JSCAI
The official journal of the Society for Cardiovascular Angiography & Interventions

Meta-analysis

Long-term Incidence of Myocardial Infarction and Death After CABG and PCI for Isolated Left Anterior Descending Artery Disease: A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Background: To compare the long-term incidence of myocardial infarction (MI) and death in patients randomized to coronary artery bypass grafting (CABG) vs percutaneous coronary intervention (PCI) for treatment of isolated left anterior descending (LAD) coronary artery disease.

Methods: We systematically identified all randomized controlled trials comparing PCI with stenting to CABG with a left internal mammary artery (LIMA) graft in patients with isolated LAD disease who had at least 4 years of follow-up. The primary outcome of interest was MI. Secondary outcomes were all-cause mortality and target vessel revascularization (TVR).

Results: Four trials were included in the current analysis, with a total of 573 patients randomized to CABG with a LIMA (n = 285) vs PCI (n = 288) and followed for 4 to 10 years. At latest follow-up (weighted mean 8.3 years), there was no statistically significant difference in the risk of MI between CABG and PCI (relative risk [RR], 1.33; 95% CI, 0.62-2.83; $P = .46$), nor was there a statistically significant difference in mortality between the groups (RR, 1.04; 95% CI, 0.70-1.65; $P = .84$). There was a significantly lower risk of TVR after CABG compared with PCI (RR, 0.27; 95% CI, 0.15-0.46; $P < .001$).

Conclusions: The current meta-analysis suggests that there is insufficient evidence that CABG with a LIMA confers protection against MI or death compared to PCI with a stent for isolated LAD disease. CABG was, however, associated with reduced rates of TVR.

Introduction

The optimal revascularization strategy for patients with isolated disease of the left anterior descending (LAD) coronary artery is uncertain in part due to the limited number of randomized controlled trials (RCTs) comparing clinical outcomes with percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) in patients with isolated LAD disease.[1,2] CABG has been suggested to be associated with improved long-term survival compared with PCI in patients with complex multivessel disease by preventing late myocardial infarction (MI) arising not only from severe target lesions but also from proximal nonobstructive vulnerable plaques.[1,3,4] In this regard, it has been stated that the left internal mammary artery (LIMA) grafted to the mid or distal LAD confers the greatest survival benefits and protection against MI. Conversely, PCI has been described as having no impact on proximal nonstented lesions and is thought to prevent late MI only by focal treatment of flow-limiting lesions.[5]

Despite these considerations, PCI is commonly used to treat isolated LAD disease due to its minimally invasive nature with low rates of early morbidity and mortality. However, there is little data evaluating the long-term differences in the occurrence of MI and death in patients with isolated LAD disease treated with CABG vs PCI.[5] We therefore

DOI of original article: https://doi.org/10.1016/j.jscai.2023.100611.

Abbreviations: CABG, coronary artery bypass graft; LAD, left anterior descending artery; LIMA, left internal mammary artery; MI, myocardial infarction; MIDCAB, minimally invasive direct coronary artery bypass; PCI, percutaneous coronary intervention.

Keywords: coronary artery bypass grafting; death; left anterior descending artery; myocardial infarction; percutaneous coronary intervention.

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https://doi.org/10.1016/j.jscai.2023.100636
Received 21 November 2022; Received in revised form 12 March 2023; Accepted 14 March 2023
Available online 19 May 2023

hypothesized that CABG does not confer a long-term reduction in MI and death when compared to PCI and performed a systematic meta-analysis to evaluate the long-term differences in outcomes in patients undergoing CABG with a LIMA vs PCI with a stent for isolated LAD disease.

Methods

Data sources and search strategies

An investigator and a senior librarian (M.P. and L.P.) independently conducted a comprehensive search of eligible studies from January 1, 2002 to June 4, 2022. Two additional investigators (M.V.M. and J.B.) reviewed the eligible studies and ensured that they met the inclusion criteria. The databases included Ovid MEDLINE Epub Ahead of Print, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. Additional studies were retrieved using reference lists of included articles, abstracts, and expert bibliographies. We limited our search to publications in the English language and in humans.

