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Stent versus bypass grafting for the treatment of left main stem disease: a meta-analysis of six randomised controlled trials

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KEYWORDS

- coronary artery bypass grafting
- left main stem
- meta-analysis
- percutaneous coronary intervention

Abstract

Aims: We performed a meta-analysis of all randomised controlled trials to compare percutaneous coronary intervention (PCI) with stents versus coronary artery bypass grafting (CABG) for the treatment of left main stem disease.

Methods and results: We searched PubMed, the Cochrane Library, ClinicalTrials.gov, and major cardiovascular congresses for articles comparing PCI versus CABG for the treatment of left main stem disease. We utilised either fixed or random effects models to calculate the pooled risk ratio (RR) and 95% confidence interval (CI). Six trials with a total of 4,717 patients treated with either PCI (n=2,355) or CABG (n=2,362) were eligible and included. There were no differences in all-cause (RR: 1.03, 95% CI: 0.84-1.25, p=0.78) and cardiac mortality (RR: 1.03, 95% CI: 0.78-1.37, p=0.83) between PCI- and CABG-treated patients at the longest available follow-up. PCI-treated patients had a higher incidence of repeat revascularisation (RR: 1.65, 95% CI: 1.40-1.94, p<0.0001). However, there was no difference in myocardial infarction (RR: 1.36, 95% CI: 0.87-2.12, p=0.17) and stroke (RR: 0.86, 95% CI: 0.44-1.69, p=0.66).

Conclusions: There are no differences in mortality, myocardial infarction and stroke in PCI- or CABG-treated patients with left main stem disease. However, PCI-treated patients are more likely to need repeat revascularisation.

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Introduction

The optimal revascularisation strategy for patients with unprotected left main stem (LMS) disease remains debatable. Cohen and Gorlin published a case series of coronary artery bypass grafting (CABG) in unprotected LMS in 1975 showing a long-term mortality benefit[1]. Subsequently, several registries and randomised controlled trials (RCT) confirmed the survival benefit of CABG over medical treatment, especially in moderate- to high-risk groups[2,3]. Traditionally, percutaneous coronary intervention (PCI) for unprotected LMS has remained a class III indication (i.e., harmful) in the international guidelines[4,5]. However, with recent technical and technological advances, PCI has challenged the supremacy of CABG and has been the subject of several RCT. European Society of Cardiology (ESC) revascularisation guidelines in 2014 for the first time upgraded PCI for LMS to a class I indication for patients with LMS disease and a SYNTAX score ≤22 (and class IIa for patients with a SYNTAX score 23-32) based on data from the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial[6,7]. Two more large clinical trials, NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis) and EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation), have been reported since then[8,9]. The results of these trials provide important but somewhat divergent data. We have therefore performed an updated meta-analysis of all RCT to evaluate clinical outcomes with PCI using stents compared with CABG in patients with unprotected LMS disease.

Methods

SEARCH STRATEGY AND SELECTION CRITERIA

Randomised trials comparing PCI with a stent versus CABG were searched in PubMed, the Cochrane Library, and ClinicalTrials.gov, as well as major cardiovascular congresses. The search was limited to the English language. The subject keywords percutaneous coronary intervention, angioplasty, stents, left main stem, bypass grafting and randomised trial were applied to identify studies. The last search was performed in January 2017 by two independent investigators (J-Z. Cai and Y-X. Zhu).

INCLUSION AND EXCLUSION CRITERIA

Two investigators independently screened the title and abstract of the retrieved reports and reviewed the full articles of relevant citations in detail. Any discrepancies or disagreements were settled by a third investigator. Only randomised controlled clinical trials comparing clinical outcomes between CABG and PCI using stents for the treatment of unprotected LMS disease and with a fully published status were included. The clinical outcomes of interest were all-cause death, cardiac death, myocardial infarction (MI), stroke, and repeat revascularisation. We evaluated clinical outcomes for each trial at one year as well as at the longest reported follow-up. The risk of bias for individual trials was assessed in accordance with the Cochrane Collaboration's tool.

STATISTICAL ANALYSIS

Risk ratio (RR) and mean differences with 95% confidence interval (CI) were utilised as summary statistics. The Mantel-Haenszel fixed effects model and inverse variance fixed effects model were used for categorical variables and continuous variables, respectively. We performed the I^2 test and chi-square test to evaluate heterogeneity among studies. An I^2 >50% or p-value <0.10 was considered as significant heterogeneity. A random effects model was performed to calculate the risk estimation if a significant heterogeneity was detected. Sensitivity analyses were carried out by omitting one study at a time. The Egger's linear regression tests were employed to test for funnel plot asymmetry at the p<0.10 level of significance. All the statistical analyses were performed using Review Manager, Version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata, Version 13.0 (StataCorp., College Station, TX, USA).

Results

Six eligible RCT were identified after the screening process, as illustrated in **Figure 1**. The trials included were PRECOMBAT[10] (Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) with five-year follow-up, SYNTAX[7] with five-year follow-up, LE MANS[11] (left main stenting) trial with 10-year follow-up, Boudriot et al[12] with one-year follow-up, NOBLE[8] with five-year follow-up, and EXCEL[9] with three-year follow-up. These trials randomised 4,717 patients with unprotected LMS disease to treatment with either PCI with stents (n=2,355) or CABG (n=2,362) and are summarised in **Table 1**.

