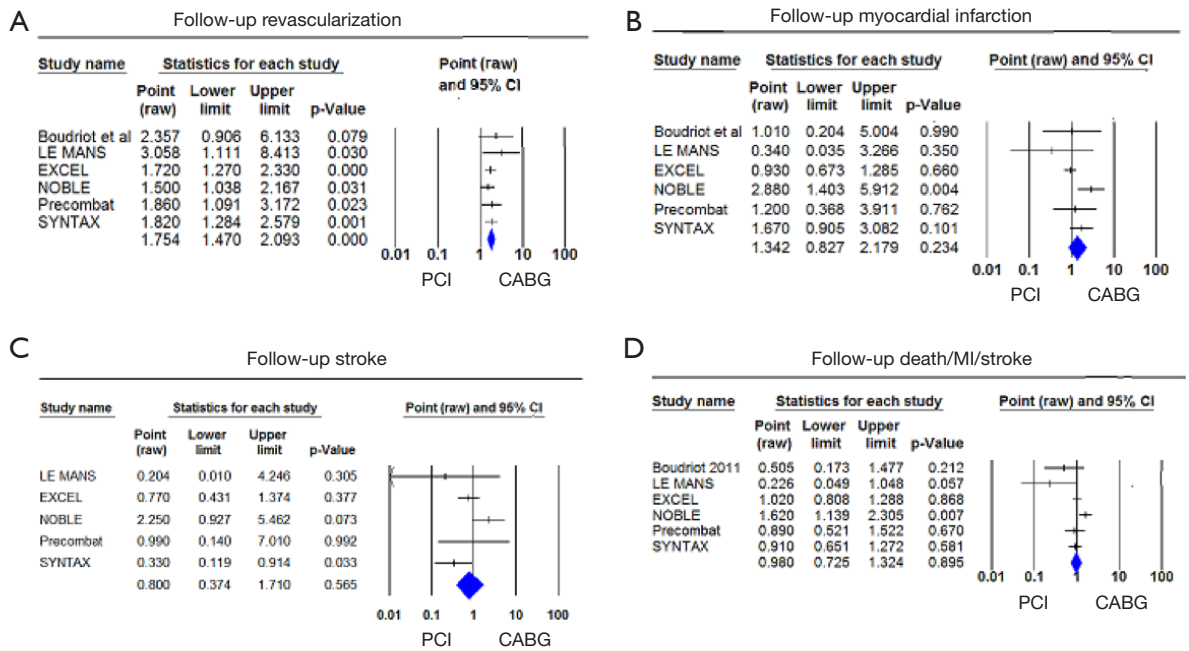

Figure 5 Comparison of secondary outcomes. (A) Follow-up repeated revascularization; (B) follow-up myocardial infarction; (C) follow-up stroke; and (D) follow-up mortality/myocardial infarction/stroke (incidence rate ratio). CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

a similar long-term composite risk of death, myocardial infarction, or stroke (HR =1.06, 95% CI, 0.82–1.37), is also associated with greater rates of unplanned revascularization (HR =1.74, 95% CI, 1.47–2.07).

Interestingly, the introduction of new generation DES did not shift the results in favor of PCI, as shown in our subgroup analysis. Recent evidence from our group elicit the doubt that new generation DES could have significantly worse results in the treatment of LMD, as suggested by the fact that second-generation DES, but not BMS, and first-generation DES were associated with a significantly increased risk of death/myocardial infarction/stroke when compared with CABG (20).

Another important finding is that the advantage for the CABG group in terms of primary outcome is independent of SYNTAX score, although it is progressively more evident in the 1st and 3rd SYNTAX score tertile subgroups (IRR =1.292, 95% CI, 1.040–1.604, P=0.021 and IRR =1.55, 95%

CI, 1.184–2.023, P=0.001).

Finally, unique to our report, as compared to prior works on the topic (19), is the fact that we were able to demonstrate that results were not affected by age, gender or diabetes.

This study shares the limitations of aggregate data analyses. The included trials were performed in different years, by different institutions using different protocols and definitions and some degree of heterogeneity is very likely to exist. Also, procedural aspects of both PCI and CABG (type of stents, use of arterial grafts or off-pump technique) varied considerably between different studies. Finally, meta-regression analyses can be viewed only as exploratory in this setting.

In conclusion, our results support the concept that CABG remains the therapy of choice for the treatment of unprotected LMD, especially for patients with high SYNTAX score.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 MOOSE checklist for meta-analyses of observational studies

Item No.	Recommendation	Page No.
Reporting of background should include		
1	Problem definition	455
2	Hypothesis statement	455
3	Description of study outcome(s)	455
4	Type of exposure or intervention used	455
5	Type of study designs used	455
6	Study population	455
Reporting of search strategy should include		
7	Qualifications of searchers (e.g., librarians and investigators)	455
8	Search strategy, including time period included in the synthesis and key words	455
9	Effort to include all available studies, including contact with authors	455
10	Databases and registries searched	455
11	Search software used, name and version, including special features used (e.g., explosion)	455
12	Use of hand searching (e.g., reference lists of obtained articles)	455
13	List of citations located and those excluded, including justification	*Figure S1*
14	Method of addressing articles published in languages other than English	455
15	Method of handling abstracts and unpublished studies	455
16	Description of any contact with authors	455
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	455
18	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	455
19	Documentation of how data were classified and coded (e.g., multiple raters, blinding and interrater reliability)	455
20	Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	455
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	455
22	Assessment of heterogeneity	455
23	Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	455–456
24	Provision of appropriate tables and graphics	See tables and figures
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	See figures
26	Table giving descriptive information for each study included	*Tables 1,2*
27	Results of sensitivity testing (e.g., subgroup analysis)	456–458; supplementary figures
28	Indication of statistical uncertainty of findings	456–458; supplementary figures
29	Quantitative assessment of bias (e.g., publication bias)	*Figure S2*
30	Justification for exclusion (e.g., exclusion of non-English language citations)	*Figure S1*
31	Assessment of quality of included studies	*Figure S2*
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	460-461
33	Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	458-461
34	Guidelines for future research	460-461
35	Disclosure of funding source	461

From reference (2). Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United Sates. August 2012.

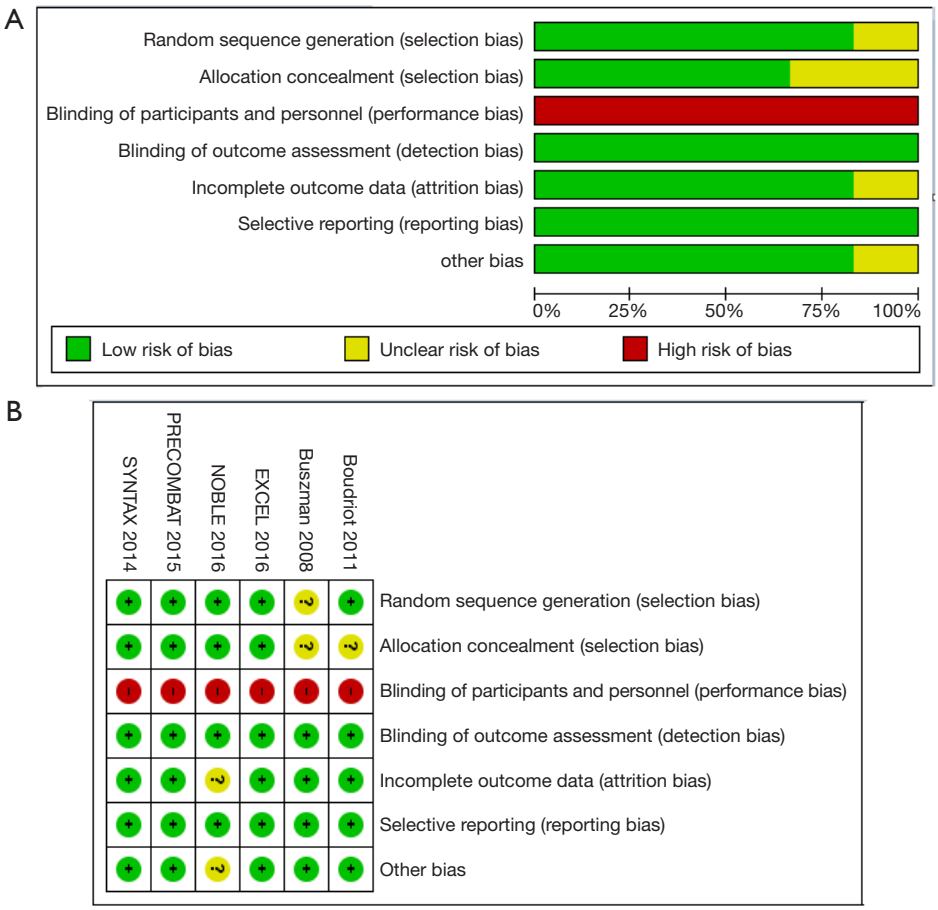

Figure S1 Risk of bias. (A) Assessment and (B) summary of included randomized controlled trials.

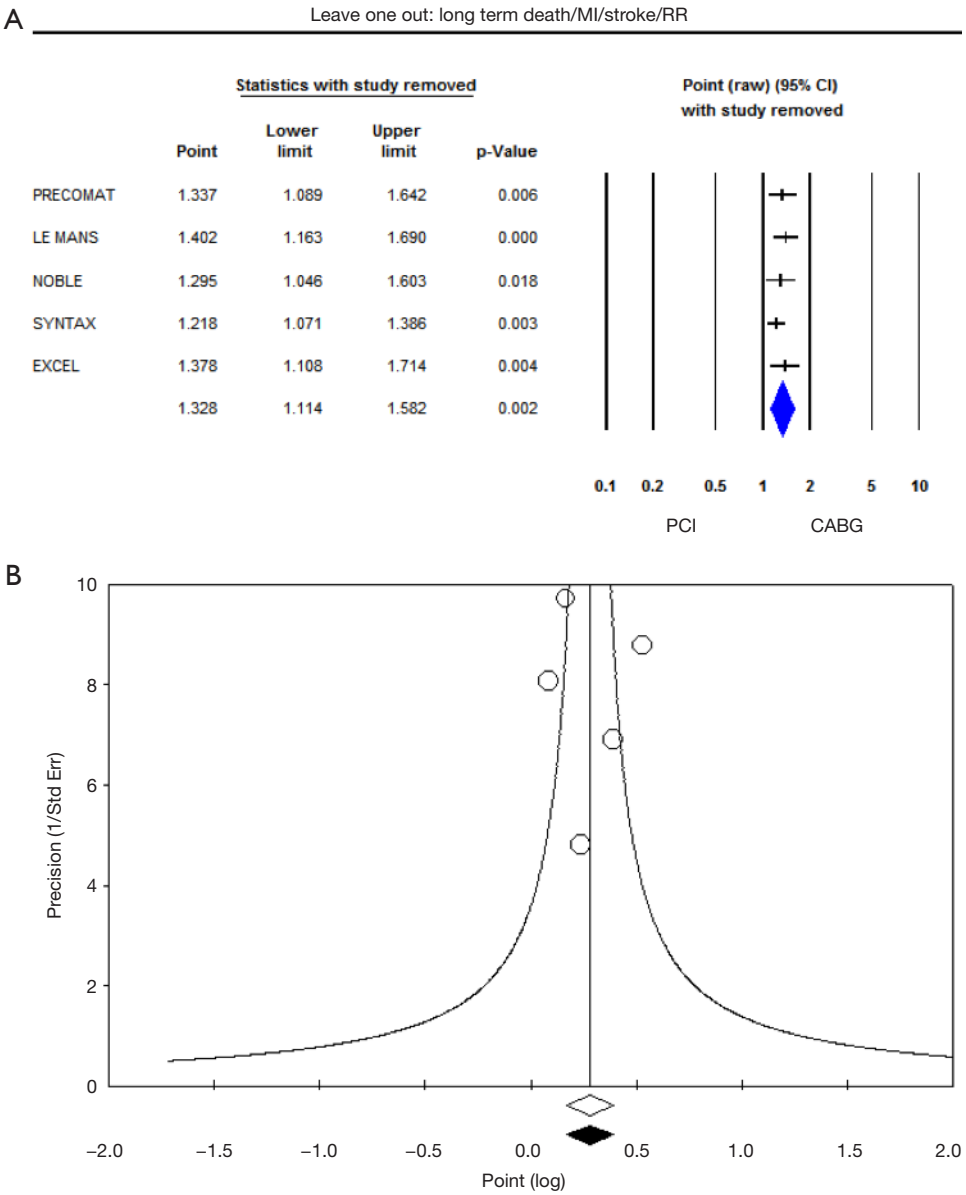

Figure S2 Follow-up death/MI/stroke/RR. (A) Leave-one-out analysis; and (B) funnel plot with trim and fill method. CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

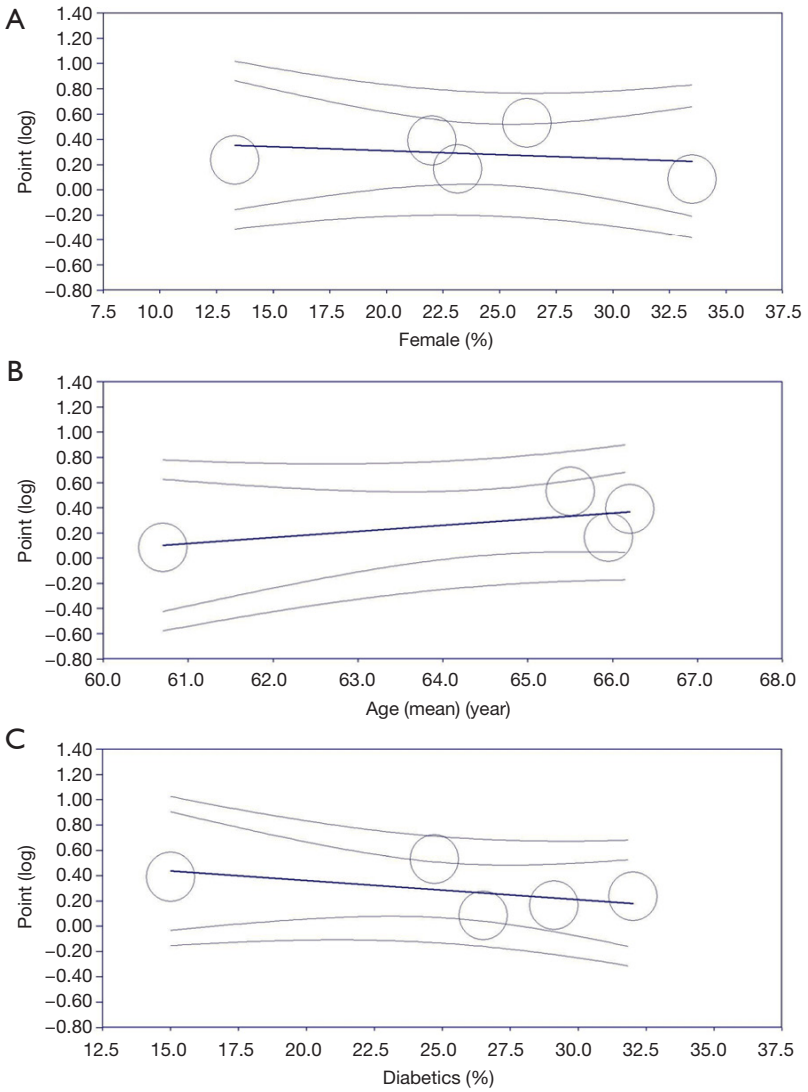

Figure S3 Meta-regression for the primary outcome: (A) female gender; (B) mean age; and (C) diabetes.

Table S2 Subgroup analyses for the primary outcome

Variable	Number of studies	IRR	95% CI	Overall effect (Z value, P value)	Heterogeneity (I^2, P value)	Tau squared
Stent category						
BMS	2	1.548	1.184–2.023	3.200, P=0.001	34.017, P=0.218	0.015
DES	3	1.218	1.038–1.430	2.416, P=0.016	25.839, P=0.260	0.005
Mean SYNTAX Tertiles						
1st Tertile	2	1.292	1.040–1.604	2.314, P=0.021	38.065, P=0.204	0.010
2nd Tertile	1	1.090	0.855–1.390	0.694, P=0.488	0.000, P=1	0.000
3rd Tertile	2	1.548	1.184–2.023	3.200, P=0.001	34.017, P=0.218	0.015

BMS, bare metal stent; DES, drug eluting stent; IRR, incidence rate ratio; MI, myocardial infarction; RR, repeated revascularization.