Critical appraisal of a decade of left main revascularisation meta-analyses

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ABSTRACT

Background

The optimal revascularisation strategy for patients with left-main coronary artery disease (LMCAD) is a compelling topic. After the publication of recent trials, numerous meta-analyses on percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) were published. This study reviewed the extent of meta-analyses on PCI versus CABG in LMCAD.

Methods and Results

A systematic search in online databases was performed to identify meta-analyses on PCI versus CABG in LMCAD. Meta-analyses that reported associations between revascularisation and clinical outcomes were included.. Study outcomes were reported according to descriptive statistics, without pooling study outcomes. Fifty-one meta-analyses were included. Of those, 33 became available after EXCEL and NOBLE trial publication. The composite of major adverse cardiac (and cerebrovascular) events were reported in 41, and 49 reported all-cause mortality. Results varied, depending on (i) randomized versus observational data, or a combination of both, (ii) methodology and effect-measures to report treatment-differences, (iii) varying sample sizes, and (iv) the year of publication.

Conclusions

The number of meta-analyses on PCI versus CABG in patients with LMCAD, is disproportionate and urges the need for quality over quantity. To ensure high-quality publications, we call on all authors, editors and reviewers to appraise the evidence already available and join forces to conduct individual patient data pooled analyses instead.

Keywords

Coronary artery bypass; percutaneous coronary intervention; left main, meta-analyses; MACCE; all-cause mortality

INTRODUCTION

Meta-analyses are systematic reviews that pool study-outcomes to increase statistical power and provide a higher level of evidence than is often possible with single studies. Therefore, meta-analyses are frequently consulted by healthcare professionals and inform medical guidelines.[1]

The number of meta-analyses increased substantially in the field of cardiovascular medicine and determining the optimal strategy for patients with left main coronary artery disease (LMCAD) remains a fiercely debated subject. Over the past decades, numerous randomized studies assessed clinical outcomes after percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) in patients with LMCAD.[2-6] Two randomized controlled trials (RCTs) that contributed considerably to the evidence are the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main revascularisation and NOBLE (Nordic Baltic British left main revascularisation trials.[7, 8] Additionally, several non-randomized observational studies have reported results of CABG versus PCI. Pooling of observational data with randomized studies may lead to inter-study variability related to study design, sample size, baseline characteristics and outcomes, making it challenging to adequately appraise all scientific evidence available.

A meta-analysis, if performed correctly, can be helpful. However, an excess of meta-analyses, as was noticed over the recent decade, could lead to overlapping and redundant outcomes.[9] Therefore, this study critically appraised the extent of potential overlap and shortcomings by systematically reviewing the contemporaneous published meta-analyses on PCI versus CABG in LMCAD, with a special focus on those published after the EXCEL and NOBLE publications.

METHODS

Search strategy

On November 7th, 2018, a systematic literature search, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline[10] (Supplementary Appendix), was performed in Embase, Medline Ovid and Cochrane databases to identify meta-analyses on PCI versus CABG in LMCAD. The search contained the following key words or synonyms: “left main coronary artery disease”, “percutaneous coronary intervention”, “coronary artery bypass grafting” and “meta-analysis”. A detailed search strategy is reported in the Supplementary Appendix.

Meta-analyses comparing revascularisation strategies for LMCAD, by PCI with any stent(s) versus CABG, and reported clinical outcomes were included. Titles and abstracts were first screened for inclusion. When eligible, full-text English articles were subsequently reviewed independently by two authors (CA and DT). Predefined exclusion criteria were: (i) conference abstracts, (ii) absence of a LMCAD population, (iii) subgroups of patients with LMCAD, (iv) absence of effect estimates, (vi) individual patient pooled analyses or (vii) systematic reviews. Incongruities were resolved by agreement between two authors (CA and DT).

Data extraction

The following study details were extracted: year of publication, authors, journal, number of patients (total, CABG, and PCI) and the number of included individual randomized controlled trials (RCTs) and observational studies. Postoperative outcomes with an effect estimate (hazard, odds, risk ratios or incidence rate ratios) were extracted, along with the model used for analysis (fixed or random effects model). "Combined long-term follow-up" is defined as meta-analyses reporting a pooled event-rate at follow-up with varying durations (e.g. combination of 1, 3 and 5-year follow-up data).

Clinical outcomes that were extracted included major adverse cardiac (and cerebrovascular) events (MAC(C)E), according to the definitions used by the individual included meta-analyses, such as (i) death, stroke or myocardial infarction (MI) or as (ii) death, stroke, MI or any form of repeat revascularisation (for example; target-vessel revascularisation or ischemia-driven revascularisation All-cause mortality rates were also extracted.

Study outcomes

The primary endpoint consisted of a summary of MAC(C)E and all-cause mortality outcomes at combined long-term follow-up reported by meta-analyses published after EXCEL and NOBLE. Additionally, a summary of MAC(C)E and all-cause mortality outcomes at 1-year and combined long-term follow-up was provided for all included meta-analyses. The present report had no intention to determine which revascularisation strategy would be preferable for patients with LMCAD and rather focused on providing an overview of the currently available literature. Therefore, pooled outcomes of treatment effects are not provided.

Statistical analyses

Results are reported according to descriptive methods. All risk estimates reported, reflect a "PCI versus CABG" comparison. When an included meta-analysis reported

"CABG versus PCI" risk estimates, these were recalculated to represent "PCI versus CABG" comparisons. Forest plots were used to visualize the spread of varying study outcomes for MAC(C)E and all-cause mortality. Plots were constructed with Prism 8 (GraphPad Software, San Diego, CA, USA).

RESULTS

Study selection

The systematic search resulted in 402 articles. After excluding duplicates, screening titles and abstracts, 128 articles remained for full text reading (Figure 1). Of these, 77 were excluded based on the pre-specified criteria. Finally, 51 meta-analyses were included in the present study, of which 33 were published after EXCEL and NOBLE (Table 1 and Supplementary Appendix Table S1).[11-61]

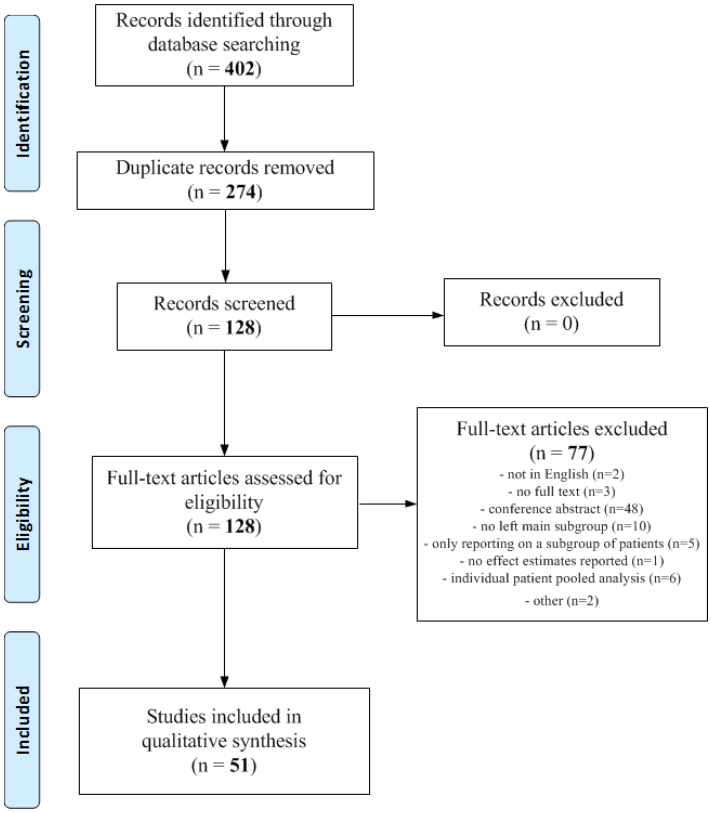

Figure 1. Flowchart of the comprehensive systematic search for meta-analyses PCI versus CABG in LMACD.
Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, LMCAD: left main coronary artery disease.

Table 1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51).

					Follow up duration					
Year	Author	Journal	PCI (n)	CABG (n)	≤30d	1y	3y	≥5y	Combined	MAC(C)E†
2018	Ali[52]	Medicine (Baltimore)	10424	11408	X	-	-	-	X	Stroke, death, MI or revascularisation
2018	Benedetto[53]	J Thorac Cardiovasc Surg	*	*	-	-	-	-	X	Death, MI or stroke
2018	Bertaina[54]	J Cardiovasc Med (Hagerstown)	8501	10813	-	-	-	-	X	Death, MI, definite or probable ST, TVR
2018	Cui[55]	J Geriatr Cardiol	6333	7797	-	-	-	-	X	Death, MI or stroke
2018	Khan[56]	Heart Lung Circul	2349	2351	X	X	-	X	-	MI, stroke, death or TVR
2018	Kodumuri[57]	Am J Cardiol	5017	5267	-	-	-	-	X	Death, MI, stroke or RR
2018	Moore[58]	Heart Lung Circul	2197	2197	-	-	-	-	X	Death, MI or CVA
2018	Rahouma[59]	Ann. cardiothorac. surg.	2349	2351	-	-	-	-	X	Death, MI, stroke or RR
2018	Takagi[60]	Catheter Cardiovasc Interventions	6009	6378	-	-	-	-	X	Death, MI and RRV (with/without stroke)
2018	Verdoia[61]	Angiology	2297	2298	-	-	-	-	X	Major Adverse Cardiovascular Events*
2017	Bajaj[30]	Eur Heart J Qual Care Clin Outcomes	2349	2351	-	X	-	-	X	Death, stroke, MI or RR
2017	Chang[31]	Ann Thorac Surg	*	*	X	X	-	-	X	Death, stroke, MI or TVR
2017	DeRosa[32]	BMC Cardiovasc Disord	2249	2250	-	-	-	-	X	Death, stroke, MI or RR
2017	Gao[33]	Oncotarget	2297	2298	-	X	-	-	X	Death, stroke, MI or RR
2017	Garg[34]	Am J Cardiol	2297	2298	-	-	-	-	X	*
2017	Giacoppo[35]	JAMA Cardiol	2197	2197	-	-	-	-	X	Death, stroke or MI
2017	Khan[36]	Am J Cardiol	2349	2351	-	X	-	-	X	Death, MI, stroke or RR
2017	Khan[37]	Am J Cardiol	3197	3340	-	-	-	X	-	Death, nonfatal MI, stroke or RR
2017	Laukkanen[38]	Open Heart	2149	2351	X	X	-	-	X	Death, MI, CVA or stroke, or TVR
2017	Mahmoud[39]	Catheter Cardiovasc Interventions	2349	2351	X	X	-	-	X	Death, MI, stroke or revascularisation
2017	Palmerini[40]	Am Heart J	2347	2339	X	-	-	-	X	Death, stroke, MI or UR