ALL-CAUSE AND CARDIAC DEATH

All-cause mortality was reported in all six trials. The pooled RR showed no significant differences between PCI- and CABG-treated

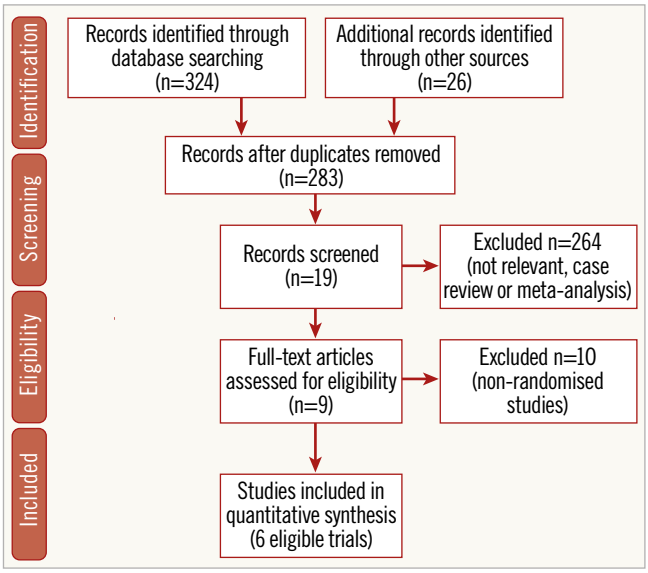

Figure 1. *Study flow chart. Flow diagram illustrating the screening and study selection process for the meta-analysis.`*

Table 1. Study and patient characteristics.

Study	Treatment (n)		Follow-up (years)	Definition of primary MACCE	Age		Male		DM		Multivessel		SYNTAX score	
					PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG
LE MANS	BMS/DES (52)	CABG (53)	10	Cardiac death, MI, RR, ST, or stroke	61 (11)	61 (8)	60	73	19	17	60	75	25 (9)	25 (7)
Boudriot et al	SES (100)	CABG (101)	1	Death, MI, and RR	66 (n/a)	69 (n/a)	72	77	40	33	37	45	24 (n/a)	23 (n/a)
PRECOMBAT	SES (300)	CABG (300)	5	Death, MI, stroke, or ischaemia-driven TVR	62 (10)	63 (10)	76	77	34	33	84	71	24 (9)	26 (11)
SYNTAX	PES (357)	CABG (348)	5	Death, MI, stroke, and RR	65 (10)	66 (10)	72	76	24	26	70	66	30 (14)	30 (13)
NOBLE	BES/PES/SES (598)	CABG (603)	5	Death, non-procedural MI, RR, or stroke	66 (10)	66 (9)	80	76	15	15	(n/a)	(n/a)	23 (8)	22 (8)
EXCEL	EES (948)	CABG (957)	3	Death, stroke, MI, or ischaemia-driven revascularisation	66 (10)	66 (10)	76	78	30	28	52	51	21 (6)	21 (6)

Values are mean (SD) or %. BES: biolimus-eluting stents; CABG: coronary artery bypass grafting; DES: drug-eluting stents; DM: diabetes mellitus; EES: everolimus-eluting stents; MI: myocardial infarction; PES: paclitaxel-eluting stents; RR: repeat revascularisation; SES: sirolimus-eluting stents; ST: stent thrombosis; TVR: target vessel revascularisation

groups for all-cause mortality at one-year (RR: 0.81, 95% CI: 0.59-1.12, p=0.21; I^2=0%) **(Figure 2A)** or long-term (RR: 1.03, 95% CI: 0.84-1.25, p=0.78; I^2=18%) **(Figure 2B)** follow-up. Cardiac death was reported in only two trials at one-year follow-up leading to statistical heterogeneity (I^2=62), and in four trials at long-term follow-up (I^2=25%). Nevertheless, there was no difference in cardiac death at one-year (RR: 1.03, 95% CI: 0.38-2.78, p=0.95) or long-term (RR: 1.03, 95% CI: 0.78-1.37, p=0.83) follow-up.

MYOCARDIAL INFARCTION

MI was reported in all six trials, although there were differences in the definition of MI, especially preprocedural MI. There was no significant difference in MI at one-year (RR: 0.86, 95% CI: 0.65-1.14, p=0.30; I^2=0%) **(Figure 3A)** or the longest available follow-up (RR: 1.36, 95% CI: 0.87-2.12, p=0.17; I^2=51%) **(Figure 3B)** between PCI- and CABG-treated patients. However, analysing only non-procedural MI revealed that, whilst there was no difference at one year (RR: 1.17, 95% CI: 0.77-1.76, p=0.46; I^2=0%) **(Figure 3C)**, CABG-treated patients had lower rates of MI (RR: 1.73, 95% CI: 1.27-2.35, p=0.0005; I^2=0%) **(Figure 3D)** at long-term follow-up. As the EXCEL trial reported spontaneous (as opposed to non-procedural) MI, sensitivity analysis excluding EXCEL also showed a reduction in MI among CABG-treated patients (RR: 1.79, 95% CI: 1.22-2.62, p=0.003; I^2=7%).

