Interactive CardioVascular and Thoracic Surgery 32 (2021) 530–536
doi:10.1093/icvts/ivaa301

BRIEF COMMUNICATION

Cite this article as: Urso S, Sadaba R, Nogales E, González JM, Tena MÁ, Paredes F *et al*. Major cardiovascular events at 5 years in surgical versus percutaneous revascularization for left main stem disease: an updated meta-analysis. Interact CardioVasc Thorac Surg 2021;32:530–6.

Major cardiovascular events at 5 years in surgical versus percutaneous revascularization for left main stem disease: an updated meta-analysis

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Received 1 August 2020; received in revised form 24 October 2020; accepted 31 October 2020

Summary

The aim of the present study was to analyse the incidence of major adverse cardiovascular events in patients undergoing either coronary artery bypass grafting (CABG) or percutaneous coronary intervention with drug-eluting stents for left main stem disease. Five manuscripts publishing 5-year results of 4 trials (SYNTAX, PRECOMBAT, NOBLE and EXCEL) were included. Overall meta-analysis with inclusion of the 5-year results from the EXCEL trial using the protocol definition for myocardial infarction showed that CABG is associated with a significant reduction in the risk of major adverse cardiovascular events (MACE) (risk ratio = 0.74; 95% confidence interval = 0.68–0.80). When the universal definition was used to define myocardial infarction in the EXCEL trial, the analysis demonstrated a larger benefit of coronary surgery in terms of reduction in the risk of MACE (risk ratio = 0.70; 95% confidence interval = 0.63–0.76). Non-significant differences were detected in terms of risk of overall mortality, cardiac mortality or stroke. In conclusion, this meta-analysis shows that CABG significantly reduces the risk of MACE in patients with left main stem disease. The inclusion of the 5-year results of the EXCEL trial using third universal definition amplifies the benefit of CABG over percutaneous coronary intervention.

Keywords: Meta-analysis • Coronary artery bypass grafting • Drug-eluting stent • Left main disease • Percutaneous coronary intervention

INTRODUCTION

The treatment strategy in patients with left main stem disease (LMD) has been the subject of much debate. Most of this debate has originated from the recent publication of the 5-year results of the EXCEL trial [1], as its methodology, especially in defining myocardial infarction (MI) events, has raised some concerns [2]. This debate has motivated the publication of the EXCEL 5-year results [3] applying the third universal definition (UD) of MI [4].

The aim of the present study was to analyse the incidence of major adverse cardiovascular events (MACE) and cardiac mortality in patients undergoing either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with drug-eluting stents (DES) for LMD.

The present study includes, in 2 different setting of analyses, the original definition and the third UD of MI events reported by the EXCEL trial.

PATIENTS AND METHODS

A literature search (date: 14 March 2020) was carried out using the PubMed, Google Scholar, MEDLINE, Embase and Cochrane databases restricting such search to randomized clinical trial (RCT). In our search, the 'study type' filter was applied and as option was selected: 'randomized clinical trial'. The following Medical Subject Heading terms were used for the search: drug-eluting stent AND coronary artery bypass AND left main.

Population, intervention, comparison, outcomes and study design were the following:

i. Participants: patients undergoing myocardial revascularization because of LMD.
ii. Intervention: CABG.
iii. Comparison: PCI with DES.
iv. Outcomes: MACE, each of its components (5-year rates of overall mortality, periprocedural and spontaneous myocardial

infarction, stroke, repeat revascularization), and cardiac mortality.

v. Study design: RCTs.

The exclusion criteria applied were the following: (i) articles no reporting 5-year individual and composite MACE results; (ii) study design other than RCT; (iii) study population with coronary disease other than LMD; (iv) percutaneous population treated with non-drug-eluting stents; and (v) <90% of the sample population achieving 5-year follow-up time.

Data abstraction

The following study characteristics were recorded: design, sample population size, level of evidence according to the Oxford Centre for Evidence-Based Medicine classification (http://www.cebm.net/index.aspx? o=5653), percentage of the population achieving 5 years of follow-up, overall rate of mortality, MI, stroke, repeated revascularization, MACE and MI definitions for each trial (Supplementary Material, Data S1, Tables 1 and 2).

The internal validity and risk of bias of included trials were appraised according to the Cochrane Collaboration Methods [5] (Supplementary Material, Data S1 and Table 3).