Rct (N)	Obs (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
5	24	X	-	X	X	X	X	OR		1.22 (0.95-1.56)		0.83 (0.60-1.15)
6	-	X	X	X	X	X	X	IRR		0.99 (0.70-1.40)		
6	20	X	X	X	X	X	X	OR		1.10 (1.07-1.14)		0.94 (0.89-1.00)
4	12	X	-	-	X	X	X	HR		0.94 (0.86-1.03)		1.11 (0.92-1.32)
6	-	X	X	X	X	X	X	RR	1.15 (0.92-1.45)		0.67 (0.43-1.06)	
4	8	X	-	-	X	X	X	OR		1.23 (1.01-1.51)		0.97 (0.74-1.26)
4	-	X	-	-	X	X	X	OR		1.37 (1.18-1.58)		1.08 (0.86-1.35)
6	-	X	X	X	X	X	X	IRR		1.328 (1.114-1.582)		0.947 (0.711-1.262)
5	17	X	-	X	X	X	X	HR		1.42 (1.28-1.58)		1.03 (0.90-1.18)
5	-	X	-	X	X	X	X	OR		1.16 (0.98-1.37)		0.88 (0.60-1.29)
6	-	X	X	X	X	X	X	RR	1.17 (0.94-1.44)	1.21 (1.05-1.40)	0.68 (0.44-1.06)	0.98 (0.78-1.25)
5	-	X	X	X	X	-	-	RR	1.20 (0.94-1.54)	1.25 (1.05-1.49)	0.66 (0.38-1.15)	0.81 (0.62-1.08)
5	-	X	X	-	X	X	X	OR		1.33 (1.12-1.58)		1.04 (0.82-1.32)
5	-	X	-	X	X	X	X	RR	1.15 (0.92-1.44)	1.26 (1.11-1.44)	0.70 (0.45-1.09)	1.05 (0.85-1.31)
5	-	X	-	X	X	X	X	OR				1.01 (0.76-1.34)
4	-	X	-	-	X	X	X	HR		1.06 (0.85-1.32)		1.04 (0.81-1.33)
6	-	X	X	X	X	X	X	HR	1.03 (0.69-1.52)	1.16 (0.95-1.43)	0.71 (0.47-1.06)	1.03 (0.80-1.33)
4	5	X	-	-	X	X	X	OR				
6	-	X	X	X	X	X	X	HR	1.16 (0.94-1.44)	1.27 (1.12-1.44)	0.66 (0.42-1.04)	1.04 (0.81-1.33)
6	-	X	X	X	X	X	X	RR	1.21 (0.97-1.51)	1.19 (1.01-1.41)	0.76 (0.45-1.30)	0.94 (0.73-1.22)
6	-	X	X	X	X	X	X	OR		1.27 (1.12-1.45)		0.99 (0.76-1.30)

Table 1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51). (*continued*)

					Follow up duration					
Year	**Author**	**Journal**	**PCI (n)**	**CABG (n)**	**≤30d**	**1y**	**3y**	**≥5y**	**Combined**	**MAC(C)E†**
2017	Putzu[41]	Int J Cardiol	*	*	X	X	-	-	X	Death, stroke or MI*
2017	Qian[42]	Am J Cardiol	2297	2298	-	X	-	-	X	Study specific definitions of MACCE†
2017	Sá[39]	Braz J Cardiovasc Surg	2297	2298	-	X	-	-	-	Death, MI, stroke or TVR
2017	Sardar[44]	Am J Cardiol	2303	2309	-	X	-	-	X	Death, stroke,MI or any revascularisation
2017	Shah[45]	Am J Cardiol	2349	2351	-	X	X	X	X	Death, recurrent MI, RR and stroke
2017	Sharma[46]	Cardiovasc Ther	2349	2351	X	X	X	X	X	Death, MI, stroke or revascularisation
2017	Spinthakis[47]	Int J Cardiol	2297	2298	-	X	X	X	-	-
2017	Testa[48]	PLoS ONE	2347	2339	-	X	-	-	X	Death, stroke or MI
2017	Upadhaya[49]	J Card Surg	2297	2298	-	-	-	-	X	Study specific definitions of MACCE†
2017	Ye[50]	Medicine (Baltimore)	2349	2351	-	-	-	-	X	Death, MI, stroke and revascularisation
2017	Zhang[51]	BMC Med	10406	12081	-	-	-	-	X	Death, MI, stroke or RR
2016	Nerlekar[29]	Circ Cardiovasc Interventions	2297	2297	-	X	-	-	X	Death, MI, stroke, or RR

Overview of characteristics on PCI versus CABG in LMCAD published by meta-analysis published after EXCEL and NOBLE trial.

Risk estimates representing CABG versus PCI, provided by included meta-analyses, were recalculated to represent PCI versus CABG risk estimates. X = **YES** , - = **NO**. *this specific outcome was not specified in this meta-analysis. †MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. #the correct reference was missing in the original meta-analysis.

Abbreviations used: CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, PCI: percutaneous coronary intervention, LMCAD: left main coronary artery disease, RCTs: randomized controlled trials, Obs.: Observational, Ref.: reference, LA: longest available follow-up, MI; myocardial revascularisation, RR/RRV; repeat revascularisation, TVR: target vessel revascularisation, ST; stent thrombosis, OR: odds ratio, HR: hazard ratio, RR: risk ratio, IRR: incidence rate ratio, UR: unplanned revascularisation.

Rct (N)	Obs (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
5	-	X	-	X	X	X	X	OR			0.69 (0.44-1.10)	1.08 (0.86-1.35)
5	-	X	-	X	X	X	X	RR	1.14 (0.91-1.42)	1.27 (1.13-1.43)	0.78 (0.56-1.08)	1.05 (0.83-1.34)
5	-	X	-	X	X	X	X	RR	1.05 (0.82-1.36)		1.03 (0.80-1.32)	
5	-	X	-	X	X	X	X	OR	0.73 (0.52-1.01)	1.36 (1.18-1.57)	0.71 (0.44-1.12)	1.03 (0.79-1.35)
6	-	X	X	X	X	X	X	RR	1.15 (0.91-1.44)	1.20 (1.03-1.41)	0.68 (0.44-1.06)	0.98 (0.78-1.25)
6	-	X	X	X	X	X	X	OR	1.15 (0.88-1.51)	1.36 (1.18-1.58)	0.67 (0.43-1.06)	1.06 (0.82-1.38)
5	-	X	-	X	X	X	X	OR			0.70 (0.44-1.12)	
6	-	X	X	X	X	X	X	OR	1.02 (0.76-1.36)	1.02 (0.76-1.38)	0.81 (0.63-1.03)	1.00 (0.77-1.31)
5	-	X	-	X	X	X	X	OR		1.36 (1.18-1.58)		1.03 (0.78-1.35)
6	-	X	X	X	X	X	X	RR		1.21 (1.05-1.40)		0.98 (0.78-1.25)
6	22	X	X	X	X	X	X	HR		1.42 (1.14-1.77)		1.05 (0.92-1.20)
5	-	X	-	X	X	X	X	OR	1.14 (0.86-1.49)	1.36 (1.18-1.58)		1.03 (0.78-1.35)

Published meta-analyses

The number of published meta-analyses increased over the past decade, especially after the publication of the randomized EXCEL and NOBLE trials (Figure 2).[7, 8] Several journals published more than one meta-analysis, with one journal publishing 10 meta-analyses on PCI versus CABG for LMCAD. Meta-analyses predominantly reported risk estimates according to odds, risk or hazard ratios.

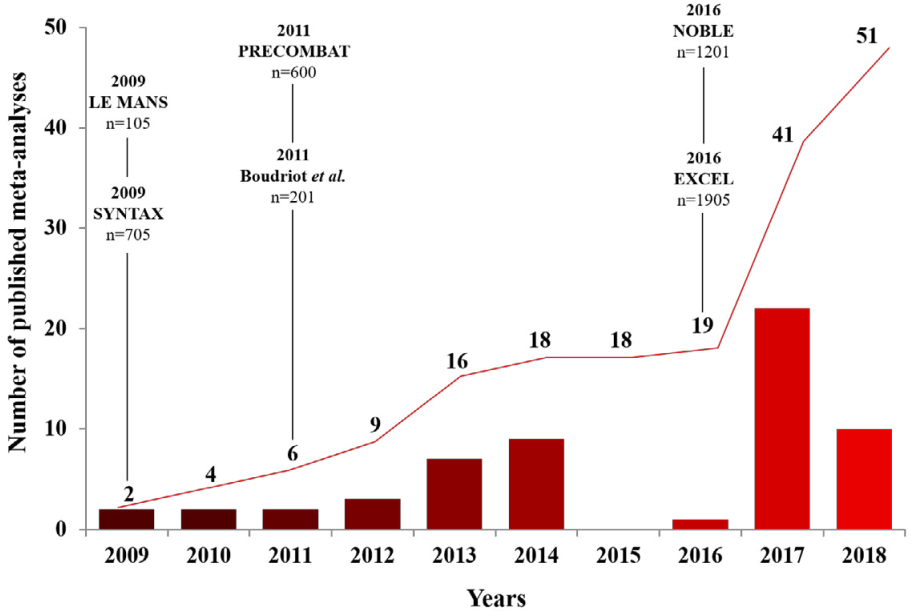

Figure 2. Representation of published randomized clinical trials and meta-analyses on PCI versus CABG in LMCAD over the past decade. The red bars represent the amount of published meta-analyses per year. The red curve represents the cumulative amount of published meta-analyses over the past decade. The main randomized studies that published data on PCI versus CABG in LMCAD are indicated by black lines and names with the intention-to-treat sample sizes.

Meta-analyses after EXCEL and NOBLE

Thirty-three meta-analyses were published after EXCEL and NOBLE. Of these, 32 included EXCEL and NOBLE in addition to results from 3 or 4 other RCTs in their analysis. MAC(C)E outcomes, at combined long-term follow-up, were reported by 26 studies (Table 1, Figure 3), while 27 meta-analyses reported all-cause mortality at combined long-term follow-up (Table 1, Figure 4).

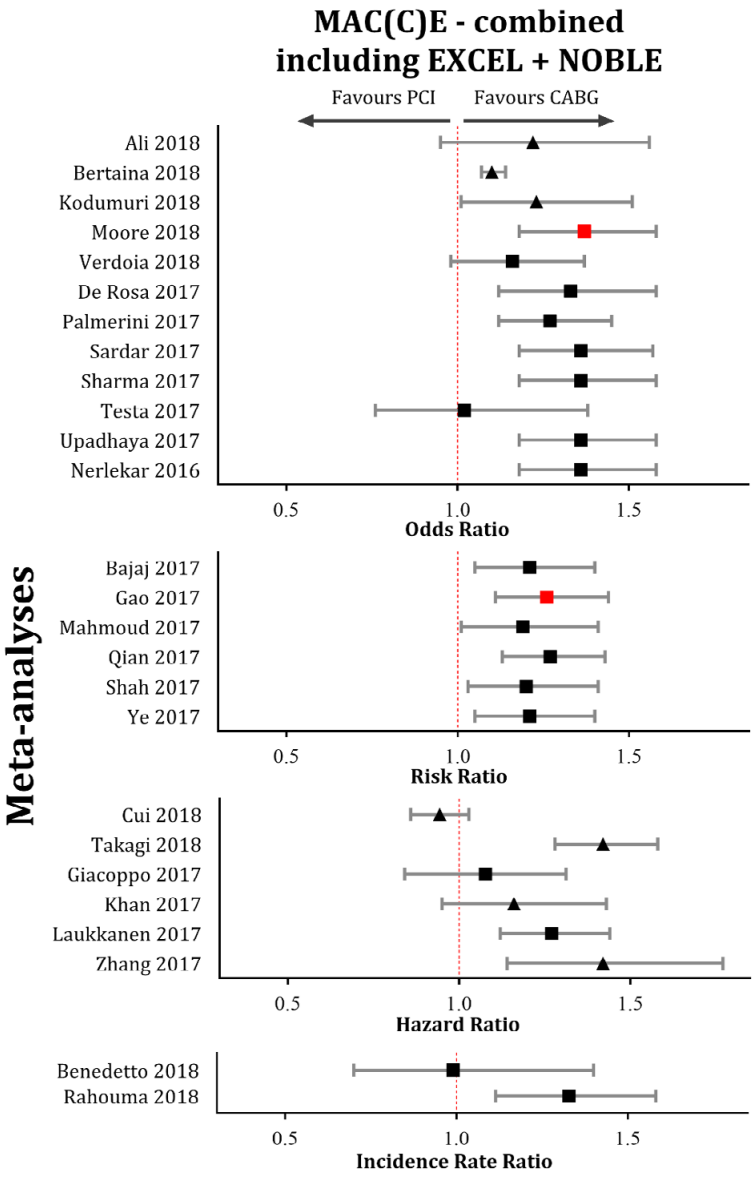

Figure 3. Forest plot representation of MAC(C)E outcomes, at longest follow-up available, reported by those meta-analyses published after the NOBLE and EXCEL trials. Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses.

Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

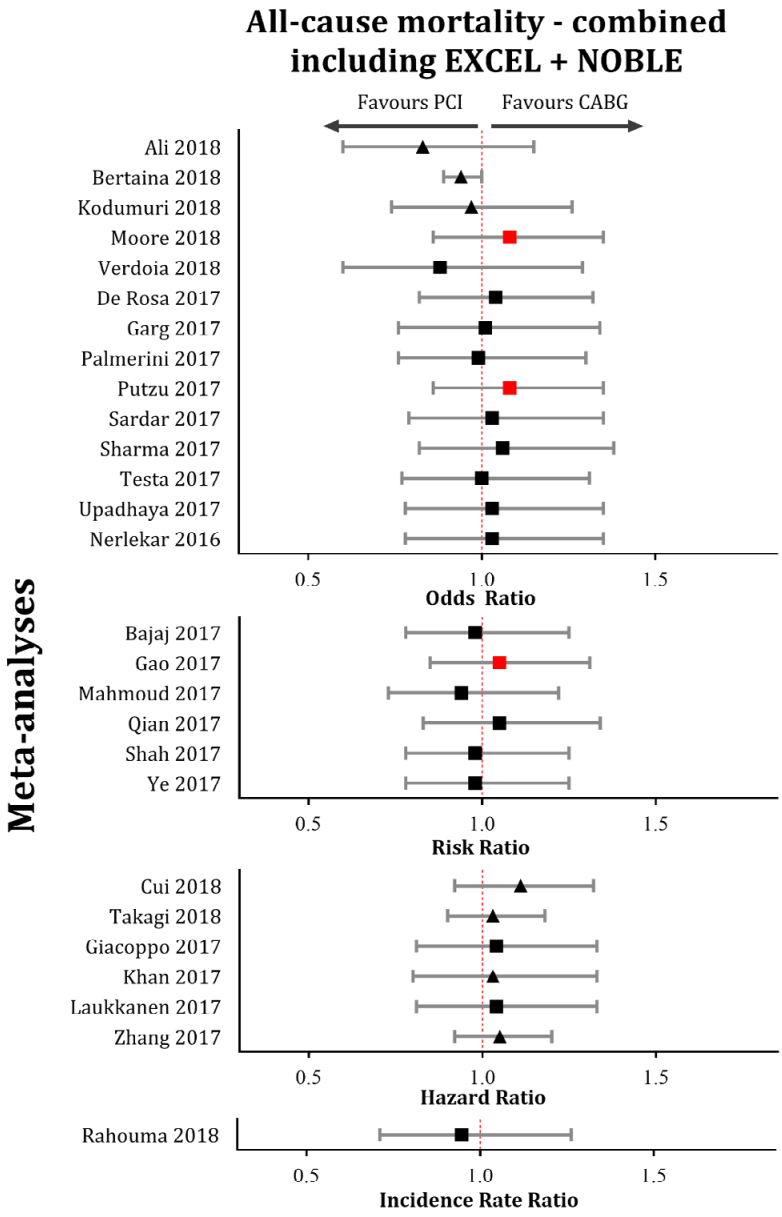

Figure 4. Forest plot representation of all-cause mortality outcomes, at longest follow-up available, reported by those meta-analyses published after the NOBLE and EXCEL trials. Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses.

Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

Meta-analyses that included the same RCTs (SYNTAX, Boudriot *et al.*, PRECOMBAT, EXCEL, NOBLE with/without LE MANS) reported varying sample sizes, ranging from 4594 to 4700 patients, while the overall intention-to-treat population consists of 4595 patients (5 RCTs) and 4700 (5 RCTs plus LE MANS, respectively) (Table 1). Eleven meta-analyses reported MAC(C)E risk estimates at combined long-term follow-up varying from 0.99 (95%CI: 0.70-1.40) to 1.36 (95%CI: 1.18-1.58), although the composite of MAC(C)E differed among trials. MAC(C)E-specific definitions used by the various trials are reported in the Supplementary Appendix (Table S2). Ten meta-analyses reported risk estimates of all-cause mortality at combined long-term follow-up, varying from 0.94 (95%CI: 0.73-1.22) to 1.06 (95%CI:0.82-1.38). Two meta-analyses that also included observational data reported similar outcomes as compared studies only including RCTs.[51, 54]

Published meta-analyses over the past decade

Since 2009, 41 meta-analyses reported MAC(C)E outcomes (Table S1). Of those, 33 reported outcomes at combined long-term follow-up (Figure S1) and 22 reported outcomes at 1-year (Table 1, Figure S2). All-cause mortality, at combined long-term follow-up, was reported by 38 meta-analyses (Table S1, Figure S3). Twenty-seven studies reported all-cause mortality at 1-year (Figure S4). Meta-analyses that only included RCTs reported similar all-cause death outcomes compared with those including also observational data.

DISCUSSION

Fifty-one meta-analyses covering the exact same topic were identified, and of these, 33 emerged over the past three years after the publications of the randomized EXCEL and NOBLE trials. Sixteen meta-analyses were published from 2009 to 2013 and this number more than doubled (n=35) from 2014 to 2018. While this study did not perform a meta-analysis of meta-analyses and had no intention on determining the preferred revascularisation strategy for LMCAD, it systematically reviewed the abundancy of meta-analyses on PCI versus CABG in LMCAD over the past decade. Interestingly, the reported outcomes differed between meta-analyses due to several methodological reasons. Although meta-analyses (should) aim to present the highest level of evidence, there are multiple shortcomings which are summarized below.[9, 62, 63]

There were methodological limitations in the design of many meta-analyses. The reported sample-sizes varied without explanation. Several studies combined the in-

tention-to-treat populations with as-treated populations. Many (n=38) meta-analyses report all-cause mortality at long-term follow-up, while the duration of follow-up differed significantly between trials. The SYNTAX trial for instance, reported 5-year follow-up, while EXCEL reported 3-year follow-up. Inclusion of studies with different follow-up durations could result in an under- or overestimation of the outcome, as it is well known that risk differences of MI and repeat revascularisation diverge over time, favoring CABG.[2, 7, 8, 64, 65] This is most evident in the landmark analysis of the EXCEL trial for the composite endpoint of death, stroke or MI: 0-30 days (HR: 0.61 (95% CI: 0.42-0.88)) versus >30 days -3 year (HR: 1.44 (95% CI: 1.06-1.96)).[7, 66]

Additionally, the statistical models used in the meta-analyses differed. Besides reporting various effect-measures, meta-analyses either used a random-effect or a fixed-effect model. A fixed-effect model assumes that the treatment-effect is similar across studies, while a random-effect model accounts for differences in treatment effect, study populations or follow-up length.[67] Some of the meta-analyses that included SYNTAX, Boudriot *et al.*, PRECOMBAT, EXCEL and NOBLE used a random-effect model while others used a fixed-effect model. Moreover, meta-analyses that included observational studies, with substantial variations in follow-up time and patients baseline characteristics, used a fixed-effect model.

Finally, composite outcomes with different definitions were pooled. The definitions of MAC(C)E differed among SYNTAX[65], EXCEL[7], and NOBLE (Table S2)[8], but some meta-analyses did not take into account these differences in the composite endpoints. This, however, is crucial information for both patient and physicians when deciding on the preferred treatment.

To diminish the overlap in future meta-analyses, it is recommended to register the rationale and protocol of a new meta-analysis at an online registration platform.[68] Finally, a preferable alternative for performing a meta-analysis is to conduct an individual patient data pooled analysis.[69, 70] Pooling individual patient data overcomes the different methods of reporting and analyzing data by individual studies. It has the advantage to use all available raw patients characteristics, account for missing variables, use accurate follow-up data and a standardized statistical method for analysis.[69]

CONCLUSION

The present study identified 51 meta-analyses covering the exact same topic of PCI versus CABG revascularisation in patients with LMCAD. With the publications of longer-term follow-up of the SYNTAX and EXCEL trials, one could anticipate another surge of meta-analyses. To ensure high quality studies and reduce overlapping publications, we call on all authors, editors and reviewers to critically appraise the evidence already available and use online meta-analyses registration platforms to avoid potential overlap. Collaborating and focusing research capacities, by conducting individual patient data pooled analyses could enable us to work more efficiently and ensure reporting the highest quality of available evidence.

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CONFLICT OF INTEREST

Dr. Kappetein and dr. Head report to work as employees of Medtronic, outside the submitted work. All other authors declare no competing interests relevant to this publication.

REFERENCES

1. Evidence-Based Medicine Working G. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992;**268**:2420-5.
2. Morice MC, Serruys PW, Kappetein AP. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. Circulation 2014;**129**:2388-94.
3. Buszman PE, Buszman PP, Kiesz RS. Early and long-term results of unprotected left main coronary artery stenting: the LE MANS (Left Main Coronary Artery Stenting) registry. J Am Coll Cardiol 2009;**54**:1500-11.
4. Ahn JM, Roh JH, Kim YH. Randomized Trial of Stents Versus Bypass Surgery for Left Main Coronary Artery Disease: 5-Year Outcomes of the PRECOMBAT Study. J Am Coll Cardiol 2015;**65**:2198-206.
5. Boudriot E, Thiele H, Walther T. 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.
6. Park S-J, Ahn J-M, Kim Y-H. Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease. New England Journal of Medicine 2015;**372**:1204-1212.
7. Stone GW, Sabik JF, Serruys PW. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. N Engl J Med 2016;**375**:2223-2235.
8. Makikallio T, Holm NR, Lindsay M. 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**:2743-2752.
9. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. BMJ 2013;**347**:f4501.
10. Moher D, Liberati A, Tetzlaff J. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med 2009;**3**:e123-30.
11. Naik H, White AJ, Chakravarty T. A Meta-Analysis of 3,773 Patients Treated With Percutaneous Coronary Intervention or Surgery for Unprotected Left Main Coronary Artery Stenosis. JACC Cardiovasc Interventions 2009;**2**:739-747.
12. Takagi H, Kawai N, Umemoto T. Stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: A meta-analysis of comparative studies. J Thorac Cardiovasc Surg 2009;**137**:e54-e57.
13. Lee MS, Yang T, Dhoot J. Meta-Analysis of Clinical Studies Comparing Coronary Artery Bypass Grafting With Percutaneous Coronary Intervention and Drug-Eluting Stents in Patients With Unprotected Left Main Coronary Artery Narrowings. Am J Cardiol 2010;**105**:1070-1075.
14. Takagi H, Matsui M, Umemoto T. Increased late mortality with percutaneous stenting for unprotected left main coronary artery stenosis relative to coronary artery bypass grafting: A meta-analysis of observational studies. J Thorac Cardiovasc Surg 2010;**139**:1351-1353.
15. Capodanno D, Stone GW, Morice MC. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol 2011;**58**:1426-32.