Eligible studies met the following inclusion criteria: (1) RCTs of PCI with a stent (bare metal stent [BMS] or drug-eluting stent) vs CABG with a LIMA in patients with isolated LAD disease; (2) incidences of death and MI were reported with TVR reporting being optional; (3) follow-up duration of $\geq$4 years. Included studies were assessed using the Cochrane Risk of Bias tool (Supplemental Figure S1).[6] Funnel plots to assess publication bias were not included due to there being <10 trials included in our meta-analysis.

Data extraction

Data extraction was performed by 2 independent investigators (M.P. and J.B.) and confirmed by a third independent investigator (J.W.M.). Each study was independently summarized with variables including first author, year of publication, population characteristics, design, follow-up, use of cardiopulmonary bypass, and clinical outcomes.

Outcomes of interest and definitions

To determine whether CABG confers a benefit in preventing MI in patients with isolated LAD disease, the primary outcome of interest was MI (both Q wave and non-Q wave, procedural and nonprocedural) at latest follow-up. Secondary outcomes included all-cause death and target vessel revascularization (TVR) at latest follow-up.

Statistical methodology

Statistical analysis was conducted according to Cochrane collaboration recommendations and quality of reporting of meta-analysis guidelines.[6] Outcomes were analyzed on an intention-to-treat basis. Random-effect meta-analyses were performed using the restricted maximum likelihood estimator. As a sensitivity analysis, fixed-effect analyses were also performed using a Mantel–Haenszel model. All outcomes were assessed as relative risks (RR) at the time of last follow-up available for each trial. Heterogeneity was assessed using the I^2 statistic, with <25% defined as low heterogeneity, 25% to 50% defined as moderate heterogeneity, and >50% defined as high heterogeneity.[7] Continuous data are expressed as mean $\pm$ standard deviation unless otherwise stated, and statistical significance was set at