Data analysis

Computations were carried out with R Core Team 2020 software (R Version 3.6.3) (https://www.r-project.org) for statistical computing (R Foundation for Statistical Computing, Vienna, Austria). The present meta-analysis was decided *a priori* to be carried out using a random effects model because of the expected variety in the sample populations.

All study items were processed as binary outcomes. These, obtained from crude number of events, were analysed to compute individual and pooled risk ratios (RRs) with pertinent 95% confidence intervals (95% CIs) with equivalence set at 1, RR < 1 favouring the CABG and RR > 1 favouring the PCI group. Sensitivity analysis was performed by removing each study, 1 by 1, and repeating the meta-analysis for the primary end-point to check for the influence of individual results on the overall results (Supplementary Material, Data S2). The risk of publication bias was assessed by funnel plot (Supplementary Material, Data S2). Statistical significance was set at the 2-tailed 0.05 level for hypothesis testing. Unadjusted *P*-values are reported. No correction for multiple testing was carried out. This meta-analysis was carried out according to the methodology previously described [6], in compliance with the Cochrane Collaboration (https://www.cochrane.org/) and PRISMA statement [7].

RESULTS

The results of our literature search are described in the PRISMA flow diagram (Supplementary Material, Data S2). To the 66 articles obtained by our original search, we posteriorly added the data from the reply of the EXCEL trial Authors published in July 2020 [3] in which MI events were reported according to the third UD [4].

Our review included 5-year results from 4 trials: SYNTAX [8], PRECOMBAT [9], NOBLE [10] and EXCEL [1, 3]. The included trials randomized 4394 patients (2197 to CABG and 2197 to PCI with DES).

Quantitative data synthesis

Two trial-level meta-analyses were carried out: the first one studied the 5-year results reported by the original papers of all the included studies. In the second one, the 5-year results of MI data obtained from the original 5-year EXCEL trial publication [1] were replaced by those recorded according to the UD of MI, which were published posteriorly [3].

The results of the first analysis are the following:

CABG significantly reduced the relative risk of MACE: 627/2197 (28.5%) in the CABG group vs 855/2197 (38.9%) in the PCI group (RR = 0.74; 95% CI = 0.68–0.80; *P* < 0.01) (Forest plot, Fig. 1A). The sensitivity analysis showed a similar benefit (Supplementary Material, Data S2).

The benefit of CABG in terms of MACE risk was driven by the decreased risk of MI and repeated revascularization as follows: CABG significantly reduced the relative risk of myocardial infarction (including both periprocedural and spontaneous events): 136/2197 (6.2%) in the CABG group vs 188/2197 (8.6%) in the PCI group (RR = 0.69; 95% CI = 0.51–0.94; *P* = 0.02 (Forest plot, Fig. 1B). The sensitivity analysis did not detect significant difference in terms of myocardial infarction risk when omitted the NOBLE trial (RR = 0.81; 95% CI = 0.63–1.04) (Supplementary Material, Data S2).

CABG also reduced the relative risk of repeat revascularization: 220/2197 [10.0%] in the CABG group vs 378/2197 [17.2%] in the PCI group (RR = 0.58; 95% CI = 0.50–0.68; *P* < 0.01) (Forest plot, Fig.1C). The sensitivity analysis showed a similar benefit (Supplementary Material, Data S2).

No significant differences were detected between CABG and PCI in any of the remaining individual items of the composite outcomes:

- risk of overall mortality [210/2197 (9.6%) in the CABG group vs 235/2197 (10.7%) in the PCI group; RR = 0.93; 95% CI = 0.73–1.19; P = 0.57; Forest plot, Fig.1D];
- risk of cardiac mortality [117/2197 (5.3%) in the CABG group vs 127/2197 (5.8%) in the PCI group; RR = 0.95; 95% CI = 0.69–1.30; P = 0.74; Forest plot, Fig.1E); and
- risk of stroke [61/2197 (2.8%) in the CABG group vs 54/2197 (2.5%) in the PCI group; RR = 1.16; 95% CI = 0.60–2.26; P = 0.66; Forest plot, Fig. 1F]. Sensitivity analysis of the three items confirmed these results (Supplementary Material, Data S2).

Overall meta-analysis with the inclusion of data recorded according to the UD from the EXCEL trial [3] demonstrated a larger reduction of risk of MI: 95/2197 (4.3%) in the CABG group vs 182/2197 (8.3%) in the PCI group (RR = 0.52; 95% CI = 0.41–0.66; *P* < 0.01; Forest plot, Fig. 2A).