16. Zheng S, Zheng Z, Hou J. Comparison between drug-eluting stents and coronary artery bypass grafting for unprotected left main coronary artery disease: A meta-analysis of two randomized trials and thirteen observational studies. Cardiology 2011;**118**:22-32.
17. Jang JS, Choi KN, Jin HY. Meta-analysis of three randomized trials and nine observational studies comparing drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery disease. Am J Cardiol 2012;**110**:1411-1418.
18. Jiang WB, Zhao W, Huang H. Meta-analysis of effectiveness of first-generation drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary disease. Am J Cardiol 2012;**110**:1764-1772.
19. Kajimoto K, Miyauchi K, Yamamoto T. Meta-analysis of randomized controlled trials on the treatment of unprotected left main coronary artery disease: One-year outcomes with coronary artery bypass grafting versus percutaneous coronary artery intervention with drug-eluting stent. J Card Surg 2012;**27**:152-157.
20. Alam M, Huang HD, Shahzad SA. Percutaneous coronary intervention vs. coronary artery bypass graft surgery for unprotected left main coronary artery disease in the drug-eluting stents era - An aggregate data meta-analysis of 11,148 patients. Circ J 2013;**77**:372-382.
21. Athappan G, Patvardhan E, Tuzcu ME. Left main coronary artery stenosis: A meta-analysis of drug-eluting stents versus coronary artery bypass grafting. JACC Cardiovasc Interventions 2013;**6**:1219-1230.
22. Bittl JA, He Y, Jacobs AK. Bayesian Methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. Circulation 2013;**127**:2177-2185.
23. Cao C, Manganas C, Bannon P. Drug-eluting stents versus coronary artery bypass graft surgery in left main coronary artery disease: A meta-analysis of early outcomes from randomized and nonrandomized studies. J Thorac Cardiovasc Surg 2013;**145**:738-747.
24. Desch S, Boudriot E, Rastan A. Bypass surgery versus percutaneous coronary intervention for the treatment of unprotected left main disease: A meta-analysis of randomized controlled trials. Herz 2013;**38**:48-56.
25. Li Q, Zhang Z, Yin RX. Drug-eluting stents or coronary artery bypass grafting for unprotected left main coronary artery disease: a meta-analysis of four randomized trials and seventeen observational studies Review. Trials 2013;**14**:133.
26. Sá MP, Soares AM, Lustosa PC. Meta-analysis of 5,674 patients treated with percutaneous coronary intervention and drug-eluting stents or coronary artery bypass graft surgery for unprotected left main coronary artery stenosis. Eur J Cardiothorac Surg 2013;**43**:73-80.
27. Al Ali J, Franck C, Filion KB. Coronary artery bypass graft surgery versus percutaneous coronary intervention with first-generation drug-eluting stents: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv 2014;**7**:497-506.
28. Benedetto U, Ng C, Smith R. Coronary artery bypass grafting is superior to first-generation drug-eluting stents for unprotected left main coronary artery disease: An updated meta-analysis of 4 randomized, controlled trials. J Thorac Cardiovasc Surg 2014;**148**:2430-2432.
29. Nerlekar N, Ha FJ, Verma KP. Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interventions 2016;**9**.

30. Bajaj NS, Patel N, Kalra R. Percutaneous coronary intervention vs. coronary artery bypass grafting for left main revascularization: An updated meta-analysis. Eur Heart J Qual Care Clin Outcomes 2017;**3**:173-182.
31. Chang YS, Wang JX, Chang DW. Outcomes of Coronary Artery Bypass and Stents for Unprotected Left Main Coronary Stenosis. Ann Thorac Surg 2017;**104**:630-637.
32. De Rosa S, Polimeni A, Sabatino J. Long-term outcomes of coronary artery bypass grafting versus stent-PCI for unprotected left main disease: a meta-analysis Review. BMC Cardiovasc Disord 2017;**17**:240.
33. Gao L, Liu Y, Sun Z. Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass graft surgery in left main coronary artery disease an updated meta-analysis of randomized clinical trials. Oncotarget 2017;**8**:66449-66457.
34. Garg A, Rao SV, Agrawal S. Meta-Analysis of Randomized Controlled Trials of Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease. Am J Cardiol 2017;**119**:1942-1948.
35. Giacoppo D, Colleran R, Cassese S. Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients With Left Main Coronary Artery Stenosis: A Systematic Review and Meta-analysis. JAMA Cardiol 2017;**2**:1079-1088.
36. Khan AR, Golwala H, Tripathi A. Meta-analysis of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease. Am J Cardiol 2017;**119**:1949-1956.
37. Khan MR, Kayani WT, Ahmad W. Meta-Analysis of Comparison of 5-Year Outcomes of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients With Unprotected Left Main Coronary Artery in the Era of Drug-eluting Stents. Am J Cardiol 2017;**120**:1514-1520.
38. Laukkanen JA, Kunutsor SK, Niemela M. All-cause mortality and major cardiovascular outcomes comparing percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: a meta-analysis of short-term and long-term randomised trials. Open Heart 2017;**4**:e000638.
39. Mahmoud AN, Elgendy IY, Mentias A. Percutaneous coronary intervention or coronary artery bypass grafting for unprotected left main coronary artery disease. Catheter Cardiovasc Interventions 2017;**90**:541-552.
40. Palmerini T, Serruys P, Kappetein AP. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: A meta-analysis of 6 randomized trials and 4,686 patients. Am Heart J 2017;**190**:54-63.
41. Putzu A, Gallo M, Martino EA. Coronary artery bypass graft surgery versus percutaneous coronary intervention with drug-eluting stents for left main coronary artery disease: A meta-analysis of randomized trials. Int J Cardiol 2017;**241**:142-148.
42. Qian C, Feng H, Cao J. Meta-Analysis of Randomized Control Trials Comparing Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Significant Left Main Coronary Narrowing. Am J Cardiol 2017;**119**:1338-1343.
43. Sá MPBO, Soares AF, Miranda RGA. CABG Surgery Remains the best Option for Patients with Left Main Coronary Disease in Comparison with PCI-DES: Meta-Analysis of Randomized Controlled Trials. Braz J Cardiovasc Surg 2017;**32**:408-416.

44. Sardar P, Giri J, Elmariah S. Meta-Analysis of Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Coronary Narrowing. Am J Cardiol 2017;**119**:1746-1752.
45. Shah R, Morsy MS, Weiman DS. Meta-Analysis Comparing Coronary Artery Bypass Grafting to Drug-Eluting Stents and to Medical Therapy Alone for Left Main Coronary Artery Disease. Am J Cardiol 2017;**120**:63-68.
46. Sharma SP, Dahal K, Khatra J. Percutaneous coronary intervention vs coronary artery bypass grafting for left main coronary artery disease? A systematic review and meta-analysis of randomized controlled trials. Cardiovasc Ther 2017;**35**.
47. Spinthakis N, Farag M, Gorog DA. Percutaneous coronary intervention with drug-eluting stent versus coronary artery bypass grafting: A meta-analysis of patients with left main coronary artery disease. Int J Cardiol 2017;**249**:101-106.
48. Testa L, Latib A, Bollati M. Unprotected left main revascularization: Percutaneous coronary intervention versus coronary artery bypass. An updated systematic review and meta-analysis of randomised controlled trials. PLoS ONE 2017;**12**.
49. Upadhaya S, Baniya R, Madala S. Drug-eluting stent placement versus coronary artery bypass surgery for unprotected left main coronary artery disease: A meta-analysis of randomized controlled trials. J Card Surg 2017;**32**:70-79.
50. Ye Y, Yang M, Zhang S. Percutaneous coronary intervention versus cardiac bypass surgery for left main coronary artery disease: A trial sequential analysis. Medicine (Baltimore) 2017;**96**:e8115.
51. Zhang XL, Zhu QQ, Yang JJ. Percutaneous intervention versus coronary artery bypass graft surgery in left main coronary artery stenosis: a systematic review and meta-analysis Review. BMC Med 2017;**15**:84.
52. Ali WE, Vaidya SR, Ejeh SU. Meta-analysis study comparing percutaneous coronary intervention/drug eluting stent versus coronary artery bypass surgery of unprotected left main coronary artery disease: Clinical outcomes during short-term versus long-term (> 1 year) follow-up. Medicine (Baltimore) 2018;**97**:e9909.
53. Benedetto U, Taggart DP, Sousa-Uva M. New-generation stents compared with coronary bypass surgery for unprotected left main disease: A word of caution. J Thorac Cardiovasc Surg 2018;**155**:2013-2019.e2016.
54. Bertaina M, De Filippo O, Iannaccone M. Percutaneous coronary intervention or coronary artery bypass graft in left main coronary artery disease: a comprehensive meta-analysis of adjusted observational studies and randomized controlled trials. J Cardiovasc Med (Hagerstown) 2018;**19**:554-563.
55. Cui KY, Lyu SZ, Song XT. Long term outcomes of drug-eluting stent versus coronary artery bypass grafting for left main coronary artery disease: A meta-analysis. J Geriatr Cardiol 2018;**15**:162-172.
56. Khan SU, Rahman H, Arshad A. Percutaneous Coronary Intervention Versus Surgery in Left Main Stenosis–A Meta-Analysis and Systematic Review of Randomised Controlled Trials. Heart Lung Circul 2018;**27**:138-146.
57. Kodumuri V, Balasubramanian S, Vij A. A Meta-Analysis Comparing Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Disease. Am J Cardiol 2018;**121**:924-933.

58. Moore P, Burrage M, Garrahy P. Drug-Eluting Stents Versus Coronary Artery Bypass Grafts for Left Main Coronary Disease: A Meta-Analysis and Review of Randomised Controlled Trials. Heart Lung Circul 2018;**27**:1437-1445.
59. Rahouma M, Abouarab A, Di Franco A. Percutaneous coronary intervention versus coronary bypass surgery for unprotected left main disease: a meta-analysis of randomized controlled trials. Ann. cardiothorac. surg. 2018;**7**:454-462.
60. Takagi H, Ando T, Umemoto T. Drug-eluting stents versus coronary artery bypass grafting for left-main coronary artery disease. Catheter Cardiovasc Interventions 2018;**91**:697-709.
61. Verdoia M, Barbieri L, Kedhi E. Percutaneous Versus Surgical Revascularization for Left Main or Multivessel Coronary Artery Disease: Results From a Large-Scale Meta-Analysis in the Era of Drug-Eluting Stents. Angiology 2018;**69**:812-824.
62. Higgins J, Thompson S, Deeks J. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. J Health Serv Res Policy 2002;**7**:51-61.
63. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. Milbank Q 2016;**94**:485-514.
64. Mohr FW, Morice MC, Kappetein AP. 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.
65. Serruys P, Morice M, Kappetein A. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;**360**:961-72.
66. Ruel M, Falk V, Farkouh ME. Myocardial Revascularization Trials. Circulation 2018;**138**:2943-2951.
67. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;**342**:d549.
68. *PROSPERO*. https://www.crd.york.ac.uk/PROSPERO/.
69. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;**340**:c221.
70. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. Eur Heart J 2014;**35**:3336-45.