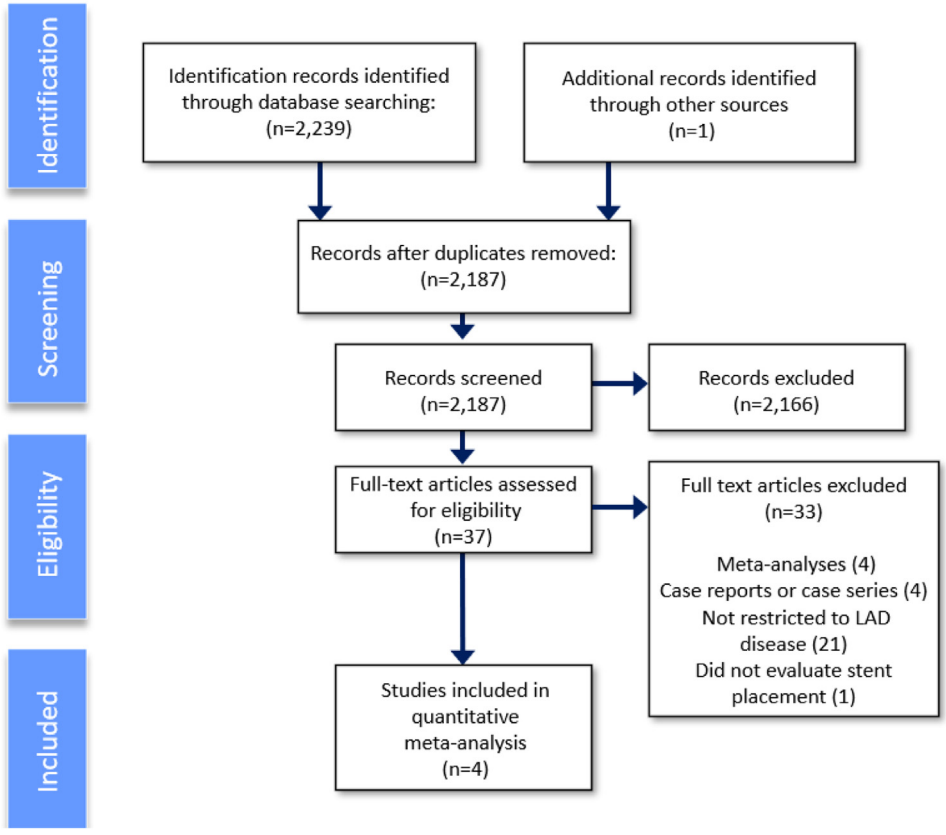


Figure 1.
CONSORT diagram. LAD, left anterior descending artery.

Table 1. Description of the 4 studies included in the meta-analysis.

Reference, year	Geography of enrollment	Enrollment period	Longest follow-up, y	Total enrolled	Age, y (mean)	Male (%)	LIMA use (%)	Stent use (%)	Stent type
Blazek et al,[11] 2013	Germany	June 1997-June 2001	10	220	62.1	74.5	100	100	BMS
Drenth et al,[10] 2004	The Netherlands	March 1997-September 1999	4	102	60.5	76.5	100	100	BMS
Goy et al,[8] 2008	Europe	October 1994-March 1998	10	121	59.5	79.3	100	100	BMS
Blazek et al,[9] 2015	Germany	January 2003-October 2007	7	129	66.0	70.0	100	100	DES

BMS, bare meta stent; DES, drug-eluting stent; LIMA, left internal mammary artery.

$P < .05$. All analyses were performed with the *metafor* package from R version 4.2.1.

Results

Studies and patients

The search yielded 2239 relevant reports, 4 of which met all inclusion criteria[8–11] (Figure 1). A total of 573 patients were randomized, including 285 patients to CABG and 288 patients to PCI. All studies were found to be of moderate-to-high or high quality by the Cochrane bias tool. Details from each study are shown in Table 1. The study population had a mean age of 62.0 years, and the majority of patients were male. A LIMA was used in all patients in the CABG arm whereas a stent was used in all patients in the PCI arm (mostly BMSs). The longest follow-up from each study ranged from 4 to 10 years (weighted mean average 8.3 years). The end points of death, MI, and TVR were available from all 4 trials.

Risk of MI

As shown in the Central Illustration, MI during follow-up occurred in 39 patients, with 22 MIs after CABG and 17 after PCI. There was no statistically significant difference in the risk of MI between groups (RR, 1.33; 95% CI, 0.62-2.83; $P = .46$). There was low heterogeneity between studies ($I^2 = 19.0\%$).

Risk of all-cause mortality

As shown in Figure 2, all-cause mortality during follow-up occurred in 81 patients, with 42 deaths in the CABG group and 39 deaths in the PCI group. There was no statistically significant difference in the risk of all-cause mortality between groups (RR, 1.04; 95% CI, 0.70-1.55; $P = .84$). There was no heterogeneity between studies ($I^2 = 0\%$).

Risk of TVR

As shown in Figure 3, TVR during follow-up occurred in 73 patients, including 14 patients after CABG and 59 patients after PCI. The risk of TVR was significant reduced after CABG compared with PCI (RR, 0.27; 95% CI, 0.15-0.46; $P < .001$). There was no heterogeneity between studies ($I^2 = 0\%$).