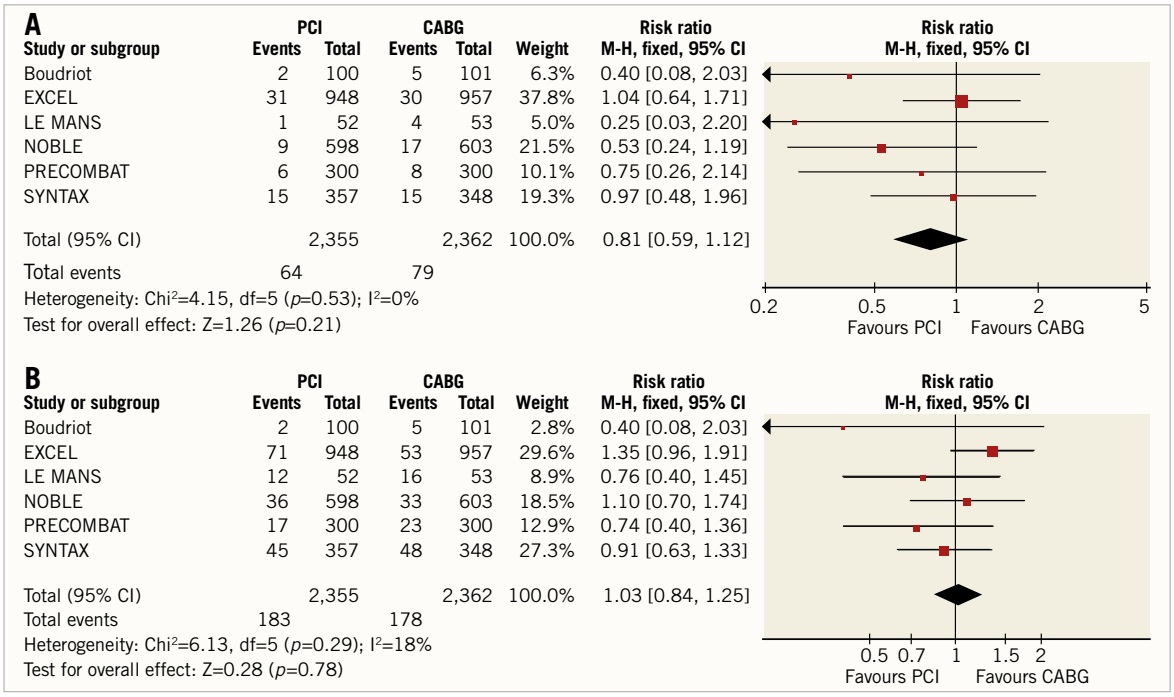

Figure 2. *Forest plots of risk ratios for all-cause mortality between PCI- and CABG-treated groups. There was no difference in all-cause mortality at one-year (A) or long-term (B) follow-up. The size of data markers indicates the weight of each trial included in the meta-analysis for all-cause death. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention*

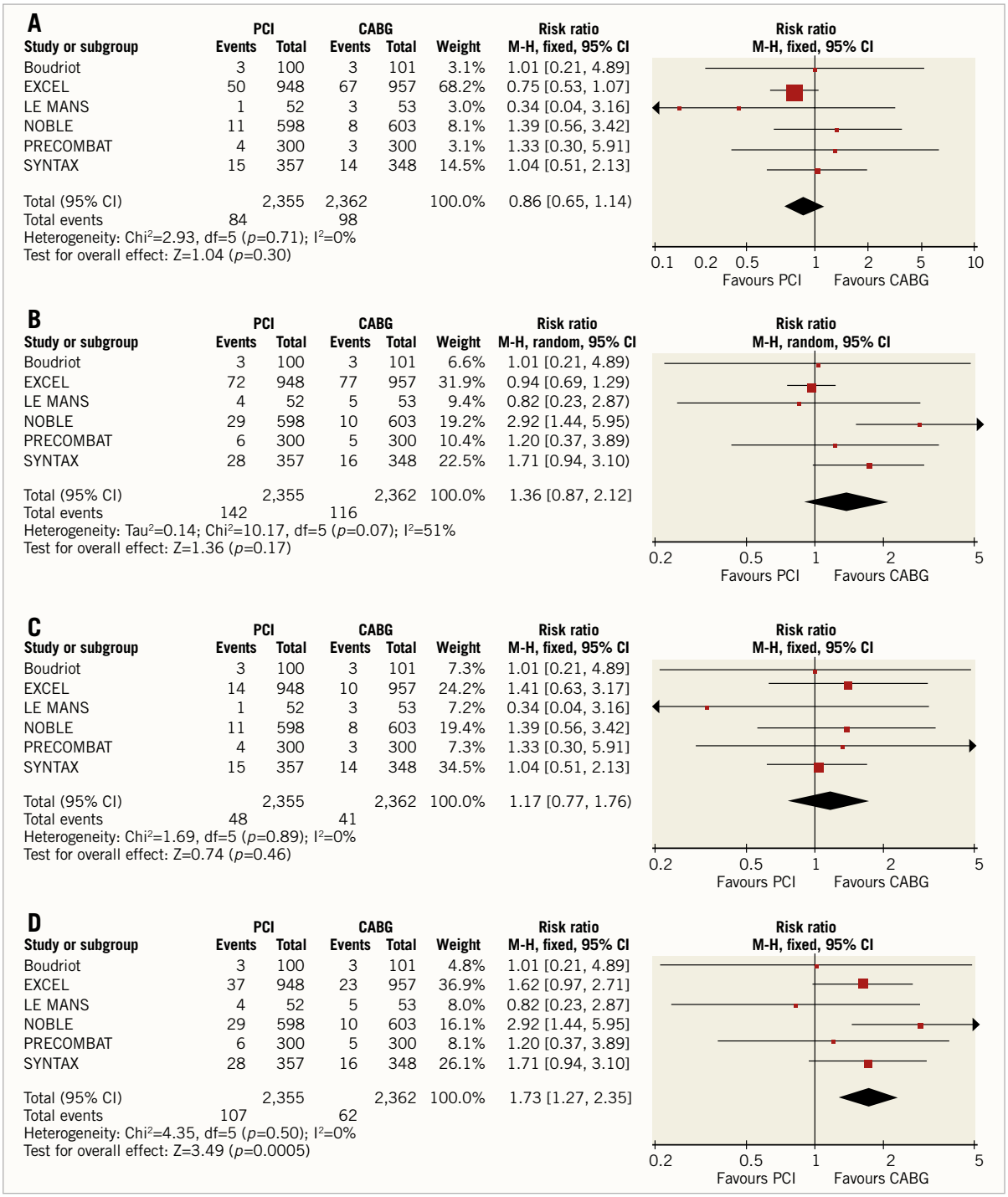

Figure 3. *Risk ratios for myocardial infarction between PCI- and CABG-treated groups. Forest plots showing risk ratio for all MI at one-year (A), all MI at long-term follow-up (B), non-procedural MI at one-year (C) and non-procedural MI at long-term follow-up (D). The size of data markers indicates the weight of each trial included in the meta-analysis for myocardial infarction. CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention*

STROKE AND REPEAT REVASCULARISATION

Stroke was reported in five trials. There was a lower incidence of stroke in PCI-treated patients at one year (RR: 0.39, 95% CI: 0.21-0.70, p=0.002; I^2=0%) **(Figure 4A)**, but there was no difference between revascularisation strategies at long-term follow-up (RR: 0.86, 95% CI: 0.44-1.69, p=0.66; I^2=51%) **(Figure 4B)**.

Repeat revascularisation was reported in all trials. PCI-treated patients had a higher incidence of repeat revascularisation at one year (RR: 1.80, 95% CI: 1.35-2.40, p<0.0001; I^2=0%) **(Figure 4C)**

as well as at long-term follow-up (RR: 1.65, 95% CI: 1.40-1.94, p<0.0001; I^2=19%) **(Figure 4D)**.

