Systematic Review and Meta-Analysis

Medicine®

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Percutaneous coronary intervention versus cardiac bypass surgery for left main coronary artery disease

A trial sequential analysis

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Abstract

Background: Several updated meta-analyses comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) for left main coronary artery disease (LM CAD) have been published recently. However, the risk of false-positive results could be high in conventional updated meta-analyses due to repetitive testing of accumulating data. Therefore, we compared these treatment approaches via trial sequential analysis (TSA).

Methods: The MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases were searched for published randomized controlled trials (RCTs) or subgroups of RCTs comparing PCI and CABG in patients with LM CAD. The primary outcome was major cardiac and cerebrovascular adverse events (MACCE). TSA was used to confirm the conclusions derived from conventional meta-analysis.

Results: Six RCTs with 4700 patients were included. PCI was associated with a greater risk of MACCE compared with CABG (pooled relative risk [RR] 1.21, 95% confidence interval [CI]: 1.05–1.40, $P = .008$). In addition, PCI resulted in a significantly higher risk of revascularization than CABG (pooled RR 1.61, 95% CI: 1.33–1.95, $P < .0001$). TSA provided firm evidence for the reduction of MACCE and revascularization with CABG compared with PCI (cumulative z-curve crossed the monitoring boundary). In the subgroup analysis, CABG was better than PCI in patients with SYNTAX score >32 (pooled RR 1.41, 95% CI: 1.12–1.76, $P = .003$), which was confirmed by the TSA. There was no difference in patients with a SYNTAX score from 0 to 32.

Conclusions: In patients with LM CAD, CABG may be better than PCI for reducing MACCE due to a reduced risk of revascularization. CABG remains the first choice for LM CAD patients with high anatomic complexity, while PCI could be an alternative for those with low-to-moderate anatomic complexity.

Abbreviations: CABG = coronary artery bypass grafting, LM = left main, LM CAD = LM coronary artery disease, PCI = percutaneous coronary intervention, RCTs = randomized controlled trials, TCT = Transcatheter Cardiovascular Therapeutics, TSA = trial sequential analysis.

Keywords: coronary artery disease, coronary bypass graft surgery, left main coronary artery, percutaneous coronary intervention

1. Introduction

Due to the anatomy of the left main (LM) coronary artery, LM coronary artery disease (LM CAD) has been proven to be associated with poor prognosis and high mortality.[1] Coronary artery bypass grafting (CABG) surgery was once considered standard care for patients with LM CAD. However, evidence from randomized controlled trials (RCTs) has indicated that percutaneous coronary intervention (PCI) might be a reasonable alternative for LM CAD.[2–5] A meta-analysis of 4 RCTs indicated that 1-year rates of major adverse cardiac and cerebrovascular events (MACCE) were comparable after PCI and CABG.[6] A pooled analysis of individual patient-level data from the SYNTAX and PRECOMBAT trials found that CABG and PCI resulted in similar rates of the safety composite endpoint of death, myocardial infarction, or stroke.[7] In addition, in patients with isolated LM or LM+ 1-vessel disease, PCI was associated with lower all-cause and cardiac mortality compared to CABG.[7] Based on previous evidence, current guidelines recommend PCI as alternative revascularization strategy for LM CAD with low or intermediate anatomic complexity (Class II).[8]

At the 2016 Transcatheter Cardiovascular Therapeutics (TCT) meeting, the results of 2 large RCTs comparing PCI with CABG were published with different conclusions. The NOBLE trial suggested that CABG might be better than PCI in patients with LM CAD,[9] while the EXCEL trial concluded that PCI with everolimus-eluting stents is not inferior to CABG in LM CAD patients with low or intermediate SYNTAX scores (by site

Editor: Danny Chu.

PROSPERO Registration number: CRD42016033624 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016033624).

Funding: This work was supported by the CAMS Major Collaborative Innovation Project (No. 2016-I2M-1-011).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2017) 96:41(e8115)

Received: 10 May 2017 / Received in final form: 12 August 2017 / Accepted: 1 September 2017

http://dx.doi.org/10.1097/MD.0000000000008115

assessment).[10] Since then, several updated meta-analyses performed using conventional methods have been published.[11–13] However, when a meta-analysis is updated over time, as new trials are completed, the risk of random error increases, which is similar to the interim analyses in a single trial.[14] Trial sequential analysis (TSA) is a methodology combining conventional meta-analysis with thresholds for declaring significance in the context of a sequential meta-analysis performed before the required infromation size has been reached.[15] It is reported that TSA avoids the increased risk of false positives that occurs for repeated updates of meta-analyses.[16]

Thus, we conducted a TSA of published RCTs comparing the clinical outcomes after PCI versus CABG in patients with LM CAD to verify the conclusions derived from conventional meta-analysis.