SUPPLEMENTARY MATERIALS

Detailed description of the used search terms

The following search terms was used in the **Embase database**: "('percutaneous coronary intervention'/exp OR 'stent'/exp OR 'coronary stenting'/exp OR ((percutan* NEAR/6 (interven* OR approach* OR revascul*)) OR stent* OR pci):ab,ti) AND ('coronary artery bypass graft'/exp OR 'coronary artery bypass surgery'/de OR 'bypass surgery'/de OR 'coronary artery surgery'/de OR 'off pump coronary surgery'/de OR 'heart muscle revascularisation'/de OR (revascularisation/de AND surgery/de) OR (bypass* OR shunt* OR graft* OR cabg OR (revascular* NEAR/3 (surg* OR myocard* OR muscl*))):ab,ti) AND ('left coronary artery'/de OR ((left NEAR/3 (coronar* OR main*)) OR lmca OR ulcma):ab,ti) AND ('meta analysis'/exp OR 'meta analysis (topic)'/de OR 'systematic review'/de OR 'systematic review (topic)'/de OR (((meta OR pooled) NEAR/3 analys*) OR metaanalys* OR (systematic* NEAR/3 review*)):ab,ti)".

The search term for the **Medline Ovid database** was as follows: "(exp Percutaneous Coronary Intervention/ OR exp Stents/ OR ((percutan* ADJ6 (interven* OR approach* OR revascul*)) OR stent* OR pci).ab,ti.) AND (exp Coronary Artery Bypass/ OR Myocardial Revascularization/ OR (bypass* OR shunt* OR graft* OR cabg OR (revascular* ADJ3 (surg* OR myocard* OR muscl*))).ab,ti.) AND (((left ADJ3 (coronar* OR main*)) OR lmca OR ulcma).ab,ti.) AND (Meta-Analysis as Topic/ OR Meta-Analysis / OR (((meta OR pooled) ADJ3 analys*) OR metaanalys* OR (systematic* ADJ3 review*)).ab,ti.)".

Finally, the following search term was used for the **Cochrane database**: "(((percutan* NEAR/6 (interven* OR approach* OR revascul*)) OR stent* OR pci):ab,ti) AND ((bypass* OR shunt* OR graft* OR cabg OR (revascular* NEAR/3 (surg* OR myocard* OR muscl*))):ab,ti) AND (((left NEAR/3 (coronar* OR main*)) OR lmca OR ulcma):ab,ti)

SUPPLEMENTAL TABLE

Table S1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51).

						Follow up duration					
Year	Author	Journal	Total patients (n)	PCI (N)	CABG (N)	≤30d	1y	3y	≥5y	Combined	MAC(C)E†
2018	Ali *et al.*[1]	Medicine (Baltimore)	21832	10424	11408	X	-	-	-	X	Stroke, death, MI or revascularisation
2018	Benedetto *et al.*[2]	J Thorac Cardiovasc Surg	4654	*	*	-	-	-	-	X	Death, MI or stroke
2018	Bertaina *et al.*[3]	J Cardiovasc Med (Hagerstown)	19314	8501	10813	-	-	-	-	X	Death, MI, definite or probable ST, TVR
2018	Cui *et al.*[4]	J Geriatr Cardiol	14130	6333	7797	-	-	-	-	X	Death, MI or stroke
2018	Khan *et al.*[5]	Heart Lung Circul	4700	2349	2351	X	X	-	X	-	MI, stroke, death or TVR
2018	Kodumuri *et al.*[6]	Am J Cardiol	10284	5017	5267	-	-	-	-	X	Death, MI, stroke or RR
2018	Moore *et al.*[7]	Heart Lung Circul	4404	2197	2197	-	-	-	-	X	Death, MI or CVA
2018	Rahouma *et al.*[8]	Ann. cardiothorac. surg.	4700	2349	2351	-	-	-	-	X	Death, MI, stroke or RR
2018	Takagi *et al.*[9]	Catheter Cardiovasc Interventions	12387	6009	6378	-	-	-	-	X	Death, MI and RRV (with/ without stroke)
2018	Verdoia *et al.*[10]	Angiology	4595	2297	2298	-	-	-	-	X	Major Adverse Cardiovascular Events*
2017	Bajaj *et al.*[11]	Eur Heart J Qual Care Clin Outcomes	4700	2349	2351	-	X	-	-	X	Death, stroke, MI or RR
2017	Chang *et al.*[12]	Ann Thorac Surg	2343	*	*	X	X	-	-	X	Death, stroke, MI or TVR
2017	De Rosa *et al.*[13]	BMC Cardiovasc Disord	4499	2249	2250	-	-	-	-	X	Death, stroke, MI or RR
2017	Gao *et al.*[14]	Oncotarget	4595	2297	2298	-	X	-	-	X	Death, stroke, MI or RR
2017	Garg *et al.*[15]	Am J Cardiol	4595	2297	2298	-	-	-	-	X	*
2017	Giacoppo *et al.*[16]	JAMA Cardiol	4394	2197	2197	-	-	-	-	X	Death, stroke or MI
2017	Khan *et al.*[17]	Am J Cardiol	4700	2349	2351	-	X	-	-	X	Death, MI, stroke or RR
2017	Khan *et al.*[18]	Am J Cardiol	6637	3197	3340	-	-	-	X	-	Death, nonfatal MI, stroke or RR

Rct. (N)	Obs. (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
5	24	X	-	X	X	X	X	OR	-	1.22 (0.95-1.56)	-	0.83 (0.60-1.15)
6	-	X	X	X	X	X	X	IRR	-	0.99 (0.70-1.40)		-
6	20	X	X	X	X	X	X	OR	-	1.10 (1.07-1.14)	-	0.94 (0.89-1.00)
4	12	X	-	-	X	X	X	HR	-	0.94 (0.86-1.03)	-	1.11 (0.92-1.32)
6	-	X	X	X	X	X	X	RR	1.15 (0.92-1.45)	-	0.67 (0.43-1.06)	-
4	8	X	-	-	X	X	X	OR	-	1.23 (1.01-1.51)	-	0.97 (0.74-1.26)
4	-	X	-	-	X	X	X	OR	-	1.37 (1.18-1.58)	-	1.08 (0.86-1.35)
6	-	X	X	X	X	X	X	IRR	-	1.328 (1.114-1.582)	-	0.947 (0.711-1.262)
5	17	X	-	X	X	X	X	HR	-	1.42 (1.28-1.58)	-	1.03 (0.90-1.18)
5	-	X	-	X	X	X	X	OR	-	1.16 (0.98-1.37)	-	0.88 (0.60-1.29)
6	-	X	X	X	X	X	X	RR	1.17 (0.94-1.44)	1.21 (1.05-1.40)	0.68 (0.44-1.06)	0.98 (0.78-1.25)
5	-	X	X	X	X	-	-	RR	1.20 (0.94-1.54)	1.25 (1.05-1.49)	0.66 (0.38-1.15)	0.81 (0.62-1.08)
5	-	X	X	-	X	X	X	OR		1.33 (1.12-1.58)		1.04 (0.82-1.32)
5	-	X	-	X	X	X	X	RR	1.15 (0.92-1.44)	1.26 (1.11-1.44)	0.70 (0.45-1.09)	1.05 (0.85-1.31)
5	-	X	-	X	X	X	X	OR	-	-	-	1.01 (0.76-1.34)
4	-	X	-	-	X	X	X	HR	-	1.06 (0.85-1.32)	-	1.04 (0.81-1.33)
6	-	X	X	X	X	X	X	HR	1.03 (0.69-1.52)	1.16 (0.95-1.43)	0.71 (0.47-1.06)	1.03 (0.80-1.33)
4	5	X	-	-	X	X	X	OR	-	-	-	-

Table S1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51). (*continued*)

						Follow up duration					
Year	Author	Journal	Total patients (n)	PCI (N)	CABG (N)	≤30d	1y	3y	≥5y	Combined	MAC(C)E†
2017	Laukkanen *et al.*[19]	Open Heart	4700	2149	2351	X	X	-	-	X	Death, MI, CVA or stroke, or TVR
2017	Mahmoud *et al.*[20]	Catheter Cardiovasc Interventions	4700	2349	2351	X	X	-	-	X	Death, MI, stroke or revascularisation
2017	Palmerini *et al.*[21]	Am Heart J	4686	2347	2339	X	-	-	-	X	Death, stroke, MI or UR
2017	Putzu *et al.*[22]	Int J Cardiol	4595	*	*	X	X	-	-	X	Death, stroke or MI*
2017	Qian *et al.*[23]	Am J Cardiol	4595	2297	2298	-	X	-	-	X	Study specific definitions of MACCE†
2017	Sá *et al.*[24]	Braz J Cardiovasc Surg	4595	2297	2298	-	X	-	-	-	Death, MI, stroke or TVR
2017	Sardar *et al.*[25]	Am J Cardiol	4612	2303	2309	-	X	-	-	X	Death, stroke,MI or any revascularisation
2017	Shah *et al.*[26]	Am J Cardiol	4700	2349	2351	-	X	X	X	X	Death, recurrent MI, RR and stroke
2017	Sharma *et al.*[27]	Cardiovasc Ther	4700	2349	2351	X	X	X	X	X	Death, MI, stroke or revascularisation
2017	Spinthakis *et al.*[28]	Int J Cardiol	4595	2297	2298	-	X	X	X	-	-
2017	Testa *et al.*[29]	PLoS ONE	4686	2347	2339	-	X	-	-	X	Death, stroke or MI
2017	Upadhaya *et al.*[30]	J Card Surg	4595	2297	2298	-	-	-	-	X	Study specific definitions of MACCE†
2017	Ye *et al.*[31]	Medicine (Baltimore)	4700	2349	2351	-	-	-	-	X	Death, MI, stroke and revascularisation
2017	Zhang *et al.*[32]	BMC Med	22487	10406	12081	-	-	-	-	X	Death, MI, stroke or RR
2016	Nerlekar *et al.*[33]	Circ Cardiovasc Interventions	4594	2297	2297	-	X	-	-	X	Death, MI, stroke, or RR
2014	Al Ali *et al.*[34]	JACC Cardiovasc Interv	1506	757	749	-	-	-	-	X	-
2014	Benedetto *et al.*[35]	J Thorac Cardiovasc Surg	1611	809	802	-	-	-	-	X	*