Consequently, a larger benefit of CABG in terms of MACE was observed: [586/2197 (26.7%) in the CABG group vs 849/2197 (38.6%) in the PCI group; RR = 0.70; 95% CI = 0.63–0.76; *P* < 0.01; Forest plot, Fig. 2B].

The sensitivity analyses showed same benefit in both cases (Supplementary Material, Data S2).

Table 1: Trials characteristics Trial, author, date and country

Study type (level of Evidence)	*N* CABG versus n PCI	Type of coronary artery disease	Five-year follow-up time achievement	Type of stent	BIMA	MACCE (CABG versus PCI)	Total mortality (CABG versus PCI)	Myocardial infarction (CABG versus PCI)	Stroke (CABG versus PCI)	Repeat revascularization (CABG versus PCI)
SYNTAX, Morice *et al.* (2014), Europe and US Noninferiority RCT (level of evidence 2)	348 vs 357	LMD ± additional coronary disease	Five-year follow-up was achieved in 96.8% and 92.5% of the PCI and CABG groups	Paclitaxel eluting stent	[a]27.6%	31.0% vs 36.9%; *P* = 0.12	14.6% vs 12.8%; *P* = 0.53	4.8% vs 8.2%; *P* = 0.10	4.3% vs 1.5%; *P* = 0.03	15.5% vs 26.7%; *P* < 0.01
PRECOMBAT, Ahn *et al.* (2015), South Korea Noninferiority RCT (level of evidence 2)	300 vs 300	LMD ± additional coronary disease	Five-year follow-up was achieved in 92% of whole sample population	Sirolimus-eluting stent	No data	14.3% vs 17.5%; *P* = 0.26	7.9% vs 5.7%; *P* = 0.32	1.7% vs 2.0%; *P* = 0.76	0.7% vs 0.7%; *P* = 0.99	7.3% vs 13.0%; *P* = 0.02
NOBLE, Holm *et al.* (2019), Europe Noninferiority RCT (level of evidence 2)	592 vs 592	LMD ± additional coronary disease	Five-year follow-up was achieved in 92% of whole sample population	Biolimus-eluting stent	7.8%	19% vs 28%; *P* = 0.0002	9% vs 9%; *P* = 0.68	[b]3%.0 vs 8.0%; *P* = 0.0002	2.0% vs 4.0%; *P* = 0.11	10% vs 17%; *P* = 0.0009
EXCEL Original, Stone *et al.* (2019), Europe and US Noninferiority RCT (level of evidence 2)	957 vs 948	LMD ± additional coronary disease and SYNTAX score ≤32	Five-year follow-up was achieved in 93.2% and 90.1% of the PCI and CABG groups	Everolimus-eluting stent	24.0%	[c]24.9% vs. 31.3%; OR 0.72 (95% CI 0.58–0.88)	9.9% vs 13%; OR 0.72 (95% CI 0.54–0.97)	Protocol MI definition: 9.1% vs 10.6%; OR 0.88 (95% CI 0.64–1.19) 3 UD: 4.7% vs 9.6% (no OR provided)	3.7% vs 2.9%; OR 1.28 (95% CI 0. 76–2.17)	10.5% vs 17.2%; OR 0.56 (0.42–0.73)

Trials: EXCEL: Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease; NOBLE: Coronary Artery Bypass Grafting vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis; PRECOMBAT: Premier of Randomized Comparison of 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.

[a]Data from the whole surgical populations of the SNTAX trial (*n* = 854 patients) (Supplementary appendix, Percutaneous coronary intervention versus coronary- artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; 360:961–72.)

[b]Data of non-periprocedural myocardial infarction.

[c]Repeat revascularization events included in this MACE definition is referred only to ischaemia-driven revascularization.

BIMA: bilateral mammary artery; CABG: coronary artery bypass grafting; CI: confidence interval; DES: drug-eluting stent; LMD: left main stem disease; MACCE: major adverse cardiac or cerebrovascular events; MI: myocardial infacrtion. OR: odds ratio; PCI: percutaneous coronary intervention.