2. Methods

2.1. Ethical approval

This study analyzed the published data of previous literatures and ethical approval was not necessary.

The protocol and reporting of this meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[17] All the methods and outcomes were prespecified except for TSA, and this study has been previously registered in PROSPERO (international prospective registration of systematic reviews; registration number: CRD42016033624; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016033624).

2.2. Data sources and searches

A systematic search in the MEDLINE (1950 to December 2016), EMBASE (1966 to December 2016), and Cochrane Central Register of Controlled Trials (Issue 1 of 12, December 2016) was conducted to identify all relevant RCTs that assessed the effects of PCI versus CABG on outcomes in patients with LM CAD. In addition, a manual search of the literature was performed by screening the references of reviews and meta-analyses. The following keywords were used for the search: "left main", "percutaneous coronary intervention", and "coronary artery bypass graft".

2.3. Study selection

Two authors (YY and YZ) independently determined the eligibility of each study. Disagreement was resolved by consensus. The eligibility criteria for studies included: *study design*: RCT or prespecified subgroup of RCT; *study population*: patients with LM CAD; *interventions*: comparison of PCI to CABG; and *study outcomes*: reported clinical outcomes for no less than 1 year of follow-up. Studies were published as full-length articles in English. We did not include unpublished material or abstracts because such content may be at risk for potential bias, as they did not undergo peer review.

2.4. Data extraction

Two authors (YY and YZ) independently extracted the following information from the included studies. Disagreements were resolved by consensus. The following types of data were extracted from each included study: baseline characteristics of the study population (including mean age, gender, mean body mass index, smoking status, proportions of patients with hypertension, diabetes, smoking, and distal LM lesion, left ventricular ejection fraction, Euroscore, and SYNTAX score); number of participants in each treatment group; and study outcomes (MACCE, all-cause mortality, myocardial infarction, stroke, and revascularization).

2.5. Risk of bias assessment

The risk of bias for the eligible studies was assessed independently by 2 authors (YY and YZ) using the Cochrane Collaboration Risk of Bias Tool based on 6 domains.[18] Disagreements were resolved by discussion to arrive at a consensus. Risk of bias was described and judged in the following aspects: sequence generation for randomization; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of potential bias. Judgments were based on published articles and protocols, if available. An answer of "yes" indicates a low risk of bias, while an answer of "no" indicates a high risk of bias. If the risk of bias was unknown, or if an entry was not relevant to the study, the judgment was "unclear".

2.6. Data synthesis and analysis

Published data from all RCTs were included in the analyses, which were performed on an intention-to-treat basis. The primary outcome of the current meta-analysis was MACCE, defined as all-cause mortality, myocardial infarction, stroke, or revascularization, and secondary outcomes were the individual components of the primary outcome, including all-cause mortality, myocardial infarction, stroke, and revascularization. Pooled relative risks (RRs) were calculated using a random effects model (with the Mantel–Haenszel method). Heterogeneity among the included studies was assessed using the I^2 statistic.[19] Furthermore, the pooled RRs were calculated according to the SYNTAX scores to explore the heterogeneity. A sensitivity analysis was performed to explore the degree to which the pooled RR of the primary outcome was affected by each individual study. Begg funnel plot and Egger weighted regression statistic were used to assess publication bias.[20,21] All analyses were performed using RevMan software (Review Manager 5.3, The Cochrane Collaboration, Copenhagen, Denmark) and STATA software (version 11.0; Stata Corp, College Station, TX). All statistical tests were 2-sided, and a P-value $<.05$ was considered statistically significant.

2.7. Trial sequential analysis

Although meta-analysis results are considered the best available evidence since such analysis can increase the power and precision of the estimated intervention effects, repeated statistical tests in a meta-analysis can increase the likelihood of both false-positive and false-negative results. It was reported that a positive conclusion in about 25% of conventional meta-analyses, including studies with a small sample size, may be unreliable.[22,23] TSA can define the strength of evidence by calculating the information size. Moreover, it provides adjusted thresholds for both statistical significance and futility according the quantified strength of the evidence and the impact of multiplicity.[15,24] We constructed z-curves for both primary and secondary outcomes, and alpha conventional threshold for significance

testing was set at 5%. Adjusted significance monitoring boundaries were constructed using the O'Brien-Fleming alpha-spending method with the assumption that significance testing may have been performed each time a new trial was sequentially added to the meta-analysis. Similar to a conventional sample size calculation in a single trial, the information size calculation involves a methodology that includes type I error, type II error, the control event proportion, and the effect size. In this analysis, the required information size was estimated using $\alpha = 0.05$ (2-sided) and $\beta = 0.20$ (power 80%) for each outcome. The control event proportions were calculated from the control group of this meta-analysis. The RR reduction was estimated using the pooled results of the low-risk studies included in this meta-analysis.