COMPOSITE OF MAJOR ADVERSE CARDIOVASCULAR AND CEREBRAL EVENTS

Major adverse cardiovascular and cerebral events (MACCE) as a composite of all-cause death, MI, stroke and revascularisation could be calculated for all trials despite the differences in definition of MI, revascularisation and incomplete data about stroke. There were no differences in MACCE at one-year follow-up (RR: 0.98, 95% CI: 0.82-1.16, p=0.78; I^2=39%) **(Figure 5A)**; however, on long-term follow-up, MACCE rates were much higher in PCI-treated patients (RR: 1.25, 95% CI: 1.12-1.39, p<0.0001; I^2=36%) **(Figure 5B)**. Further analysis based on the SYNTAX score was available in five trials and showed that there was no difference in the two revascularisation strategies for a SYNTAX score 1-32

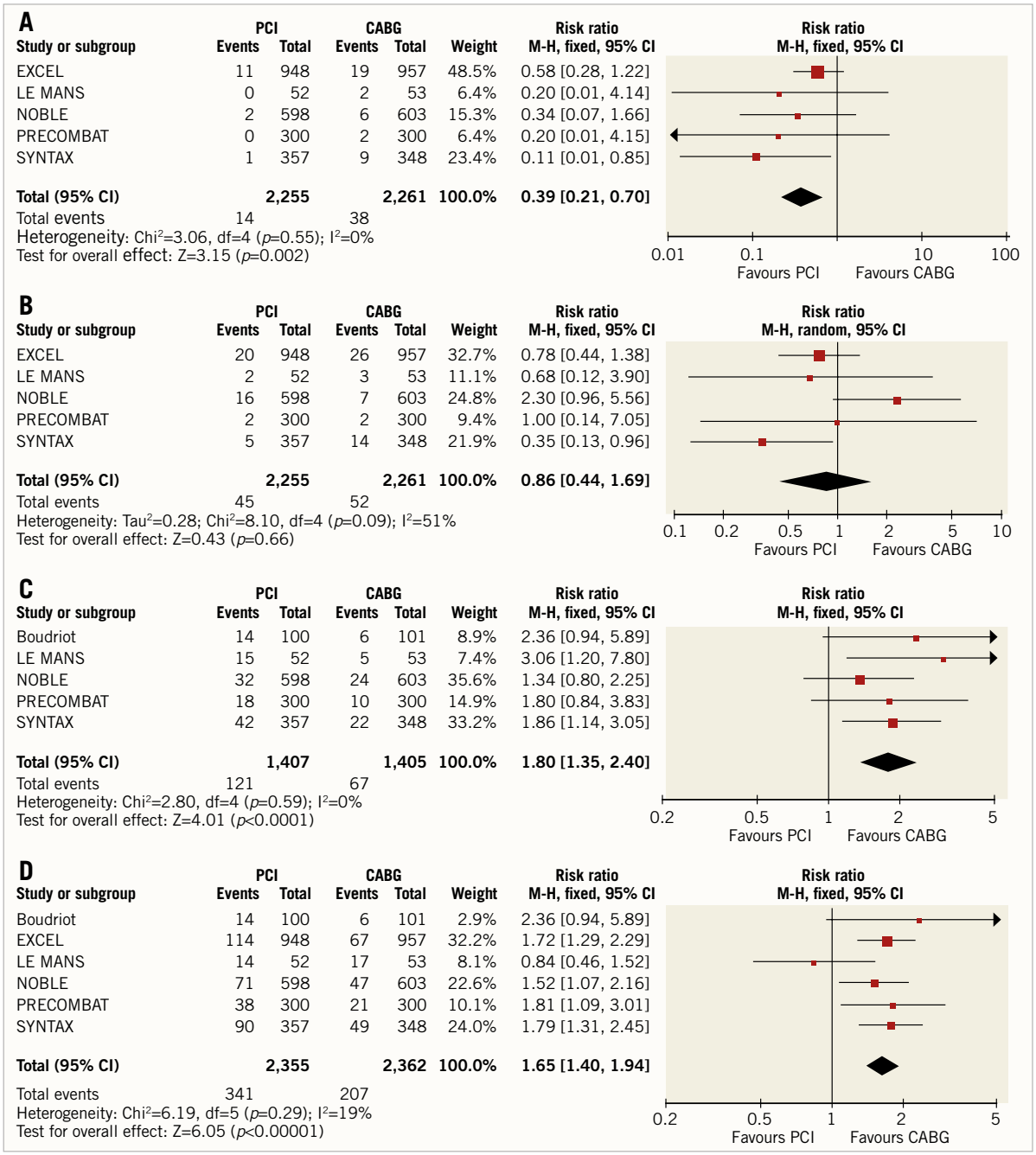

Figure 4. *Risk ratios for stroke and repeat revascularisation. Forest plots showing the risk ratio for stroke at one-year (A), stroke at long-term follow-up (B), repeat revascularisation at one-year (C) and repeat revascularisation at long-term follow-up (D) between the PCI- and CABG-treated groups. Size of data markers indicates weight of each trial included in the meta-analysis for stroke and repeat revascularisation. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention*