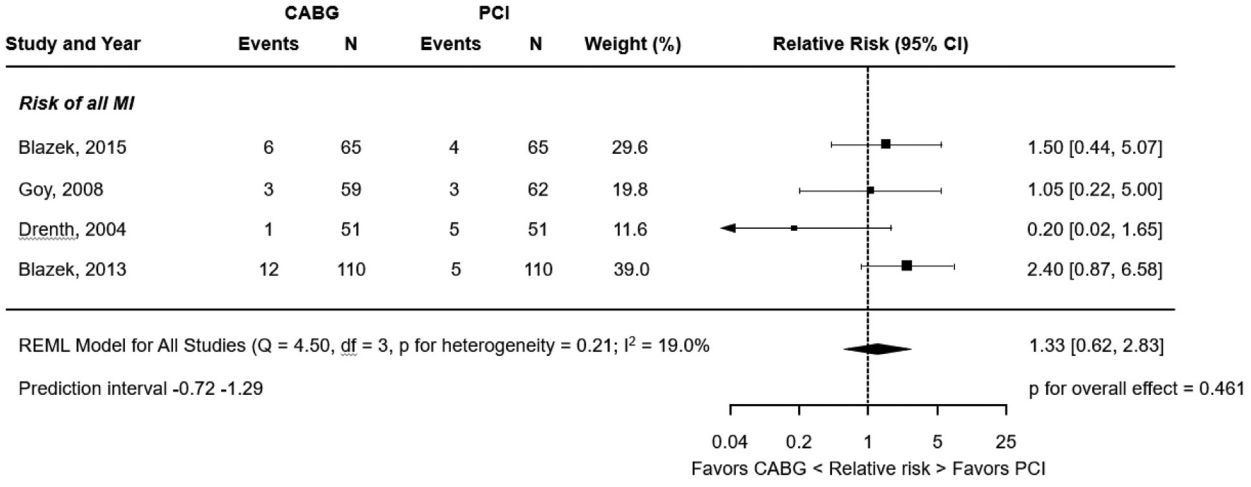
Fixed-effect analyses

Fixed-effect analyses were consistent with the random-effect findings for MI (RR, 1.41; 95% CI, 0.73-2.74), all-cause mortality (RR, 1.04; 95% CI, 0.70-1.55), and TVR (RR, 0.27; 95% CI, 0.15-0.46).

Discussion

The current meta-analysis examined the long-term clinical outcomes of patients with isolated LAD disease who were randomized to either CABG with a LIMA or PCI with a BMS or drug-eluting stent. At a longest weighted mean follow-up of 8.3 years, no differences were found in the long-term risks of MI or death between the 2 revascularization modalities. PCI was, however, associated with an increased risk of TVR compared with CABG. Our analysis is limited by wide confidence intervals and inability to ascertain timing of events, and thus, caution is warranted in drawing strong conclusions from these findings.

The reported findings question whether the long-term rates of MI (and death) are reduced by CABG compared with PCI, at least in



Central Illustration.
Risk of myocardial infarction. CABG, coronary artery bypass graft surgery; MI, myocardial infarction PCI, percutaneous coronary intervention; REML, restricted maximum likelihood.