The following conclusion can be reached with TSA: if the cumulative *z*-curve crosses the trial sequential monitoring boundary or enters the futility area, a sufficient level of evidence for the anticipated intervention effect may have been obtained and no further trials are needed; if the *z*-curve does not cross any of the boundaries and the required information size has not been reached, the evidence is insufficient and more trials should be included to clarify this issue; and if the cumulative *z*-curve exceeds the estimated information size but does not cross the traditional monitoring boundary, the negative conclusion is sufficient and no further trial is required.[25,26]

TSA was conducted using the Trial Sequential Analysis Viewer (Version 0.9.5.5 Beta. Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark).

3. Results

3.1. Study identification

In total, 1290 articles were identified from the initial search. Six RCTs published in 9 articles fulfilled the eligibility criteria and were finally included in the meta-analysis.[2–5,9,10,27–29] The literature search and study identification process is presented in Fig. 1. The total sample size of the included patients was 4700, of which 2349 patients were assigned to the PCI group and 2351 patients were assigned to the control group. The baseline characteristics of the study population in each included study are summarized in Table 1.

3.2. Risk of bias assessment

Among the 6 included studies, only 1 study provided insufficient information on sequence generation and the method of allocation concealment.[2] It was impossible to blind the intervention in these studies, and the authors judged that that the outcome measurement was not likely to be influenced by lack of blinding. All the outcomes in these studies were adjudicated by an

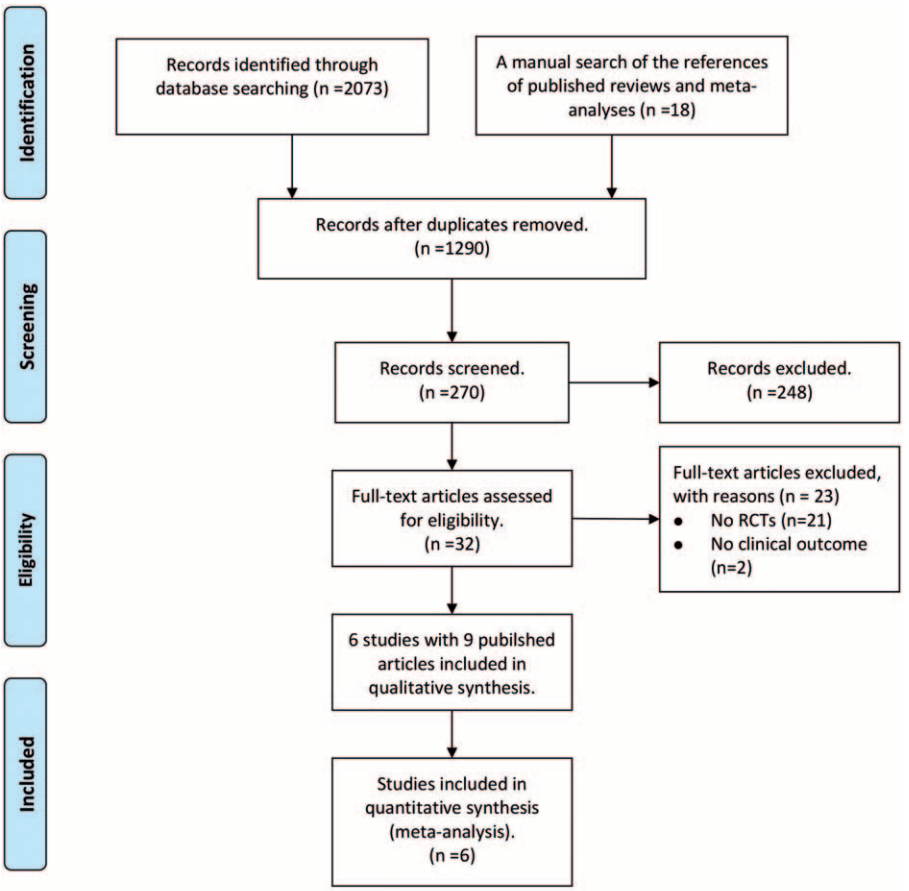

Figure 1. Flow diagram of the study selection.

Table 1

Baseline characteristics of patients in the included studies.