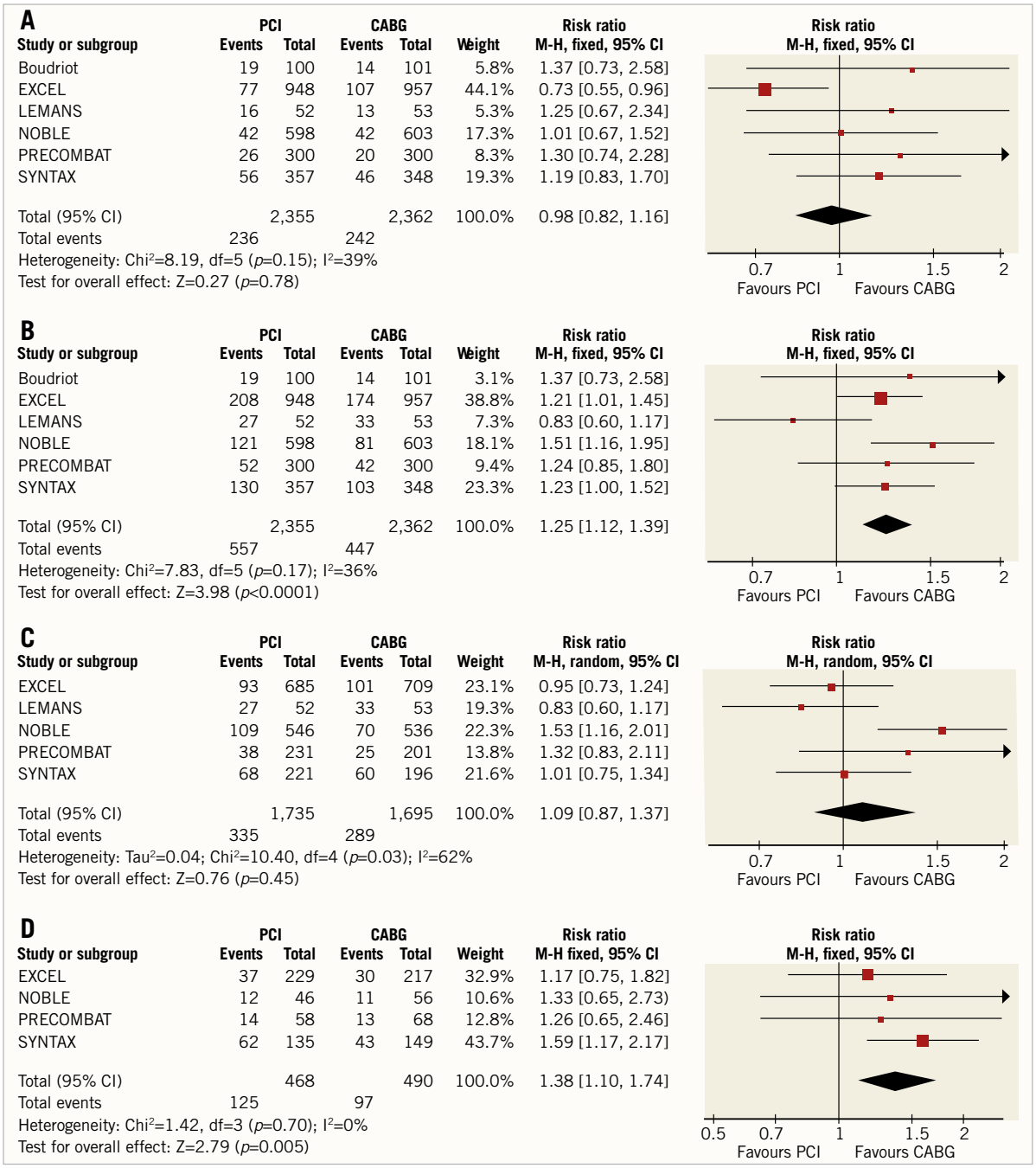

Figure 5. *Risk ratios for MACCE between the PCI- and CABG-treated groups. Forest plots showing the risk ratio for major adverse cardiovascular and cerebral events (MACCE) at one-year (A), MACCE at long-term follow-up (B), MACCE for SYNTAX score ≤32 (C) and MACCE for SYNTAX score >32 (D). The size of data markers indicates the weight of each trial included in the meta-analysis for MACCE. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention*

(RR: 1.09, 95% CI: 0.87-1.37, p=0.45; I^2=62%) **(Figure 5C)**, but superiority of CABG for a SYNTAX score of 33 or more (RR: 1.38, 95% CI: 1.10-1.74, p=0.005; I^2=0%) **(Figure 5D)**.

PUBLICATION BIAS AND SENSITIVITY ANALYSES

The risk of bias for individual trials was low in accordance with the Cochrane Collaboration's tool **(Supplementary Figure 1)**. There was no publication bias observed with Egger's linear regression except for cardiac (p=0.081) and all-cause death (p=0.064), which may be attributed to the different follow-up duration of the included studies and not all studies reporting cardiac death **(Supplementary Figure 2)**. Sub-analysis of trials using first-generation (LE MANS, Boudriot, PRECOMBAT, SYNTAX) or predominantly newer-generation stents (NOBLE and EXCEL) did

not show any major differences in MACCE **(Supplementary Figure 3)**. Finally, meta-analysis with the exclusion of the LE MANS trial (as it used both bare metal stents [BMS] and drug-eluting stents [DES]) showed no significant difference in outcomes **(Supplementary Figure 4)**.

Discussion

To date, this is the largest meta-analysis of randomised controlled trials comparing the clinical outcomes of PCI with stent(s) versus CABG for the treatment of unprotected LMS disease. We found no difference in all-cause and cardiac mortality between the two treatment strategies. All MI was similar at one year but higher afterwards in PCI-treated patients. Stroke rates were lower in PCI-treated patients at one year but the difference disappeared on long-term follow-up. Revascularisation rates remained higher in the PCI-treated group.