Rct. (N)	Obs. (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
6	-	X	X	X	X	X	X	HR	1.16 (0.94-1.44)	1.27 (1.12-1.44)	0.66 (0.42-1.04)	1.04 (0.81-1.33)
6	-	X	X	X	X	X	X	RR	1.21 (0.97-1.51)	1.19 (1.01-1.41)	0.76 (0.45-1.30)	0.94 (0.73-1.22)
6	-	X	X	X	X	X	X	OR	-	1.27 (1.12-1.45)	-	0.99 (0.76-1.30)
5	-	X	-	X	X	X	X	OR	-	-	0.69 (0.44-1.10)	1.08 (0.86-1.35)
5	-	X	-	X	X	X	X	RR	1.14 (0.91-1.42)	1.27 (1.13-1.43)	0.78 (0.56-1.08)	1.05 (0.83-1.34)
5	-	X	-	X	X	X	X	RR	1.05 (0.82-1.36)	-	1.03 (0.80-1.32)	-
5	-	X	-	X	X	X	X	OR	0.73 (0.52-1.01)	1.36 (1.18-1.57)	0.71 (0.44-1.12)	1.03 (0.79-1.35)
6	-	X	X	X	X	X	X	RR	1.15 (0.91-1.44)	1.20 (1.03-1.41)	0.68 (0.44-1.06)	0.98 (0.78-1.25)
6	-	X	X	X	X	X	X	OR	1.15 (0.88-1.51)	1.36 (1.18-1.58)	0.67 (0.43-1.06)	1.06 (0.82-1.38)
5	-	X	-	X	X	X	X	OR	-	-	0.70 (0.44-1.12)	-
6	-	X	X	X	X	X	X	OR	1.02 (0.76-1.36)	1.02 (0.76-1.38)	0.81 (0.63-1.03)	1.00 (0.77-1.31)
5	-	X	-	X	X	X	X	OR	-	1.36 (1.18-1.58)	-	1.03 (0.78-1.35)
6	-	X	X	X	X	X	X	RR	-	1.21 (1.05-1.40)	-	0.98 (0.78-1.25)
6	22	X	X	X	X	X	X	HR	-	1.42 (1.14-1.77)	-	1.05 (0.92-1.20)
5	-	X	-	X	X	X	X	OR	1.14 (0.86-1.49)	1.36 (1.18-1.58)	-	1.03 (0.78-1.35)
3	-	X	-	X	X	-	-	OR	-	-	-	1.08 (0.75-1.57)
4	-	X	X	X	X	-	-	OR	-	1.39 (1.09-1.77)	-	0.79 (0.54-1.15)

Table S1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51). (*continued*)

						Follow up duration					
Year	Author	Journal	Total patients (n)	PCI (N)	CABG (N)	≤30d	1y	3y	≥5y	Combined	MAC(C)E†
2013	Alam *et al.*[36]	Circ J	11148	4814	6334	X	X	-	X	-	Death, stroke, MI or RR
2013	Athappan *et al.*[37]	JACC Cardiovasc Interventions	14203	7055	7148	-	X	X	X	-	Death, stroke or nonfatal MI
2013	Bittl *et al.*[38]	Circulation	4574	2059	2515	-	X	X	-	-	-
2013	Cao *et al.*[39]	J Thorac Cardiovasc Surg	5628	2490	3138	X	X	-	-	X	Death, stroke, MI or RR
2013	Desch *et al.*[40]	Herz	1611	809	802	-	-	-	-	X	Death, stroke, MI or RR
2013	Li *et al.*[41]	Trials	8413	3682	4731	X	X	-	-	X	Death, MI or cerebrovascular events
2013	Sá *et al.*[42]	Eur J Cardiothorac Surg	5674	2331	3343	-	X	-	-	-	Death, stroke, MI or TVR
2012	Jang *et al.*[43]	Am J Cardiol	5079	2107	2972	-	X	-	-	-	Death, stroke, MI or TVR
2012	Jiang *et al.*[44]	Am J Cardiol	7230	2696	4534	-	-	-	-	X	Death, stroke, MI or TVR
2012	Kajimoto *et al.*[45]	J Card Surg	2601	1303	1298	-	X	-	-	-	Death, stroke, MI or TVR
2011	Capodanno *et al.*[46]	J Am Coll Cardiol	1611	809	802	-	X	-	-	-	Death, stroke, MI or TVR
2011	Zheng *et al.*[47]	Cardiology	5479	2351	3128	X	X	X	X	X	Death, stroke or MI
2010	Lee *et al.*[48]	Am J Cardiol	2905	1236	1669	-	X	-	-	-	-
2010	Takagi *et al.*[49]	J Thorac Cardiovasc Surg	2841	1198	1643	-	-	-	-	X	-
2009	Naik *et al.*[50]	JACC Cardiovasc Interventions	3773	1659	2114	-	X	X	-	-	Death, stroke or MI
2009	Takagi *et al.*[51]	J Thorac Cardiovasc Surg	2181	1006	1175	-	-	-	-	X	Death, stroke, MI or RR

Overview of characteristics reported by all included meta-analyses on PCI versus CABG in LMCAD. Meta-analyses that were published after the EXCEL and NOBLE trials are highlighted in green. Those meta-analyses that were published prior to the EXCEL and NOBLE publications are highlighted in red.
Risk estimates representing CABG versus PCI, provided by included meta-analyses, were recalculated to represent PCI versus CABG risk estimates. X = **YES** , - = **NO**. *this specific outcome was not specified in this meta-analysis. †MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. #the correct reference was missing in the original meta-analysis.
Abbreviations used: CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, PCI: percutaneous coronary intervention, LMCAD: left main coronary artery disease, RCTs: randomized controlled trials, Obs.: Observational, Ref.: reference, LA: longest available follow-up, MI; myocardial revascularisation, RR/RRV; repeat revascularisation, TVR: target vessel revascularisation, ST; stent thrombosis, OR: odds ratio, HR: hazard ratio, RR: risk ratio, IRR: incidence rate ratio, UR: unplanned revascularisation.

Rct. (N)	Obs. (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
4	23	X	X	X	X	-	-	OR	1.22 (0.94-1.58)	1.30 (1.10-1.55)	0.69 (0.49-0.97)	0.87 (0.71-1.08)
3	21	X	-	X	X	-	-	OR	0.938 (0.659-1.337)	-	0.792 (0.528-1.193)	-
4	8	X	X	X	X	-	-	OR	-	-	1.00 (0.72-1.40)	-
3	11	X	X	X	-	-	-	RR	1.53 (1.23-1.89)	1.57 (1.29-1.89)	0.71 (0.54-0.95)	0.84 (0.70-1.02)
4	-	X	X	X	X	-	-	RR	-	-	0.34 (0.09-1.24)	0.74 (0.46-1.19)
3	17	X	-	X	X	-	-	RR	-	-	0.80 (0.63-1.02)	0.79 (0.71-0.87)
3	13	X	-	X	X	-	-	OR	1.607	-	0.691	-
3	9	X	-	X	X	-	-	OR	0.70 (0.49-1.00)	-	0.68 (0.45-1.02)	-
-	25	-	-	-	-	-	-	RR	-	1.22 (0.89-1.68)	-	0.72 (0.52-1.00)
3	-	X	-	X	X	-	-	OR	-	1.81 (1.43-2.33)	-	1.09 (0.71-1.67)
4	-	X	X	X	X	-	-	OR	1.276 (0.950-1.715)	-	0.741 (0.427-1.284)	-
2	13	X	-	X	-	-	-	OR	0.95 (0.63-1.43)		0.71 (0.50-1.03)	
2	6	X	-	X	-	-	-	OR			1,40 (0.81-2.39)	
-	7	-	-	-	-	-	-	HR				1.35 (1.04-1.75)
2	8	X	X	-	-	-	-	OR	0.84 (0.57-1.22)		1.00 (0.70-1.41)	
1	5	-	X	-	-	-	-	RR		0.68 (0.32-1.46)		0.99 (0.69-1.43)

Table S2. MAC(C)E definitions used by the six included randomized trials.

Randomized Controlled Trial	Years of inclusion	Patients randomly allocated to:		MAC(C)E definition
		PCI	CABG	
SYNTAX	2005-2007	357	348	death from any cause, stroke, myocardial infarction, or repeat revascularisation
LE MANS	1997-2008	52	53	any cause, myocardial infarction, stroke, target lesion revascularisation (TLR), or acute stent thrombosis
Boudriot *et al.*	2003-2009	100	101	death from any cause, myocardial infarction, and the need for repeat revascularisation
PRECOMBAT	2004-2009	300	300	death from any cause, myocardial infarction, stroke, and ischemia-driven target-vessel revascularisation
EXCEL	2010-2014	948	957	death, stroke, or myocardial infarction
NOBLE	2008-2015	598	603	death from any cause, non-procedural myocardial infarction, repeat revascularisation or stroke

The MAC(C)E-specific definitions of the major randomized controlled trials are reported in the current table.

SUPPLEMENTAL FIGURES

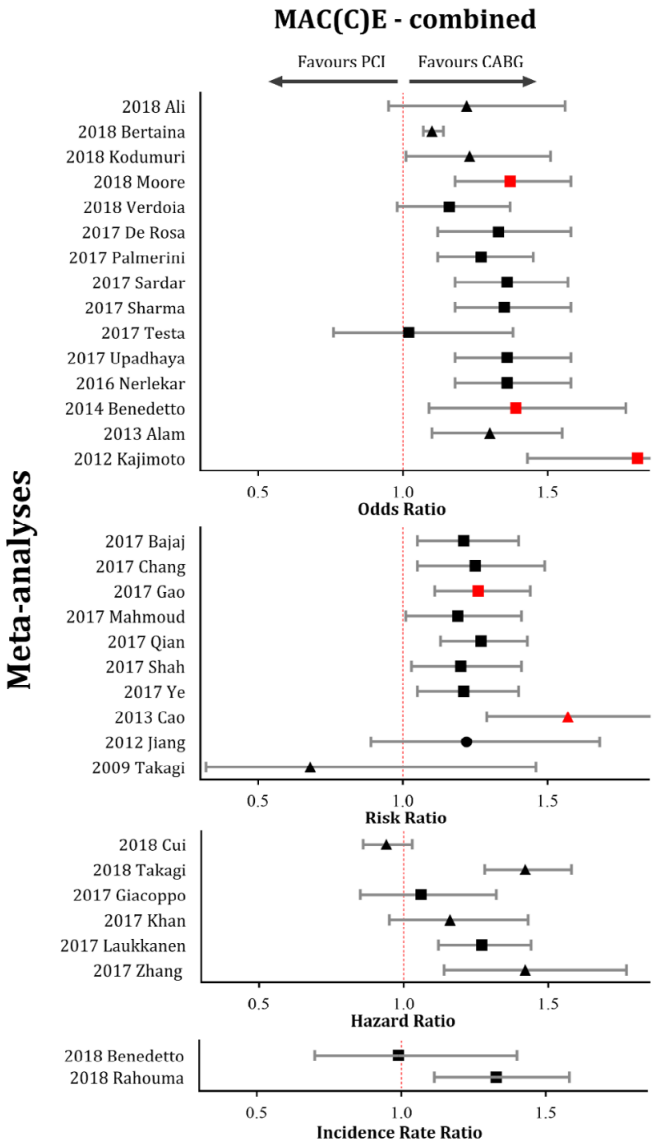

Figure S1. Forest plot representation of MAC(C)E outcomes, at longest follow-up available, reported by all included meta-analyses.
Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies, circle: only observational. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