	Age, y	Male, %	BMI, kg/m^2	DM, %	HTN, %	Smoking, %	EF, %	Euroscore	SYNTAX score	Distal LM, %	DES, %	LIMA graft, %	IVUS, %
LE MANS[27]													
PCI	60.6	60	NA	19	75	NA	53.5	3.3	25.2	56	35	/	NA
CABG	61.3	73	NA	17	70	NA	53.7	3.5	24.7	60	/	81	/
SYNTAX LM subgroup[4]													
PCI	65.4	72	28.2	23.80	66.90	17.9	NA	3.9	29.6	64.1	100	/	NA
CABG	65.5	75.6	27.7	25.60	62.40	24	NA	3.9	30.2	58.3	/	NA	/
Boudriot et al[3]													
PCI	66	72	27.2	40	82	35	65	2.4	24	74	100	/	NA
CABG	69	78	27	33	82	28	65	2.6	23	69	/	99	/
PRECOMBAT[5]													
PCI	61.8	76	24.6	34.0	54.3	29.7	61.7	2.6	24.4	66.7	100	/	91.2
CABG	62.7	77	24.5	30.0	51.3	27.7	60.6	2.8	25.8	61	/	93.6	/
NOBLE[9]													
PCI	66.2	80	27.9	15.0	65.0	19.0	60	2	22.5	81	100	/	74
CABG	66.2	76	28.1	15.0	66.0	22.0	60	2	22.4	81	/	86	/
EXCEL[10]													
PCI	66	76.2	28.6	30.2	74.5	24.1	57	NA	20.6	66.9	100	/	80
CABG	65.9	77.5	28.8	28.0	73.9	20.8	57.3	NA	20.5	62.2	/	98.8	/

BMI = body mass index, CABG = coronary artery bypass grafting, DES = drug-eluting stents, DM = diabetes mellitus, EF = ejection fraction, HTN = hypertension, IVUS = intravascular ultrasound, LIMA = left internal mammary artery, LM = left main, NA = not available , PCI = percutaneous coronary intervention.

independent events committee. All of the studies were at low risk for attrition bias and reporting bias. A summary of the risks of bias is reported in Fig. 2.

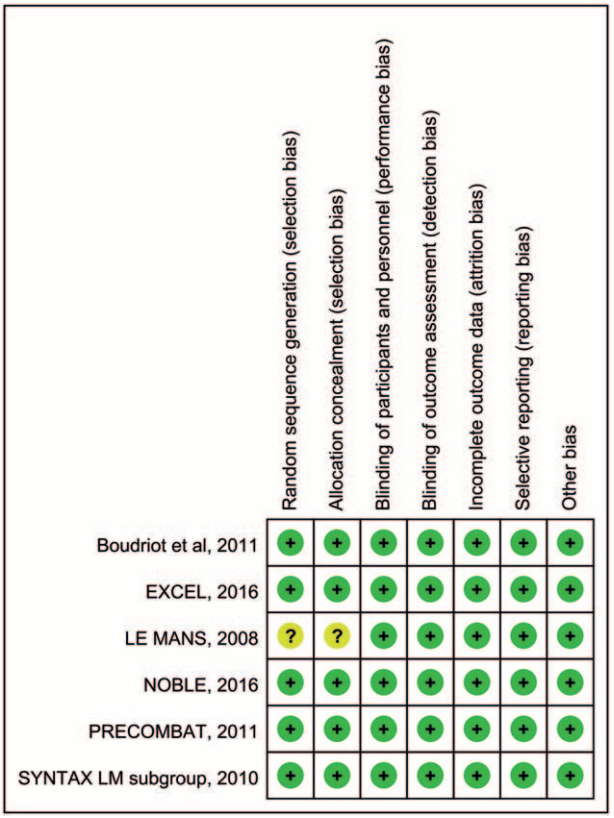

Figure 2. Risk of bias assessment.

3.3. Quantitative data analysis

Revascularization with PCI was associated with a greater risk of MACCE compared with CABG (pooled RR 1.21, 95% CI: 1.05–1.40, $P = .008$, Fig. 3A), and there was no significant heterogeneity among the included studies ($\chi^2 = 7.64$, $I^2 = 35\%$, $P = .18$). In the TSA, the cumulative z-curve crossed both the traditional boundary ($P = .05$) and the trial sequential monitoring boundary, suggesting that there is firm evidence for a reduction in the frequency of MACCE after CABG compared with PCI in patients with LM CAD.