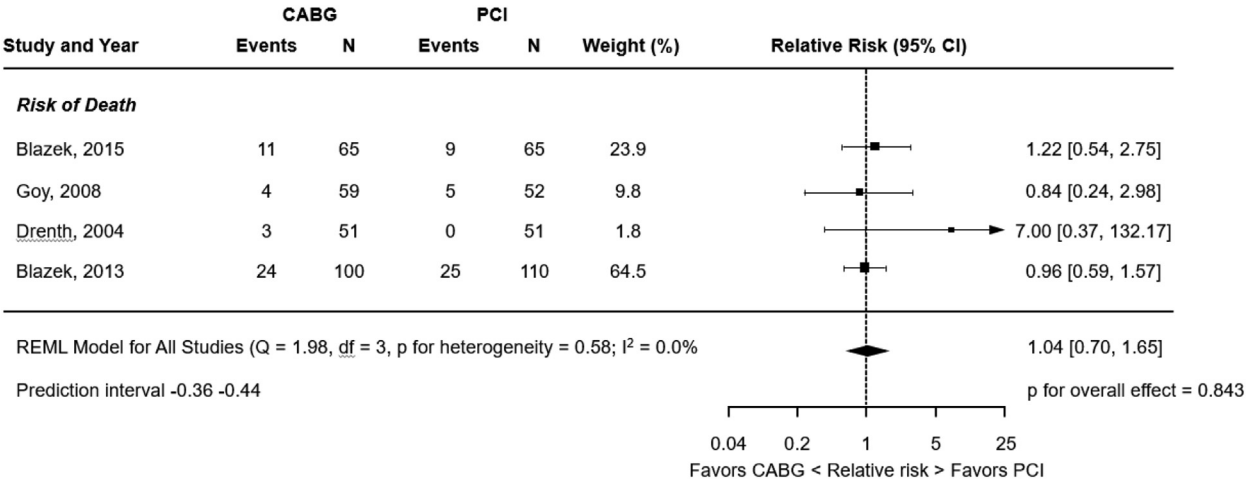


Figure 2.
Risk of all-cause mortality. CABG, coronary artery bypass graft surgery; CI, confidence interval; MI, myocardial infarction PCI, percutaneous coronary intervention; REML, restricted maximum likelihood.

patients with isolated LAD disease. Several prior meta-analyses have examined the outcomes of CABG and PCI in LAD disease (Table 2),[17] reaching varying conclusions. While an early meta-analysis suggested that cardiac events and death were reduced with surgical management of isolated LAD disease, more recent data has not shown a clear reduction in MI with CABG in these patients.[8,10,14–16] In a meta-analysis of RCTs, Kapoor et al[14] also noted no difference in MI and death, with reduced TVR and improved angina relief in patients undergoing CABG, but had shorter follow-up, included balloon angioplasty studies, and did not include additional data present in this meta-analysis. Several other previous meta-analyses with significantly shorter follow-up and variability in design from the present meta-analysis have also shown similar rates of MI and death in patients undergoing CABG or PCI for isolated LAD disease[2,12,13,15] Deo et al[2] observed no difference in mortality or MI with CABG vs PCI but found an increased rate of TVR after PCI. Since the publication of these early analyses, longer-term follow-up of the previous RCTs has been reported. Moreover, since many of these previous meta-analyses, there have been additional data included with longer follow-up in our analysis. Additionally, our study excludes balloon angioplasty studies and focuses only on patients that received stents. We have thus importantly noted that despite only including stent studies, there is only a higher risk of TVR, but not MI. Another principal difference between the present report and prior meta-analyses is the requirement for follow-up of at least 4 years in the present study, providing a long-term perspective on the outcomes of CABG and PCI for isolated LAD disease.

It has been argued that CABG may reduce the risk of late MI compared with PCI by bypassing severely diseased coronary segments as well as nonobstructive vulnerable plaques, theoretically preventing the clinical sequelae from plaque rupture and vessel occlusion, as most infarctions arise from proximal or mid vessel atherosclerosis.[3,5,18,19] In this regard, the bypass graft mimics the protection provided by native collateralization.[1,19,20] While the rate of late MIs may be reduced after CABG in patients with complex multivessel and left main disease compared with PCI,[21] such patients have substantially more diffuse atherosclerosis and greater myocardium at risk than those with single-vessel LAD disease. Thus, the results of the present study apply only to patients undergoing isolated LAD revascularization and not multivessel or left main intervention.