Table adapted from S.Urso et al. Cir Cardiov. 2018;25(2):118–124, DOI: 10.1016/j.circv.2017.10.003

Table 2: Definitions of myocardial infarction

Trial	Definition of procedural myocardial infarction	Definition of spontaneous myocardial infarction
SYNTAX (From *Am Heart J* 2006; 151:1194–204)	Within the first 7 days postintervention (PCI or CABG)—either new, abnormal Q waves and 1 ratio of peak CK-MB/peak total CK N10% or new, abnormal Q-waves and 1 plasma level of CK-MB 5× upper limit for normal.	7 days after any intervention procedure (PCI or CABG)—either new, abnormal Q waves or enzyme changes defined as >10% of the ratio of peak CK-MB/peak total CK on 1 or >1 sample (if no ratio is available—1 o>1 plasma level of CK-MB 5× upper limit for normal).
PRECOMBAT (From appendix: *N Engl J Med* 2011; 364:1718–27)	MI was defined as new Q waves and increase in the CK-MB concentration to >5 times the upper limit of the normal range, if occurring within 48 h after the procedure.	New Q waves or an increase in CK-MB concentration to greater than the upper limit of the normal range, plus ischaemic symptoms or signs, if occurring >48 h after the procedure.
NOBLE (From supplementary appendix: http://dx.doi.org/10.1016/S0140-6736(16)32052-9)	Diagnosis of procedural MI for both PCI and CABG patients was based on CK-MB elevations when available. Patients needed to have stable angina pectoris as the clinical indication OR a normal baseline CK-177 MB, TnI, TnT or highly sensitive TnT, to be assessable for procedural MI. Diagnosis required a CK-MB value above 10× URL or upper limit of normal (ULN) to establish the diagnosis. The diagnosis could also be placed by the combination of a CK-MB value above 5× URL or ULN, AND 1 or more of the following: (1) new pathological Q waves in at least 2 contiguous leads or new persistent non-rate-related left bundle branch block, or (2) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Periprocedural MI due to repeat revascularization during follow-up was assessed applying the 3rd Universal definition.	A rise in biochemical markers exceeding the decision limit for myocardial infarction (99th percentile including <10% coefficient of variation (CV)) with at least one of the following; (1) ischaemic symptoms, (2) Electrocardiogram (ECG) changes indicative of ischaemia (ST-segment (ST) elevation or depression) and (3) development of a pathological Q-wave with no relation to a PCI procedure.
EXCEL Original (From appendix: doi:10.1056/NEJMoa1610227)	Post procedure MI: Defined as the occurrence within 72 h after either PCI or CABG of either: • CK-MB >10× URL, OR • CK-MB >5× URL, PLUS • new pathological Q waves in at least 2 contiguous leads or new persistent non-rate-related LBBB, or • angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or • imaging evidence of new loss of viable myocardium or new regional wall motion abnormality-	The occurrence >72 h after any PCI or CABG of: • The rise and/or fall of cardiac biomarkers (CK-MB or troponin) >1× URL PLUS: • ECG changes indicative of new ischaemia (ST-segment elevation or depression, in the absence of other causes of ST-segment changes such as left ventricular hypertrophy or bundle branch block), or • Development of pathological Q waves (≥0.04 s in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads) of the ECG, or • Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Third universal definition (used in EXCEL recoded) (From: doi:10.1161/CIR.0b013e31826e1058)	Myocardial infarction related to PCI Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5× 99th percentile URL in patients with normal baseline values (<99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major	The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI: Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least 1 value above the 99th percentile URL and with at least one of the following:

Continued

Table 2: Continued

Trial	Definition of procedural myocardial infarction	Definition of spontaneous myocardial infarction
	coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. Myocardial infarction related to CABG Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10× 99th percentile URL in patients with normal baseline cTn values (<99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.	• Symptoms of ischaemia. • New or presumed new significant ST-segment-T wave changes or new LBBB. • Development of pathological Q waves in the ECG. • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. • Identification of an intracoronary thrombus by angiography or autopsy.

CABG: coronary artery bypass grafting; CK-MB: creatine kinase-MB; cTn: cardiac troponin; LBBB: left bundle branch block; MI: myocardial infarction; NSTEMI: Non-ST-segment elevation MI; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation MI; URL: upper reference limit.