For the secondary outcomes, there were no differences in the risks of all-cause mortality, myocardial infarction, and stroke between the PCI group and CABG group (Table 2). In the TSA, the cumulative z-curves for all-cause mortality, myocardial infarction, and stroke failed to cross both the traditional boundary ($P = .05$) and the trial sequential monitoring boundary, indicating the evidence was not conclusive for these outcomes (Supplementary Fig. 1, http://links.lww.com/MD/B901). However, the PCI group had a significantly higher risk of revascularization than the CABG group (pooled RR 1.61, 95% CI: 1.33–1.95, $P < .0001$), which was confirmed by the results of the TSA (Fig. 4).

Four of the included studies included patients with both SYNTAX scores from 0 to 32 and >32,[4,5,9,10] whereas the LE MANS and Boudriot et al studies included only or predominately patients with SYNTAX scores from 0 to 32.[2,3] In the subgroup analysis based on SYNTAX score, CABG was more beneficial than PCI in patients with a SYNTAX score >32 (pooled RR 1.41, 95% CI: 1.12–1.76, $P = .003$; Fig. 5A). In the TSA, the sample size of the meta-analysis had exceeded the required information size. The cumulative z-curve crossed both the traditional boundary ($P = .05$) and the trial sequential monitoring boundary, indicating there was solid evidence favoring CABG for a reduced risk of revascularization compared with PCI (Fig. 5B). Meanwhile, there was no difference in patients with a SYNTAX score from 0 to 32 (pooled RR 1.11, 95% CI: 0.90–1.37, $P = .31$,