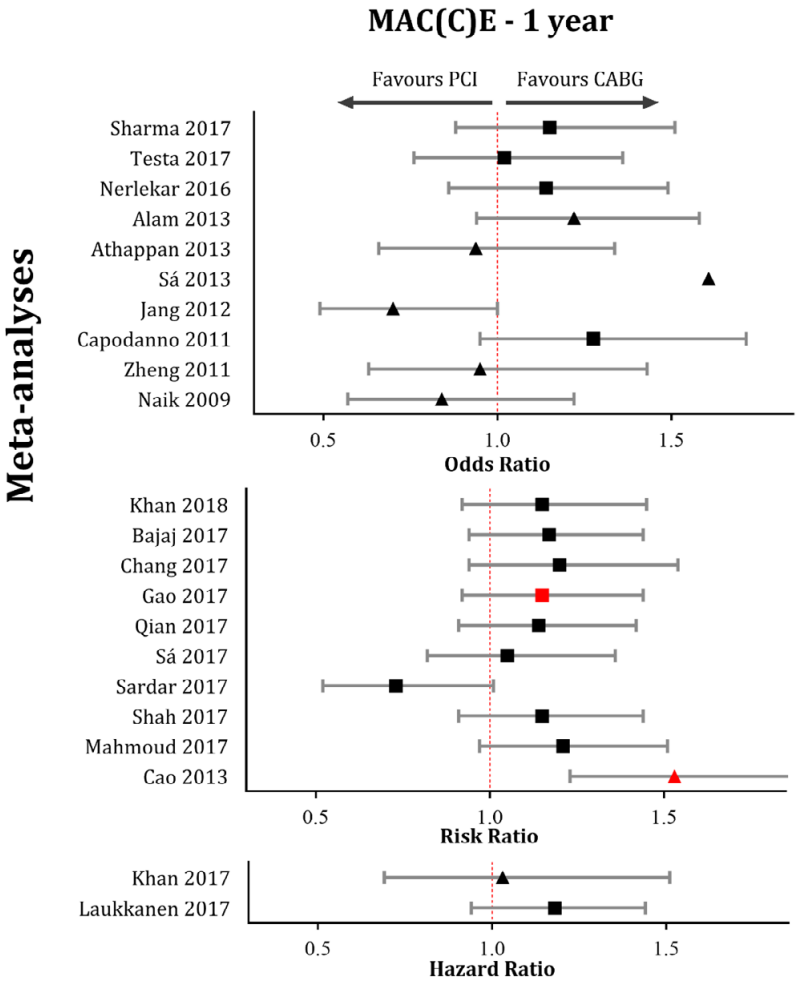

Figure S2. Supplemental Material. Forest plot representation of MAC(C)E outcomes, at 1 year, reported by all included meta-analyses.
Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses. MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

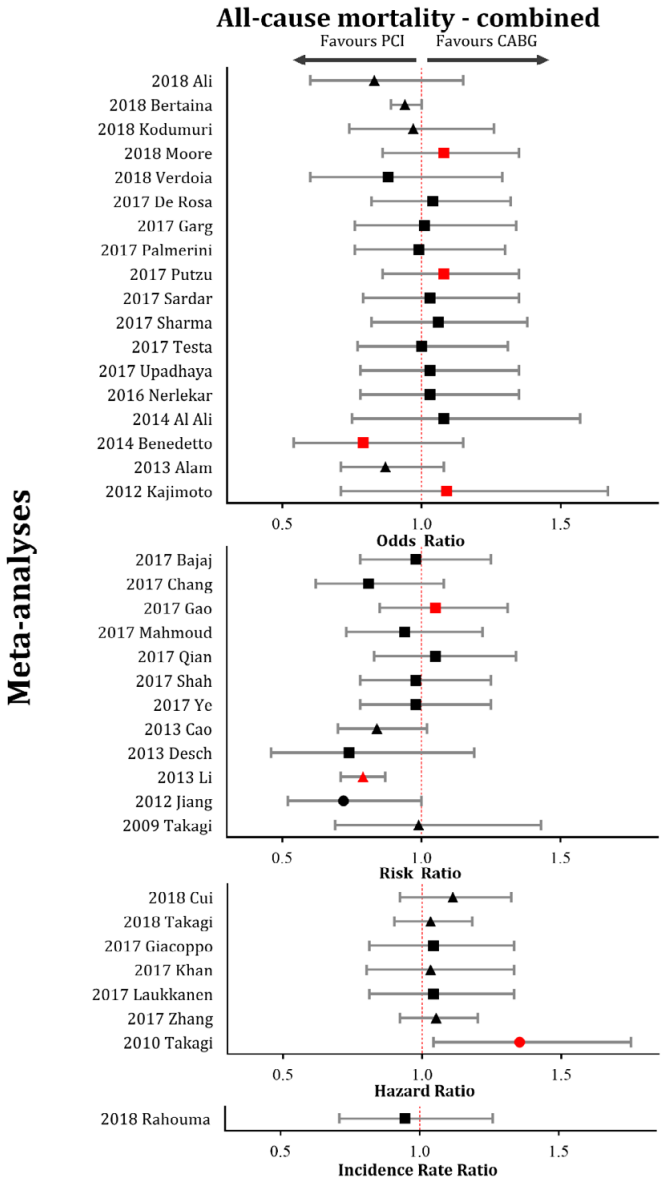

Figure S3. Forest plot representation of all-cause mortality outcomes, at combined long-term follow-up, reported by all included meta-analyses.
Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies, circle: only observational. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

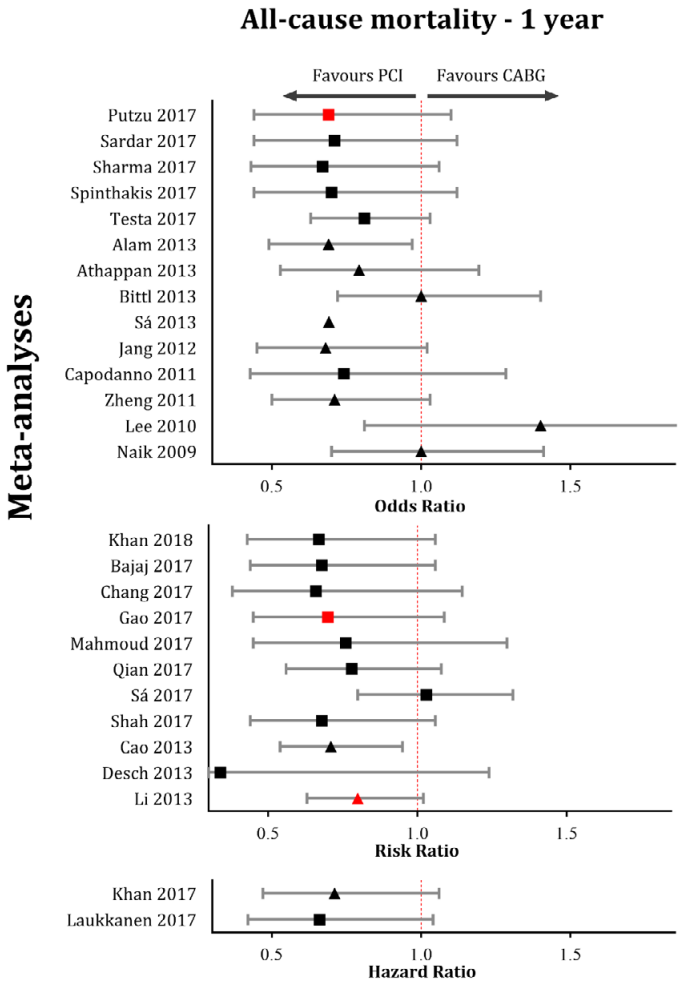

Figure S4. Supplemental Material. Forest plot representation of all-cause mortality outcomes, at 1 year, reported by all included meta-analyses.
Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

SUPPLEMANTARY REFERENCES TABLE S1

1. Ali WE, Vaidya SR, Ejeh SU, Okoroafor KU. Meta-analysis study comparing percutaneous coronary intervention/drug eluting stent versus coronary artery bypass surgery of unprotected left main coronary artery disease: Clinical outcomes during short-term versus long-term (> 1 year) follow-up. Medicine (Baltimore) 2018;**97**(7):e9909.
2. Benedetto U, Taggart DP, Sousa-Uva M, Biondi-Zoccai G, Di Franco A, Ohmes LB, Rahouma M, Kamel M, Caputo M, Girardi LN, Angelini GD, Gaudino M. New-generation stents compared with coronary bypass surgery for unprotected left main disease: A word of caution. J Thorac Cardiovasc Surg 2018;**155**(5):2013-2019.e2016.
3. Bertaina M, De Filippo O, Iannaccone M, Colombo A, Stone G, Serruys P, Mancone M, Omede P, Conrotto F, Pennone M, Kimura T, Kawamoto H, Zoccai GB, Sheiban I, Templin C, Benedetto U, Cavalcante R, D'Amico M, Gaudino M, Moretti C, Gaita F, D'Ascenzo F. Percutaneous coronary intervention or coronary artery bypass graft in left main coronary artery disease: a comprehensive meta-analysis of adjusted observational studies and randomized controlled trials. J Cardiovasc Med (Hagerstown) 2018;**19**(10):554-563.
4. Cui KY, Lyu SZ, Song XT, Yuan F, Xu F, Zhang M, Zhang MD, Wang W, Zhang DF, Dai J, Tian JF, Wang YL. Long term outcomes of drug-eluting stent versus coronary artery bypass grafting for left main coronary artery disease: A meta-analysis. J Geriatr Cardiol 2018;**15**(2):162-172.
5. Khan SU, Rahman H, Arshad A, Khan MU, Lekkala M, Yang T, Mishra A, Kaluski E. Percutaneous Coronary Intervention Versus Surgery in Left Main Stenosis–A Meta-Analysis and Systematic Review of Randomised Controlled Trials. Heart Lung Circul 2018;**27**(2):138-146.
6. Kodumuri V, Balasubramanian S, Vij A, Siddamsetti S, Sethi A, Khalafallah R, Khosla S. A Meta-Analysis Comparing Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Disease. Am J Cardiol 2018;**121**(8):924-933.
7. Moore P, Burrage M, Garrahy P, Lim R, McCann A, Camuglia A. Drug-Eluting Stents Versus Coronary Artery Bypass Grafts for Left Main Coronary Disease: A Meta-Analysis and Review of Randomised Controlled Trials. Heart Lung Circul 2018;**27**(12):1437-1445.
8. Rahouma M, Abouarab A, Di Franco A, Leonard JR, Lau C, Kamel M, Ohmes LB, Girardi LN, Gaudino M. Percutaneous coronary intervention versus coronary bypass surgery for unprotected left main disease: a meta-analysis of randomized controlled trials. Ann. cardiothorac. surg. 2018;**7**(4):454-462.
9. Takagi H, Ando T, Umemoto T. Drug-eluting stents versus coronary artery bypass grafting for left-main coronary artery disease. Catheter Cardiovasc Interventions 2018;**91**(4):697-709.
10. Verdoia M, Barbieri L, Kedhi E, Suryapranata H, De Luca G. Percutaneous Versus Surgical Revascularization for Left Main or Multivessel Coronary Artery Disease: Results From a Large-Scale Meta-Analysis in the Era of Drug-Eluting Stents. Angiology 2018;**69**(9):812-824.
11. Bajaj NS, Patel N, Kalra R, Marogil P, Bhardwaj A, Arora G, Arora P. Percutaneous coronary intervention vs. coronary artery bypass grafting for left main revascularization: An updated meta-analysis. Eur Heart J Qual Care Clin Outcomes 2017;**3**(3):173-182.