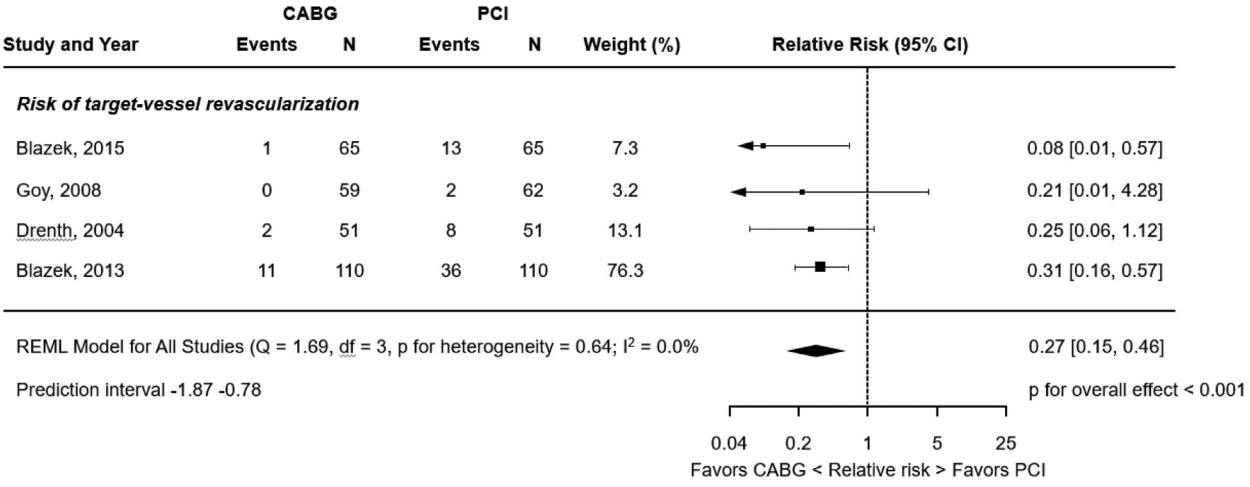


Figure 3.
Risk of target vessel revascularization. CABG, coronary artery bypass graft surgery; CI, confidence interval; MI, myocardial infarction PCI, percutaneous coronary intervention; REML, restricted maximum likelihood.

Table 2. Comparison of the present and prior meta-analyses of randomized trials of PCI vs CABG in isolated LAD disease.

Reference, year	Follow-up range	No. of RCTs	No. of observational studies	Total enrolled	Stent type(s)	Principal findings
Harskamp et al,[12] 2014	6 mo to 5 y	2	2	941	DES	Lower TVR rates with CABG but otherwise similar clinical outcomes compared to DES
Raja et al,[13] 2018	1 to 7.3 y	3	9	7710	DES	Reduced TVR with CABG, but similar mortality, MI, and MACCE compared to PCI with DES for proximal LAD disease
Kapoor et al,[14] 2008	<5 y	9	0	1210	BMS/DES	Similar survival in CABG and PCI groups, but significantly reduced angina and repeat revascularizations with CABG
Kinnaird et al,[15] 2016	6 mo to 7 y	3	8	5044	DES	Similar mortality, MI, and stroke rates to CABG at the expense of increased TVR.
Boodhwani et al,[16] 2005	6 mo to 5 y	8	9	13,319	PTCA/ BMS/ DES	Reduced MACE, mortality and MI and reduced angina with surgery
Deo et al,[2] 2014	<5 y	7	5	>2000 patients	BMS/DES	Similar survival with PCI and CABG, however higher rates of angina recurrence and TVR with PCI
Prasad et al, 2023 (present study)	4 to 10 y	4	0	573	BMS/DES	Similar long-term rates of MI and all-cause death after PCI and CABG; reduced TVR with CABG.

BMS, bare metal stent; CABG, coronary artery bypass graft surgery; DES, drug-eluting stent; LAD, left anterior descending artery; LIMA, left internal mammary artery; MACE, major adverse cardiac event; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction;. PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; RCT, randomized controlled trial; TVR, target vessel revascularization.

Prior meta-analyses have not distinguished between periprocedural and spontaneous MI and thus technically are not able to address the underlying question of whether CABG is protective purely against long-term MI.[20,22,23] While this is a limitation of our study as well, the longer-term follow-up from the present report more heavily weights the accrual of late MIs compared with early periprocedural events. With follow-up between 4 and 10 years in the 4 component studies of the present analysis, no significant difference in long-term MI risk was noted between CABG and PCI after treatment of isolated LAD disease. It is important to note however, that there is evidence of flawed data in one of the meta-analyses due to erroneous inclusion of the same study with multiple articles describing various timepoints of follow-up.[15]

Concordant with the similar risk of MI we also observed a similar risk of all-cause mortality with CABG and PCI. However, TVR was performed in substantially fewer patients during follow-up after CABG compared with PCI. These data may be useful to the heart team as they discuss the risk vs benefit profiles of each procedure in a patient with isolated LAD disease.

Limitations

An inherent issue in all meta-analyses is that the aggregate results are drawn from studies with inherent variability between patient populations and treatments. By excluding observational studies, and only including RCTs with isolated LAD disease, LIMA and stent treatment, and long-term follow-up, we have attempted to limit potential confounding. However, RCTs enroll a highly selected group of patients and may exclude higher-risk cohorts in whom equipoise between PCI and CABG does not exist (eg, extremely diffuse disease favoring CABG, or frailty or other comorbidities favoring PCI). Additionally, information about lesion complexity that may affect the relative outcomes of CABG vs. PCI was not routinely available, nor were we able to account for differences in interventional or surgical technique and operator skill/ experience in our analysis. Follow-up time varied between studies, and hazard ratios were not available, requiring a reliance on RRs at the longest follow-up time available, which may have introduced some imprecision. Additionally, it is important to consider that while we aimed to understand long-term events, the analysis may have been influenced by early events as the timing of events within each study was not able to be ascertained. Lastly, our analysis is limited by wide confidence intervals for the outcomes studied, and thus caution is warranted in drawing strong conclusions from these findings.

Conclusions

The present meta-analysis of RCTs of patients with isolated LAD disease undergoing PCI with stenting (mostly BMS) or CABG with a LIMA shows that there is insufficient evidence to establish that CABG confers protection against MI, as we note a similar risk of MI and all-cause mortality with both procedures at long-term follow-up, with an increased risk of TVR after PCI. These findings must be placed into context given the significant advances in stent technology, interventional and surgical techniques, and operator skill since these trials were conducted. Our findings suggest that in noncomplex patients with single-vessel LAD disease in whom there is equipoise for revascularization between CABG and PCI, there is insufficient evidence to suggest that CABG is associated with reduced long-term risk of MI or death when compared with PCI. Further studies examining the origin of MIs after CABG and PCI (whether type I, II, IV, or V)[24] and whether arising from the target lesion, target vessel, or nontarget vessel are needed to further delineate the causes of MI after both procedures and to explore the protective effects of CABG in patients with complex multivessel and left main disease.

Acknowledgments

We would like to acknowledge librarian Larry Popko and graphic designer Amy Mousley for their contributions to this manuscript.

Declaration of competing interest

Megha Prasad is a consultant for Abbott and Conavi and serves on a speaker's bureau for Philips. James Howard is funded by the British Heart Foundation (FS/ICRF/22/26039). Ajay Kirtane reports institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Amgen, CSI, Philips, ReCor Medical, Neurotronic, Biotronik, Chiesi, Bolt Medical, Magenta Medical, Canon, SoniVie, Shockwave Medical, and Merck. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for consulting and/or speaking engagements in which Ajay Kirtane controlled the content. Ajay Kirtane reports consulting fees from IMDS, and travel expenses/meals from Medtronic, Boston Scientific, Abbott Vascular, CSI, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. Margaret McEntegart received consultant fees or honoraria from Boston Scientific, Biosensors, Shockwave Medical, and Teleflex. Gregg Stone discloses speaker honoraria from Medtronic, Pulnovo,

Infraredx, Abiomed, and Abbott. Gregg Stone serves as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Cardiomech, Gore, Amgen, Adona Medical, and Millennia Biopharma and holds equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter. Institutional disclosures: Gregg Stone's employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-wave. Gregg Stone's daughter is an employee at IQVIA.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement and patient consent

Ethical approval was not required because this was a meta-analysis of existing clinical trials that were independently reviewed and approved by respective committees.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.100636.

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