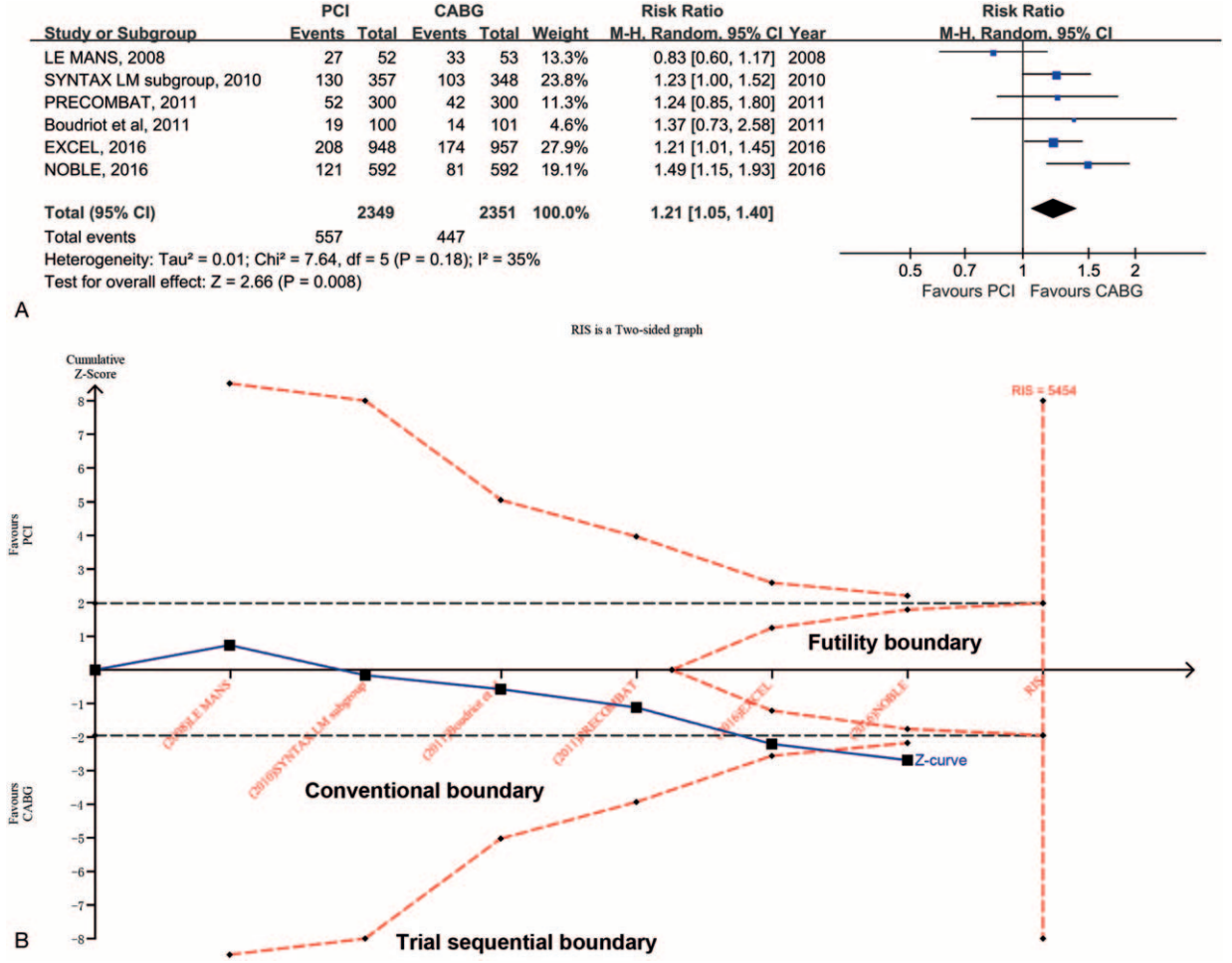

Figure 3. Pooled effect of PCI versus CABG on MACCE. (A) Results of conventional meta-analysis; (B) results of trial sequential analysis.

Fig. 5C). The results of the TSA also were not conclusive, since the cumulative *z*-curve did not cross either the traditional boundary or the trial sequential monitoring boundary (Fig. 5D).

The sensitivity analysis showed that the pooled RRs of MACCE excluding each single individual study were comparable, indicating the final results were not affected by a single study (Table 3). No significant publication bias was identified for the primary outcome, as indicated by the results of Begg test ($P = .573$) and Egger weighted regression statistic ($P = .842$).

4. Discussion

Our meta-analysis of 6 RCTs indicated that CABG was associated with a lower risk of MACCE compared with PCI in patients with LM CAD. The lower risk of revascularization in the CABG group may be the major explanation for this conclusion. TSA provided firm evidence for reduced risks of MACCE and revascularization with CABG compared with PCI. In the subgroup analysis, we found that CABG is better than PCI in patients with a high SYNTAX score, which was confirmed by the TSA. However, the evidence in patients with a low-to-moderate SYNTAX score is still not conclusive.

Meta-analyses of RCTs using the traditional method are considered to provide the best evidence. However, the results of traditional meta-analyses may be misleading due to random error. Repetitive testing is common among meta-analyses, with up to 18% of meta-analyses being reported as updates.[30] The increased risk of random error is probably caused by the repeated consideration of accumulating evidence as new trials emerge. TSA is a new methodology for meta-analysis of accumulating

Table 2

Results for secondary outcomes after PCI versus CABG.

Secondary outcomes	RR (95% CI)	*P* for RR	I^2 (%)	*P* for heterogeneity
All-cause mortality	0.98 [0.78, 1.25]	.90	24	.26
Myocardial infarction	1.35 [0.87, 2.09]	.17	50	.07
Stroke	0.74 [0.36, 1.49]	.39	48	.08
Revascularization	1.61 [1.33, 1.95]	<.001	20	.29

CI = confidence interval, RR = relative risk.