Table 3: Internal validity and risk of bias assessment

Trial	Year	Adecuate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Overall risk of bias
SYNTAX	2014	Yes	Yes	Yes	Unclear	Yes	Yes	Low
PRECOMBAT	2015	Yes	Yes	Yes	Unclear	Yes	Yes	Low
NOBLE	2019	Yes	Yes	Yes	Unclear	Yes	Yes	Low
EXCEL original	2019	Yes	Yes	Yes	Unclear	No	No	Unclear
EXCEL recoded	2020	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear

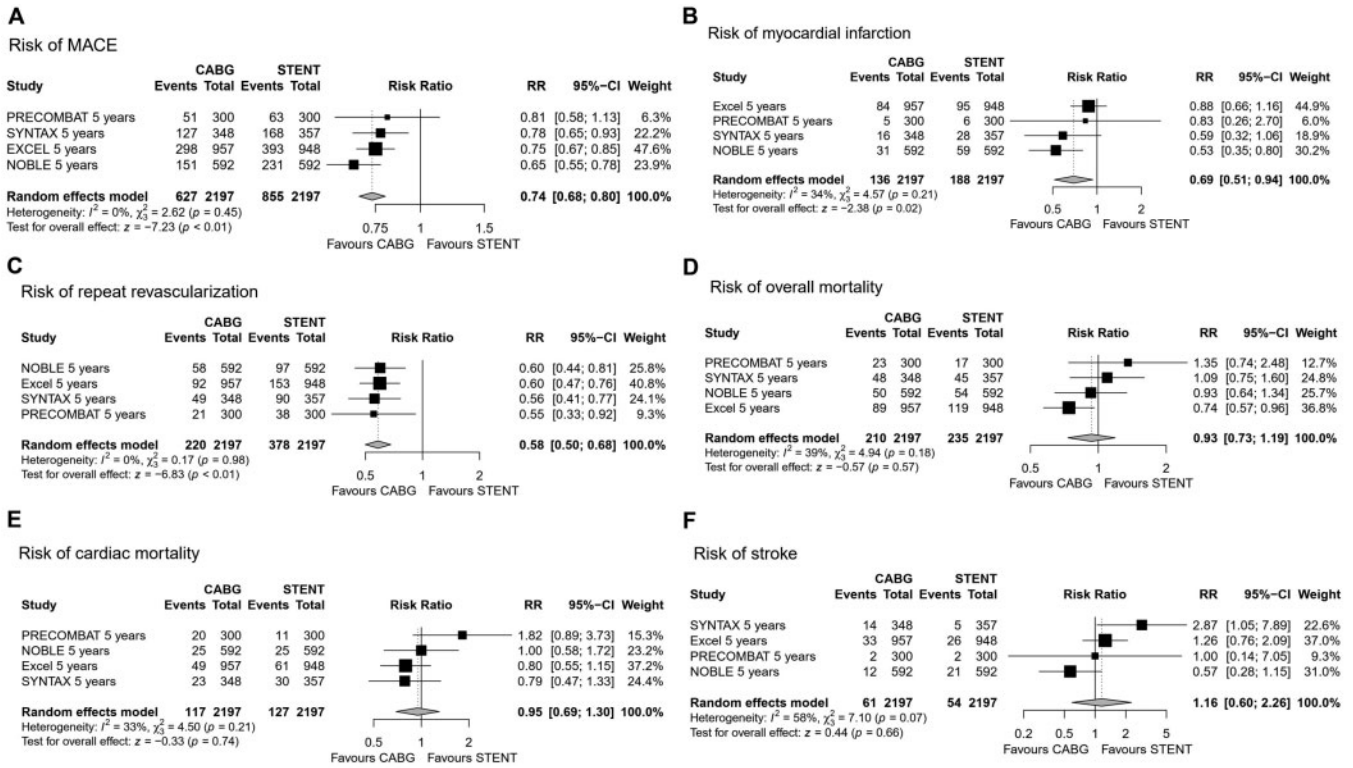

Figure 1: Myocardial infarction data from EXCEL recorded according to the original protocol definition: (**A**) Forest plot of risk of major adverse cardiovascular events. (**B**) Forest plot of risk of myocardial infarction. (**C**) Forest plot of risk of repeat revascularization. (**D**) Forest plot of risk of overall mortality. (**E**) Forest plot of risk of cardiac mortality. (**F**) Forest plot of risk of stroke. CABG: coronary artery bypass grafting; CI: confidence interval; MACE: major adverse cardiovascular events; MI: myocardial infarction; RR: risk ratio.

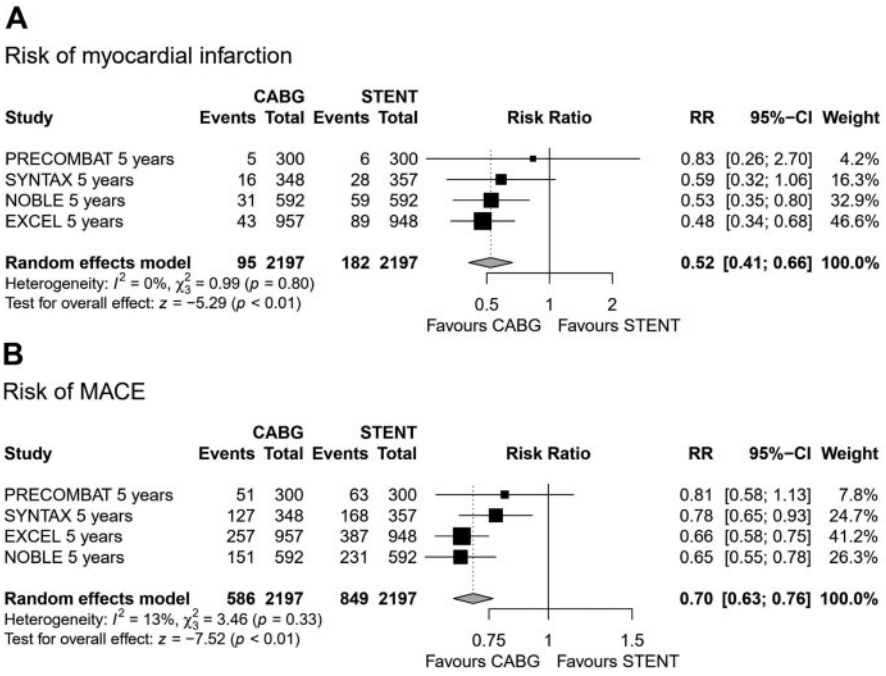

Figure 2: Myocardial infarction data from EXCEL trial recorded according to the third universal definition: (**A**) Forest plot of risk of myocardial infarction. (**B**) Forest plot of risk of major adverse cardiovascular events. CABG: coronary artery bypass grafting; CI: confidence interval; MACE: major adverse cardiovascular events. MI: myocardial infarction; RR: risk ratio; UD: universal definition.

DISCUSSION

The present meta-analysis shows that CABG significantly reduces the risk of MACE when compared with PCI in patients with LMD. This benefit, driven by the protective impact of CABG on MI and repeat revascularization, is amplified when the meta-analysis was carried out using the recoded MI data from the EXCEL trial.

We decided to include in our meta-analysis only those RCTs with a mean follow-up time of 5 years. The purpose of this decision was to avoid the confusion effect that the inclusion of populations with different follow-up times may have produced.

It is beyond the scope of this article to investigate the causes that have motivated the recodification of the MI events registered in the EXCEL trial [3]. Simply, the EXCEL trial 5-year MI data were recoded according to the third UD [4] instead of the SCAI definition used in the original EXCEL trial article [1]. Consequently, the number of patients with the recoded MI decreased by 6.3% in PCI group and by 48.8% in the CABG group [3]. As expected, the introduction of these data in the meta-analysis moved the balance in favour of the protective effect of CABG over PCI even further.

These important clinical advantages of CABG, summed to the beneficial impact in terms of repeat revascularization, make even clearer that CABG, compared with PCI, provides better results in patients with LMD.

Limitations

The present meta-analysis carries the potential bias of this specific analysis format and those of the primary studies, which populations have been through a process of selection. The format of the present meta-analysis does not allow to identify time-varying hazard ratio impacts. The included trials have used heterogenous definitions, especially to define myocardial infarction events. Due to the paucity of trials included in this meta-analysis, funnel plot to identify publication biases is difficult to be interpreted. We have not registered this study on PROSPERO.

CONCLUSION

The present meta-analysis shows that CABG significantly reduces the risk of myocardial infarction, repeat revascularization and, hence, MACE in patients with LMD.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

Author contributions

Stefano Urso: Conceptualization; Formal analysis; Investigation; Methodology; Writing—original draft. **Rafel Sadaba:** Conceptualization; Writing—review & editing. **Eliú Nogales:** Visualization. **Jesús María González:** Formal analysis. **María Ángeles Tena:** Conceptualization. **Federico Paredes:** Data curation. **Miguel González-Barbeito:** Methodology. **Francisco Portela:** Supervision.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Stephen Edward Fremes, Marc Ruel, David Taggart and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

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