The trials included in this meta-analysis had differences in inclusion/exclusion criteria, complexity of coronary disease (LMS bifurcation disease, SYNTAX score, etc.), technical aspect of the procedure (type of stent, use of intravascular ultrasound, use of arterial grafts), definition of clinical endpoints, and duration of follow-up. Despite these differences, it is reassuring to see that both PCI and CABG provided effective treatment of unprotected LMS disease with no difference in survival. The LE MANS trial was the first randomised trial of PCI (n=52) vs. CABG (n=53). Only 35% had drug-eluting stents (DES) and 81% had a left internal mammary artery but the primary outcome of major adverse cardiac events (MACE) at one year was similar in the two groups[13]. This trial now has 10-year follow-up data available showing that mortality (21.6% vs. 30.2%, p=0.41), MI (8.7% vs. 10.4%; p=0.68), stroke (4.3% vs. 6.3%, p=0.58) and repeat revascularisation rates (26.1% vs. 31.3%; p=0.39) were similar between PCI and CABG[11]. Boudriot et al (n=201) and PRECOMBAT (n=600) compared PCI with sirolimus-eluting stenting versus CABG using predominantly arterial grafts and found no difference in death or MI, whilst revascularisation rates remained high in the PCI arm[10,12]. The SYNTAX trial compared PCI with a paclitaxel-eluting stent versus CABG but also went one step further to dissect the relationship of extent/complexity of coronary disease with revascularisation strategy[7]. It showed that both PCI and CABG may provide optimal revascularisation in the lower and middle terciles of SYNTAX score but, for the high score tercile, CABG was clearly superior[7]. NOBLE (n=1,201) and EXCEL (n=1,905) have compared PCI with newer-generation DES versus CABG. In NOBLE, there was no difference in mortality (12% vs. 9%, p=0.77) and stroke (5% vs. 2%, p=0.073), but higher rates of non-procedural MI (7% vs. 2%, p=0.004) and revascularisation (16% vs. 10%, p=0.032) in the PCI group[8]. In EXCEL, there was no difference in mortality (PCI 8.2% vs. CABG 5.9%, p=0.11), cardiac death (PCI 4.4% vs. CABG 3.7%, p=0.48), stroke and MI at three years; however, ischaemia-driven revascularisation was higher in the PCI arm (12.6% vs. 7.5%, p<0.001)[9]. A recent pooled analysis at the patient level of four registries showed an association of intravascular ultrasound guidance during PCI with better outcomes in patients with left main disease undergoing revascularisation with DES. Although in most patients in the EXCEL, NOBLE and PRECOMBAT trials intravascular ultrasound was performed for guiding stent deployment, the risk of ischaemia-driven revascularisation in the PCI arm was also higher in comparison with CABG.

It is also reassuring to see that the results of RCT and our meta-analysis are consistent with several registries comparing the two revascularisation strategies for the treatment of unprotected LMS disease. In the Bologna registry (n=311), there was no difference in mortality and MI but repeat revascularisation was higher in the PCI group[14]. The DELTA registry also showed no difference in mortality, MI or stroke between PCI- (n=1,874) and CABG-treated (n=901) patients; however, revascularisation remained higher in the PCI group[15]. An Italian registry of patients with unprotected LMS stenosis treated with PCI (n=107) or CABG (n=142) reported no difference in mortality (HR: 0.3, 95% CI: 0.055-1.404, p=0.17) at one year. PCI offered a lower composite endpoint of death and/or MI (HR: 0.26, 95% CI: 0.08-0.60, p<0.001) and death, MI, or stroke (HR: 0.38, 95% CI: 0.18-0.82, p=0.01)[16]. However, repeat revascularisation was 20% in the PCI versus 4% in the CABG group. The non-randomised MAIN-COMPARE (Revascularisation for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularisation) registry assessed 1,138 patients undergoing CABG and 1,102 patients undergoing PCI (318 with BMS, 784 with DES). At three- and five-year follow-up, outcomes among a propensity-matched cohort of patients were comparable in terms of death and MACE, whereas repeat revascularisation was higher in the PCI group[17]. It would be appropriate to bear in mind that complex distal bifurcation or trifurcation LMS disease requiring multiple stents may affect PCI outcomes[18-20]. However, a study comparing PCI with DES (n=556) and CABG (n=309) in unprotected LMS bifurcation disease showed similar rates of death (HR: 0.95, 95% CI: 0.62-1.45), a similar composite endpoint of death/MI/stroke (HR: 0.97, 95% CI: 0.64-1.48) and higher repeat revascularisation with PCI (HR: 4.42, 95% CI: 2.39-8.18) at five-year follow-up. The outcomes were comparable between the simple stenting and complex stenting groups except for target vessel revascularisation (HR: 1.94, 95% CI: 1.22 to 3.10)[21].

A previous meta-analysis of four trials (without EXCEL and NOBLE) including 1,611 patients showed that PCI, as compared to CABG, was associated with a significant reduction in the risk of stroke, an increased risk of repeat revascularisation, and a similar risk of mortality or MI, resulting in a higher risk of MACE but a similar risk of MACCE[22]. Similarly, a recent meta-analysis of five trials (excluding LE MANS) showed similar results[23]. The LE MANS trial was excluded from this meta-analysis due to limited use of DES (35%). However, the LE MANS trial now has 10-year follow-up and provides useful insights into further revascularisation in both the PCI and CABG arms. Furthermore, our sensitivity analysis has shown no difference in outcomes with or without LE MANS or difference in outcomes based on type of

stent used. Due to differences in the primary composite endpoints and definition of endpoints, we have chosen to compare the individual outcomes and focused mainly on mortality, MI and stroke. Our results have therefore conclusively shown comparable hard outcomes between PCI- and CABG-treated patients with significant LMS disease.

It is reassuring to see that both PCI and CABG provide effective treatment of unprotected LMS disease with no difference in survival. There are trends towards less stroke in PCI-treated patients and less MI in CABG-treated patients. The main advantage seen with CABG was a reduction in repeat revascularisation. This difference persisted even with the use of DES. However, one may argue that, without impact on survival, the need for revascularisation is not a hard endpoint and many patients would accept it to avoid the need for CABG.

Limitations

This meta-analysis has several potential limitations. The results are based on trial level data and share the limitations of the original trials. The definitions of clinical endpoints were not identical in all studies. Follow-up data among trials were variable, ranging from one year to 10 years. Finally, the trials included in this meta-analysis used a variety of stent platforms, and most of the available data are from older and non-everolimus-eluting stents. Thus, the pooled event rates, including repeat revascularisation, may not accurately reflect the performance of any one particular stent.

Conclusions

PCI and CABG offer comparable survival in patients with unprotected LMS disease. There were trends towards less MI in the CABG group and less stroke in the PCI group. CABG is associated with a significantly lower risk of repeat revascularisation. The Heart Team should make an individualised revascularisation decision based on the extent of downstream disease (SYNTAX score >32 favouring CABG), surgical risk (high risk favouring PCI), local resources/expertise and patient preference.