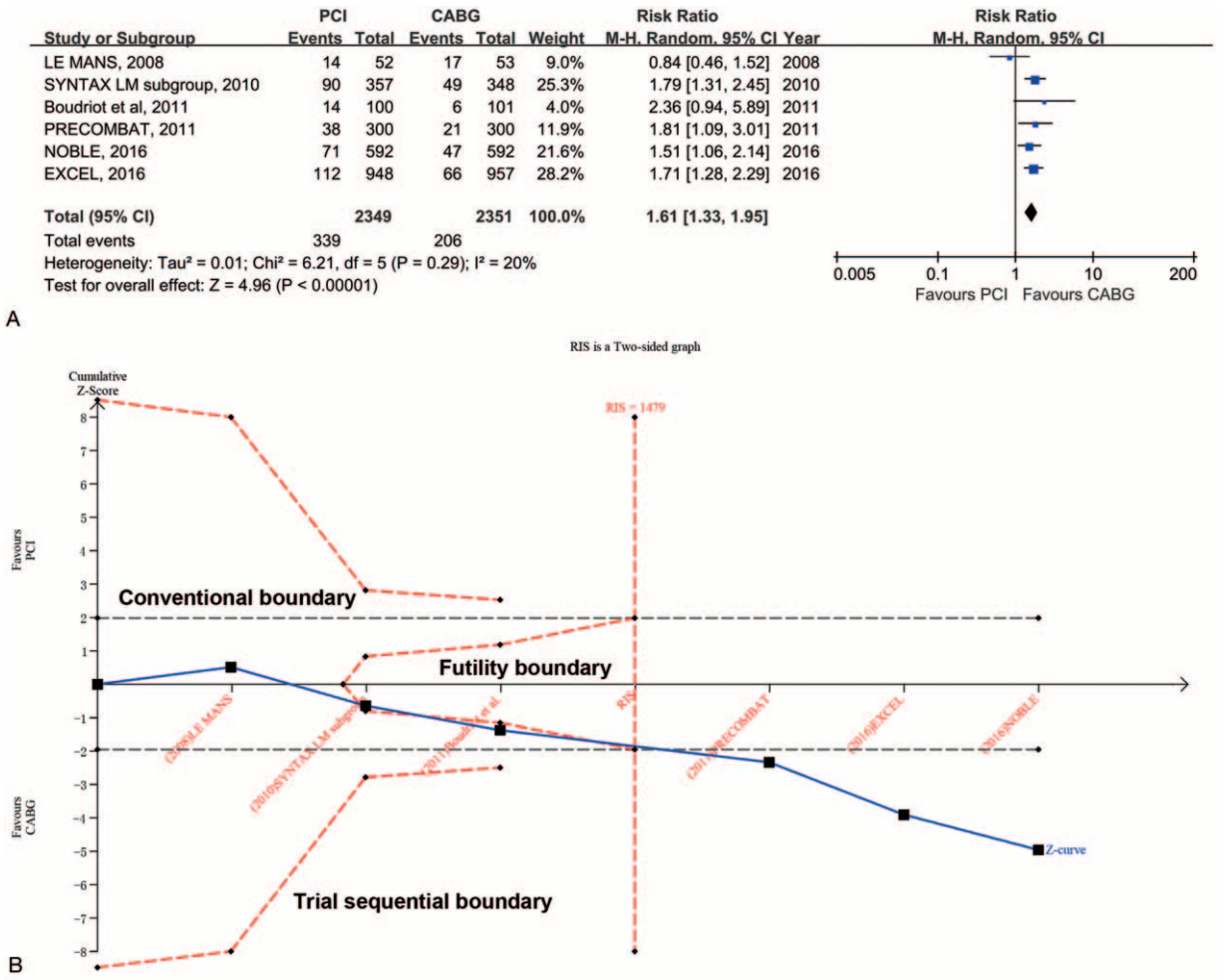

Figure 4. Pooled effect of PCI versus CABG on revascularization. (A) Results of conventional meta-analysis; (B) results of trial sequential analysis.

data, using the monitoring boundaries with an a priori information size calculation.[24] TSA can retain the desired risk of random error when repeated conventional significance testing is performed on accumulating data; thus, its conclusion may be more accurate.[24] If the TSA indicated that the evidence was conclusive, TSA may serve as a valuable tool to estimate the sample size that is needed to be able to accept or reject a certain intervention effect.[24]

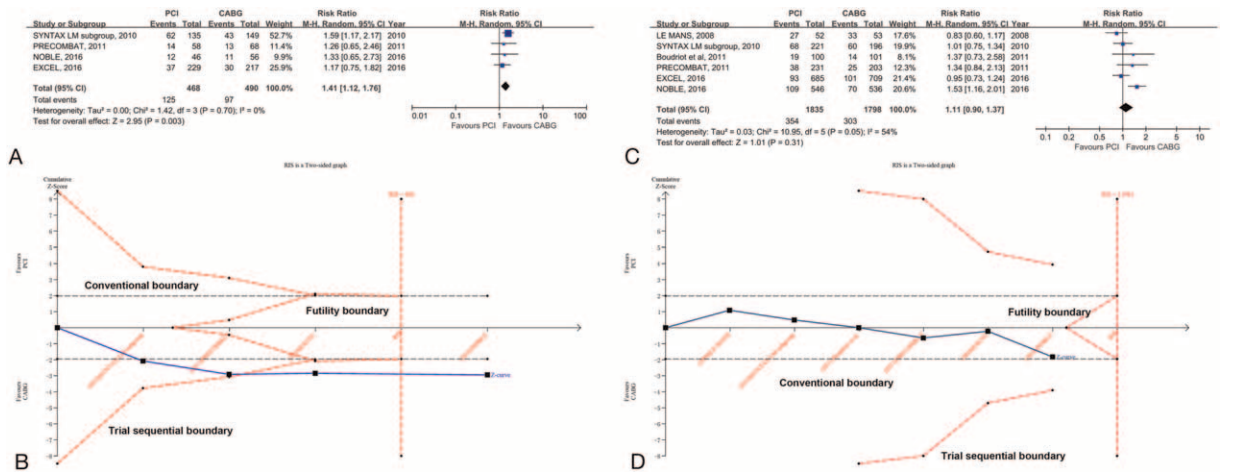

Figure 5. Pooled effect of PCI versus CABG on MACCE according to the SYNTAX score. (A) Result of conventional meta-analysis in patients with a SYNTAX score >32; (B) results of TSA in patients with a SYNTAX score >32; (C) results of conventional meta-analysis in patients with SYNTAX score ≤32; and (D) results of TSA in patients with a SYNTAX score ≤32.

Table 3

Sensitivity analysis excluding each individual included study.

Study excluded	Relative risk [95% confidence interval]	P
LE MANS[27]	1.27 [1.14, 1.43]	<.0001
SYNTAX LM subgroup[4]	1.20 [0.99, 1.46]	.06
PRECOMBAT[5]	1.21 [1.02, 1.43]	.03
Boudriot et al[3]	1.20 [1.03, 1.41]	.02
NOBLE[9]	1.16 [1.02, 1.33]	.03
EXCEL[10]	1.21 [0.99, 1.48]	.06

The EXCEL study and NOBLE study were the 2 largest RCTs assessing PCI and CABG in patients with LM CAD.[9,10] The conclusions of these 2 RCT seemed conflicting, which may be attributed to differences in the study design. First, revascularization was excluded as a primary outcome in the EXCEL study, which showed that PCI was associated with a significantly higher risk of revascularization than CABG. Meanwhile, periprocedural MI was not included in the primary outcome in the NOBLE study. Periprocedural MI is not uncommon in patients undergoing CABG; thus, it could reduce the risk of MI in the CABG group in the NOBLE study. Second, the NOBLE study had a longer follow-up period than the EXCEL study (5 years vs 3 years). Kaplan–Meier analysis of the primary outcome in the EXCEL study indicated an early beneficial effect towards PCI, which diminished in the late follow-up period. A similar pattern was also observed in the NOBLE study. This is not surprising, given that stent failure is quite frequent within 1 to 5 years while graft failure may occur in the later period (5–10 years). Third, PCI was associated with an unexplainably higher risk of stroke in the NOBLE study, which was not consistent with the findings of previous studies. In addition, differences in the types of DES and other baseline characteristics may also lead to the diversity of the conclusion.

The efficacies of PCI and CABG in LM CAD have been assessed by several real-world observational studies. A single observational study from Milan indicated that PCI was associated with a lower rate of the composite end point of death, myocardial infarction, and/or stroke (odds ratio [OR]: 0.399; 95% CI: 0.151–0.989; $P=.04$). Indeed, CABG was correlated with lower target vessel revascularization (OR: 4.411; 95% CI: 1.825–11.371; $P=.0004$).[29] The 5-year results of the MAIN COMPARE registry found no significant difference between PCI and CABG, while the risk of target vessel revascularization was significantly higher in the PCI group than in the CABG group.[31] In another LM registry study, PCI had a significantly higher accumulative 5-year incidence of death/MI/stroke than CABG, mainly due to the beneficial effect of CABG in patients with a high SYNTAX score.[32] Newly published data from China also show that PCI is a reasonable alternative to CABG for patients with less complex disease (SYNTAX score $\leq$32), whereas CABG has a greater survival benefit compared with PCI (HR 1.71; 95% CI, 1.32–2.21; $P<.001$) in patients with a SYNTAX score >32).[33]

Based on the current evidence, PCI could be considered as an alternative for CABG in LM CAD patients with low-to-moderate anatomic complexity, while CABG should be the first choice in patients with high anatomic complexity. Thus, we believe that the guideline recommendation for revascularization in patients with LM CAD did not need to be changed. However, these conclusions cannot be easily generalized to all patients with LM CAD, since the patients included in RCTs are usually stable and have fewer comorbidities. In addition, a recent study from China reported that patients who undergo LM PCI by high-volume and experienced operators have better short- and long-term prognoses, indicating that the operator's experience somehow is a major determinant of prognosis for patients undergoing LM PCI.[34]

Our study has several limitations. First, this was a study-level meta-analysis, making it impossible to assess the effects of all the confounding factors on the conclusion. Second, the definitions of revascularization and myocardial infarction differed among the included studies. Third, the duration of follow-up varied, and long-term data (>10 years) were not available in most of the studies. Finally, the type of stent, use of intravascular ultrasound, different strategies of the procedure (such as a 1-stent versus 2-stent technique in PCI and use of the LIMA graft vs saphenous vein graft in CABG) could also affect the final results.

In summary, our TSA of 6 RCTs concluded that CABG may be superior to PCI in patients with LM CAD and high anatomic complexity, due to the reduced risk of revascularization. A long-term comparison of these 2 strategies is still needed for additional verification in the future.

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