12. Chang YS, Wang JX, Chang DW. Outcomes of Coronary Artery Bypass and Stents for Unprotected Left Main Coronary Stenosis. Ann Thorac Surg 2017;**104**(2):630-637.
13. De Rosa S, Polimeni A, Sabatino J, Indolfi C. Long-term outcomes of coronary artery bypass grafting versus stent-PCI for unprotected left main disease: a meta-analysis Review. BMC Cardiovasc Disord 2017;**17**(1):240.
14. Gao L, Liu Y, Sun Z, Wang Y, Cao F, Chen Y. Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass graft surgery in left main coronary artery disease an updated meta-analysis of randomized clinical trials. Oncotarget 2017;**8**(39):66449-66457.
15. Garg A, Rao SV, Agrawal S, Theodoropoulos K, Mennuni M, Sharma A, Garg L, Ferrante G, Meelu OA, Sargsyan D, Reimers B, Cohen M, Kostis JB, Stefanini GG. Meta-Analysis of Randomized Controlled Trials of Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease. Am J Cardiol 2017;**119**(12):1942-1948.
16. Giacoppo D, Colleran R, Cassese S, Frangieh AH, Wiebe J, Joner M, Schunkert H, Kastrati A, Byrne RA. Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients With Left Main Coronary Artery Stenosis: A Systematic Review and Meta-analysis. JAMA Cardiol 2017;**2**(10):1079-1088.
17. Khan AR, Golwala H, Tripathi A, Riaz H, Kumar A, Flaherty MP, Bhatt DL. Meta-analysis of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease. Am J Cardiol 2017;**119**(12):1949-1956.
18. Khan MR, Kayani WT, Ahmad W, Hira RS, Virani SS, Hamzeh I, Jneid H, Lakkis N, Alam M. Meta-Analysis of Comparison of 5-Year Outcomes of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients With Unprotected Left Main Coronary Artery in the Era of Drug-eluting Stents. Am J Cardiol 2017;**120**(9):1514-1520.
19. Laukkanen JA, Kunutsor SK, Niemela M, Kervinen K, Thuesen L, Makikallio TH. All-cause mortality and major cardiovascular outcomes comparing percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: a meta-analysis of short-term and long-term randomised trials. Open Heart 2017;**4**(2):e000638.
20. Mahmoud AN, Elgendy IY, Mentias A, Saad M, Ibrahim W, Mojadidi MK, Nairooz R, Eshtehardi P, David Anderson R, Samady H. Percutaneous coronary intervention or coronary artery bypass grafting for unprotected left main coronary artery disease. Catheter Cardiovasc Interventions 2017;**90**(4):541-552.
21. Palmerini T, Serruys P, Kappetein AP, Genereux P, Riva DD, Reggiani LB, Christiansen E, Holm NR, Thuesen L, Makikallio T, Morice MC, Ahn JM, Park SJ, Thiele H, Boudriot E, Sabatino M, Romanello M, Biondi-Zoccai G, Cavalcante R, Sabik JF, Stone GW. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: A meta-analysis of 6 randomized trials and 4,686 patients. Am Heart J 2017;**190**:54-63.
22. Putzu A, Gallo M, Martino EA, Ferrari E, Pedrazzini G, Moccetti T, Cassina T. Coronary artery bypass graft surgery versus percutaneous coronary intervention with drug-eluting stents for left main coronary artery disease: A meta-analysis of randomized trials. Int J Cardiol 2017;**241**:142-148.

23. Qian C, Feng H, Cao J, Wei B, Wang Y. Meta-Analysis of Randomized Control Trials Comparing Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Significant Left Main Coronary Narrowing. Am J Cardiol 2017;**119**(9):1338-1343.
24. Sá MPBO, Soares AF, Miranda RGA, Araújo ML, Menezes AM, Silva FPV, Lima RC. CABG Surgery Remains the best Option for Patients with Left Main Coronary Disease in Comparison with PCI-DES: Meta-Analysis of Randomized Controlled Trials. Brazilian journal of cardiovascular surgery 2017;**32**(5):408-416.
25. Sardar P, Giri J, Elmariah S, Chatterjee S, Kolte D, Kundu A, Nairooz R, Aronow WS, Owan T, Mukherjee D, Feldman DN, Abbott JD. Meta-Analysis of Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Coronary Narrowing. Am J Cardiol 2017;**119**(11):1746-1752.
26. Shah R, Morsy MS, Weiman DS, Vetrovec GW. Meta-Analysis Comparing Coronary Artery Bypass Grafting to Drug-Eluting Stents and to Medical Therapy Alone for Left Main Coronary Artery Disease. Am J Cardiol 2017;**120**(1):63-68.
27. Sharma SP, Dahal K, Khatra J, Rosenfeld A, Lee J. Percutaneous coronary intervention vs coronary artery bypass grafting for left main coronary artery disease? A systematic review and meta-analysis of randomized controlled trials. Cardiovasc Ther 2017;**35**(3).
28. Spinthakis N, Farag M, Gorog DA, Prasad A, Mahmood H, Gue Y, Wellsted D, Nabhan A, Srinivasan M. Percutaneous coronary intervention with drug-eluting stent versus coronary artery bypass grafting: A meta-analysis of patients with left main coronary artery disease. Int J Cardiol 2017;**249**:101-106.
29. Testa L, Latib A, Bollati M, Montone RA, Colombo A, Crea F, Bedogni F. Unprotected left main revascularization: Percutaneous coronary intervention versus coronary artery bypass. An updated systematic review and meta-analysis of randomised controlled trials. PLoS ONE 2017;**12**(6).
30. Upadhaya S, Baniya R, Madala S, Subedi SK, Khan J, Velagapudi RK, Bachuwa G. Drug-eluting stent placement versus coronary artery bypass surgery for unprotected left main coronary artery disease: A meta-analysis of randomized controlled trials. J Card Surg 2017;**32**(2):70-79.
31. Ye Y, Yang M, Zhang S, Zeng Y. Percutaneous coronary intervention versus cardiac bypass surgery for left main coronary artery disease: A trial sequential analysis. Medicine (Baltimore) 2017;**96**(41):e8115.
32. Zhang XL, Zhu QQ, Yang JJ, Chen YH, Li Y, Zhu SH, Xie J, Wang L, Kang LN, Xu B. Percutaneous intervention versus coronary artery bypass graft surgery in left main coronary artery stenosis: a systematic review and meta-analysis Review. BMC Med 2017;**15**(1):84.
33. 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. Circ Cardiovasc Interventions 2016;**9**(12).
34. Al Ali J, Franck C, Filion KB, Eisenberg MJ. Coronary artery bypass graft surgery versus percutaneous coronary intervention with first-generation drug-eluting stents: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv 2014;**7**(5):497-506.
35. Benedetto U, Ng C, Smith R, Raja SG. Coronary artery bypass grafting is superior to first-generation drug-eluting stents for unprotected left main coronary artery disease: An updated meta-analysis of 4 randomized, controlled trials. J Thorac Cardiovasc Surg 2014;**148**(5):2430-2432.

36. Alam M, Huang HD, Shahzad SA, Kar B, Virani SS, Rogers PA, Paniagua D, Bozkurt B, Palacios I, Kleiman NS, Jneid H. Percutaneous coronary intervention vs. coronary artery bypass graft surgery for unprotected left main coronary artery disease in the drug-eluting stents era - An aggregate data meta-analysis of 11,148 patients. Circ J 2013;**77**(2):372-382.
37. Athappan G, Patvardhan E, Tuzcu ME, Ellis S, Whitlow P, Kapadia SR. Left main coronary artery stenosis: A meta-analysis of drug-eluting stents versus coronary artery bypass grafting. JACC Cardiovasc Interventions 2013;**6**(12):1219-1230.
38. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SLT. Bayesian Methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. Circulation 2013;**127**(22):2177-2185.
39. Cao C, Manganas C, Bannon P, Vallely M, Yan TD. Drug-eluting stents versus coronary artery bypass graft surgery in left main coronary artery disease: A meta-analysis of early outcomes from randomized and nonrandomized studies. J Thorac Cardiovasc Surg 2013;**145**(3):738-747.
40. Desch S, Boudriot E, Rastan A, Buszman PE, Bochenek A, Mohr FW, Schuler G, Thiele H. Bypass surgery versus percutaneous coronary intervention for the treatment of unprotected left main disease: A meta-analysis of randomized controlled trials. Herz 2013;**38**(1):48-56.
41. Li Q, Zhang Z, Yin RX. Drug-eluting stents or coronary artery bypass grafting for unprotected left main coronary artery disease: a meta-analysis of four randomized trials and seventeen observational studies Review. Trials 2013;**14**:133.
42. Sá MP, Soares AM, Lustosa PC, Martins WN, Browne F, Ferraz PE, Vasconcelos FP, Lima RC. Meta-analysis of 5,674 patients treated with percutaneous coronary intervention and drug-eluting stents or coronary artery bypass graft surgery for unprotected left main coronary artery stenosis. Eur J Cardiothorac Surg 2013;**43**(1):73-80.
43. Jang JS, Choi KN, Jin HY, Seo JS, Yang TH, Kim DK, Kim DS, Urm SH, Chun JH, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Meta-analysis of three randomized trials and nine observational studies comparing drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery disease. Am J Cardiol 2012;**110**(10):1411-1418.
44. Jiang WB, Zhao W, Huang H, Li CL, Zhang JH, Wang Y, Fu GS. Meta-analysis of effectiveness of first-generation drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary disease. Am J Cardiol 2012;**110**(12):1764-1772.
45. Kajimoto K, Miyauchi K, Yamamoto T, Daida H, Amano A. Meta-analysis of randomized controlled trials on the treatment of unprotected left main coronary artery disease: One-year outcomes with coronary artery bypass grafting versus percutaneous coronary artery intervention with drug-eluting stent. J Card Surg 2012;**27**(2):152-157.
46. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol 2011;**58**(14):1426-32.
47. Zheng S, Zheng Z, Hou J, Hu S. Comparison between drug-eluting stents and coronary artery bypass grafting for unprotected left main coronary artery disease: A meta-analysis of two randomized trials and thirteen observational studies. Cardiology 2011;**118**(1):22-32.

48. Lee MS, Yang T, Dhoot J, Liao H. Meta-Analysis of Clinical Studies Comparing Coronary Artery Bypass Grafting With Percutaneous Coronary Intervention and Drug-Eluting Stents in Patients With Unprotected Left Main Coronary Artery Narrowings. Am J Cardiol 2010;**105**(8):1070-1075.
49. Takagi H, Matsui M, Umemoto T. Increased late mortality with percutaneous stenting for unprotected left main coronary artery stenosis relative to coronary artery bypass grafting: A meta-analysis of observational studies. J Thorac Cardiovasc Surg 2010;**139**(5):1351-1353.
50. Naik H, White AJ, Chakravarty T, Forrester J, Fontana G, Kar S, Shah PK, Weiss RE, Makkar R. A Meta-Analysis of 3,773 Patients Treated With Percutaneous Coronary Intervention or Surgery for Unprotected Left Main Coronary Artery Stenosis. JACC Cardiovasc Interventions 2009;**2**(8):739-747.
51. Takagi H, Kawai N, Umemoto T. Stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: A meta-analysis of comparative studies. J Thorac Cardiovasc Surg 2009;**137**(1):e54-e57.