Impact on daily practice

The international guidelines, particularly those from the European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American College of Cardiology/American Heart Association[24], provide a balanced, practical, patient-oriented, and evidence-based approach for coronary revascularisation. We believe future iterations of guidelines should update PCI for LMS to a class I (level of evidence A), at least for patients with a SYNTAX score ≤32. As per guideline recommendations, use of the Heart Team for decision making and intracoronary imaging to guide PCI should remain the standard of care. The final revascularisation decision should be made by the Heart Team and the individual patient after considering the evidence base, international guidelines, contemporary practice, and local resources and expertise[25,26].

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Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Cohen MV, Gorlin R. Main left coronary artery disease. Clinical experience from 1964-1974. *Circulation.* 1975;52:275-85.

2. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, et al. 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;344:563-70.

3. 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. Long-term CASS experience. *Circulation.* 1995;91:2335-44.

4. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W; Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J.* 2005;26:804-47.

5. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB 3rd, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions Writting Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation.* 2006;113:156-75.

6. Authors/Task Force members, Windecker S, Kolh P, 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. 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 Heart J.* 2014;35: 2541-619.

7. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381:629-38.

8. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, Ravkilde J, Jensen LO, Kalinauskas G, Linder RB, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Sorensen 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 AN, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH; NOBLE study investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet.* 2016;388:2743-52.

9. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogats G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Page 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. *N Engl J Med.* 2016;375:2223-35.

10. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Chung CH, Lee JW, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med.* 2011;364:1718-27.

11. Buszman PE, Buszman PP, Banasiewicz-Szkrobka I, Milewski KP, Zurakowski A, Orlik B, Konkolewska M, Trela B, Janas A, Martin JL, Kiesz RS, Bochenek A. Left Main Stenting in Comparison With Surgical Revascularization: 10-Year Outcomes of the (Left Main Coronary Artery Stenting) LE MANS Trial. *JACC Cardiovasc Interv.* 2016;9:318-27.

12. 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;57:538-45.

13. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurakowski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymszal J, Martin JL, Tendera M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol.* 2008;51:538-45.

14. Palmerini T, Marzocchi A, Marrozzini C, Ortolani P, Saia F, Savini C, Bacchi-Reggiani L, Gianstefani S, Virzi S, Manara F, Kiros Weldeab M, Marinelli G, Di Bartolomeo R, Branzi A. Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). *Am J Cardiol.* 2006; 98:54-9.

15. Chieffo A, Meliga E, Latib A, Park SJ, Onuma Y, Capranzano P, Valgimigli M, Jegere S, Makkar RR, Palacios IF, Kim YH, Buszman PE, Chakravarty T, Sheiban I, Mehran R, Naber C, Margey R, Agnihotri A, Marra S, Capodanno D, Leon MB, Moses JW, Fajadet J, Lefevre T, Morice MC, Erglis A, Tamburino C, Alfieri O, Serruys PW, Colombo A. Drug-eluting stent for left main coronary artery disease. The DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv.* 2012;5:718-27.

16. Chieffo A, Morici N, Maisano F, Bonizzoni E, Cosgrave J, Montorfano M, Airoldi F, Carlino M, Michev I, Melzi G, Sangiorgi G, Alfieri O, Colombo A. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. *Circulation.* 2006;113:2542-7.

17. Park DW, Seung KB, Kim YH, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Yun SC, Gwon HC, Jeong MH, Jang YS, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. *J Am Coll Cardiol.* 2010;56:117-24.

18. Chieffo A, Park SJ, Valgimigli M, Kim YH, Daemen J, Sheiban I, Truffa A, Montorfano M, Airoldi F, Sangiorgi G, Carlino M, Michev I, Lee CW, Hong MK, Park SW, Moretti C, Bonizzoni E, Rogacka R, Serruys PW, Colombo A. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. *Circulation.* 2007;116:158-62.

19. Palmerini T, Sangiorgi D, Marzocchi A, Tamburino C, Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Ruffini M, Bartorelli AL, Briguori C, Vignali L, Di Pede F, Ramondo A, Inglese L, De Carlo M, Bolognese L, Benassi A, Palmieri C, Filippone V, Barlocco F, Lauria G, De Servi S. Ostial and midshaft lesions vs. bifurcation lesions in 1111 patients with unprotected left main coronary artery stenosis treated with drug-eluting stents: results of the survey from the Italian Society of Invasive Cardiology. *Eur Heart J.* 2009;30:2087-94.

20. Valgimigli M, Malagutti P, Rodriguez-Granillo GA, Garcia-Garcia HM, Polad J, Tsuchida K, Regar E, Van der Giessen WJ, de Jaegere P, De Feyter P, Serruys PW. Distal left main coronary disease is a major predictor of outcome in patients undergoing percutaneous intervention in the drug-eluting stent era: an integrated clinical and angiographic analysis based on the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registries. *J Am Coll Cardiol.* 2006;47:1530-7.

21. Chang K, Koh YS, Jeong SH, Lee JM, Her SH, Park HJ, Kim PJ, Kim YH, Chung WS, Yim HW, Park SJ, Seung KB. Long-term outcomes of percutaneous coronary intervention versus coronary artery bypass grafting for unprotected left main coronary bifurcation disease in the drug-eluting stent era. *Heart.* 2012; 98:799-805.

22. Ferrante G, Presbitero P, Valgimigli M, Morice MC, Pagnotta P, Belli G, Corrada E, Onuma Y, Barlis P, Locca D, Eeckhout E, Di Mario C, Serruys PW. Percutaneous coronary intervention versus bypass surgery for left main coronary artery disease: a meta-analysis of randomised trials. *EuroIntervention.* 2011;7: 738-46.

23. Nerlekar N, Ha FJ, Verma KP, Bennett MR, Cameron JD, Meredith IT, Brown AJ. 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. *Circ Cardiovasc Interv.* 2016 Dec;9(12).

24. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61:e78-140.

25. Iqbal J, Serruys PW, Taggart DP. Optimal revascularization for complex coronary artery disease. *Nat Rev Cardiol.* 2013;10: 635-47.

26. 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;34:2510-8.

Supplementary data

Supplementary Figure 1. Risk of bias across domains of study quality.

Supplementary Figure 2. Publication bias for studies in the meta-analysis.

Supplementary Figure 3. Risk ratios for MACCE between PCI- and CABG-treated groups according to stent type.

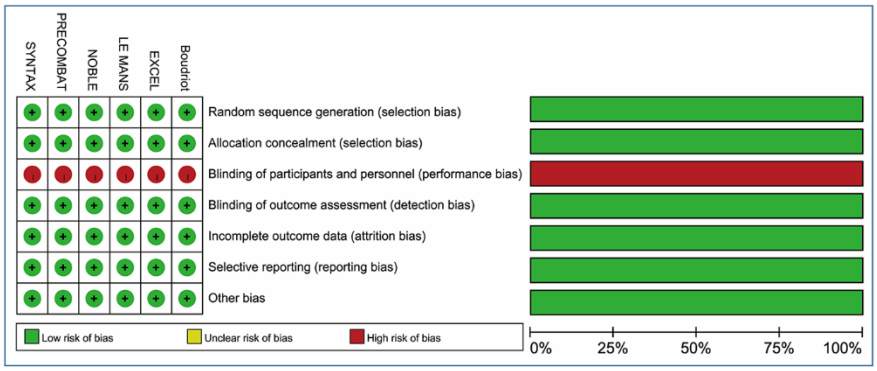
Supplementary Figure 4. Meta-analysis of five trials comparing PCI with DES vs. CABG.

The supplementary data are published online at: www.asiaintervention.org

Supplementary data

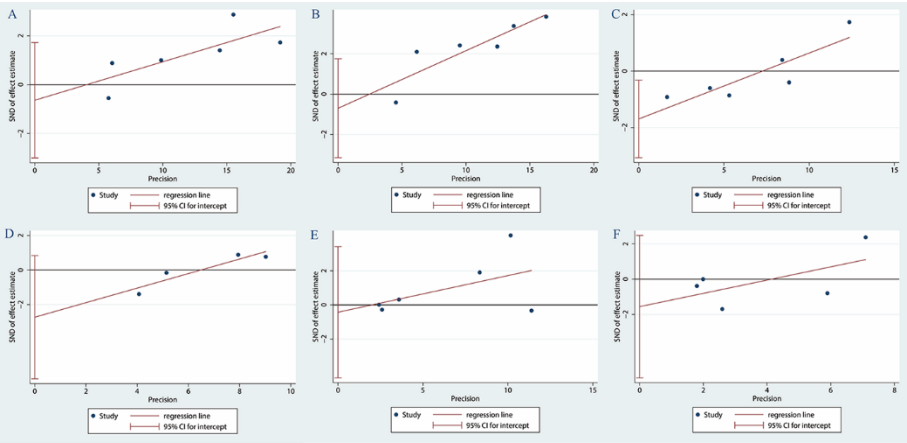
Supplementary Figure 1. Risk of bias across domains of study quality.

Proportions of studies classified as having low (green), unclear (yellow), and high (red) risk of bias according to Cochrane Collaboration's tool.



Supplementary Figure 2. Publication bias for studies in the meta-analysis.

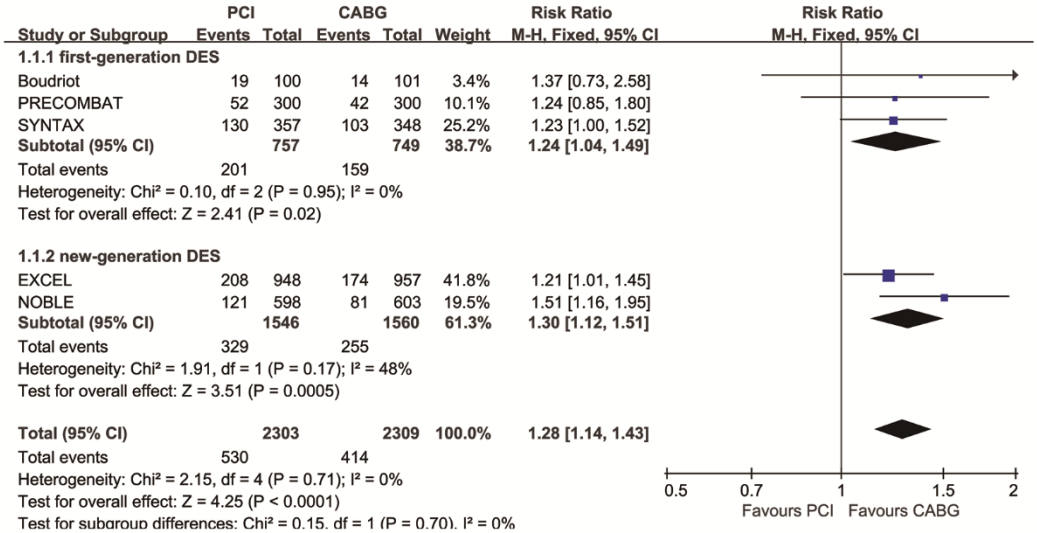
The Egger's linear regression tests for all-cause death (A), cardiac death (B), myocardial infarction (C), stroke (D), repeat revascularisation (E) and major adverse cardiovascular and cerebral events (F).



Supplementary Figure 3. Risk ratios for MACCE between PCI- and CABG-treated groups according to stent type.

Forest plots showing risk ratio for major adverse cardiovascular and cerebral events (MACCE) at long-term follow-up for trials using first-generation or predominantly newer-generation stents. The size of data markers indicates the weight of each trial included in the meta-analysis for all-cause death.

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention



Supplementary Figure 4. Meta-analysis of five trials comparing PCI with DES vs. CABG. Forest plots showing risk ratio for all-cause death (A), cardiac death (B), myocardial infarction (C), stroke (D) and repeat revascularisation (E) comparing PCI with a drug-eluting stent (DES) versus CABG in PRECOMBAT, Boudriot, SYNTAX, NOBLE and EXCEL trials. The size of data markers indicates the weight of each trial included in the meta-analysis for all-cause death.

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention