ADULT

New-generation stents compared with coronary bypass surgery for unprotected left main disease: A word of caution

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ABSTRACT

Background: With the advent of bare metal stents and drug-eluting stents, percutaneous coronary intervention has emerged as an alternative to coronary artery bypass grafting surgery for unprotected left main disease. However, whether the evolution of stents technology has translated into better results after percutaneous coronary intervention remains unclear. We aimed to compare coronary artery bypass grafting with stents of different generations for left main disease by performing a Bayesian network meta-analysis of available randomized controlled trials.

Methods: All randomized controlled trials with at least 1 arm randomized to percutaneous coronary intervention with stents or coronary artery bypass grafting for left main disease were included. Bare metal stents and drug-eluting stents of first- and second-generation were compared with coronary artery bypass grafting. Poisson methods and Bayesian framework were used to compute the head-to-head incidence rate ratio and 95% credible intervals. Primary end points were the composite of death/myocardial infarction/stroke and repeat revascularization.

Results: Nine randomized controlled trials were included in the final analysis. Six trials compared percutaneous coronary intervention with coronary artery bypass grafting (n = 4654), and 3 trials compared different types of stents (n = 1360). Follow-up ranged from 6 months to 5 years. Second-generation drug-eluting stents (incidence rate ratio, 1.3; 95% credible interval, 1.1-1.6), but not bare metal stents (incidence rate ratio, 0.63; 95% credible interval, 0.27-1.4), and first-generation drug-eluting stents (incidence rate ratio, 0.85; 95% credible interval, 0.65-1.1) were associated with a significantly increased risk of death/myocardial infarction/stroke when compared with coronary artery bypass grafting. When compared with coronary artery bypass grafting, the highest risk of repeat revascularization was observed for bare metal stents (hazard ratio, 5.1; 95% confidence interval, 2.1-14), whereas first-generation drug-eluting stents (incidence rate ratio, 1.8; 95% confidence interval, 1.4-2.4) and second-generation drug-eluting stents (incidence rate ratio, 1.8; 95% confidence interval, 1.4-2.4) were comparable.

Conclusions: The introduction of new-generation drug-eluting stents did not translate into better outcomes for percutaneous coronary intervention when compared with coronary artery bypass grafting. (J Thorac Cardiovasc Surg 2018;155:2013-19)
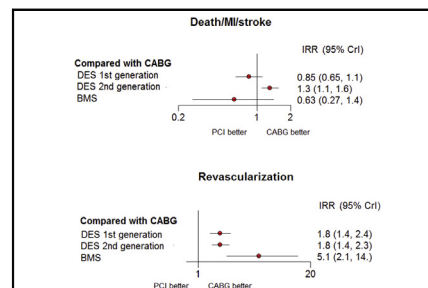
The IRR for death/MI/stroke and reintervention with BMS and first- and second-generation DESs using CABG as a comparator.

Central Message

The introduction of new-generation DESs for unprotected LMD did not translate into better clinical outcomes compared with CABG.

Perspective

Whether the evolution of stent technology has translated into better results after PCI for unprotected LMD remains unclear. The present NMA suggests that new-generation stents are not associated with better outcomes when compared with CABG.

Abbreviations and Acronyms
Bio-ES = Biolimus-eluting stent
BMS = bare metal stent
CABG = coronary artery bypass grafting
CrI = credible interval
DES = drug-eluting stent
EES = everolimus-eluting stent
IRR = incidence rate ratio
LMD = left main disease
MI = myocardial infarction
NMA = network meta-analysis
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent
RCT = randomized controlled trial
SES = sirolimus-eluting stent
ZES = zotarolimus-eluting stent

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Coronary artery bypass grafting (CABG) has long been considered superior to percutaneous coronary intervention (PCI) in the treatment of choice for unprotected left main disease (LMD).[1] However, with the advent of bare metal stents (BMSs) and first-generation drug-eluting stents (DESs), including paclitaxel-eluting stents (PESs) and sirolimus-eluting stents (SESs), PCI has emerged as an attractive alternative.[1,2] The recent introduction of second-generation DES, including everolimus-eluting stents (EESs), zotarolimus-eluting stents (ZESs), and biodegradable polymer Biolimus-eluting stents (Bio-ESs), has further promoted PCI in this setting.[3]

However, whether the evolution of stent technology has translated into better results after PCI remains unclear. Despite the lack of definitive evidence on the equipoise between PCI with second-generation DES and CABG in terms of hard clinical end points, the current trend is to perform PCI rather than CABG when technically feasible. We aimed to compare CABG with stents of different generations for LMD by performing a Bayesian network meta-analysis (NMA) of available randomized controlled trials (RCTs).

MATERIAL AND METHODS

This work was designed as a systematic review and NMA, with reporting following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[4,5]

Data Sources and Searches

We searched PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE from their inception to November 2016, without language restrictions. Search algorithm used was "left main" AND ("percutaneous coronary intervention" OR PCI OR stent*) AND ("coronary artery bypass" OR CABG OR "bypass surgery" OR "coronary bypass"). Reference lists of the identified reports and relevant reviews were manually screened by 3 reviewers (UB, ADF, LBO) to identify further relevant studies. In addition, when other meta-analyses, systematic reviews, or RCTs were found, we used backward snowballing (ie, scanning of references of retrieved articles and pertinent reviews) to obtain further studies.

Study Selection

Investigators first examined references at the title/abstract level, with divergences resolved by consensus, and then, if potentially pertinent, retrieved the complete articles. Articles were included in the present analysis if they fulfilled the following inclusion criteria: random allocation to treatment, at least 1 group randomized to CABG or PCI with stents for unprotected LMD.

Data Extraction and Quality Assessment

Baseline including SYNTAX score,[6] procedural outcome, and follow-up data were independently abstracted by 2 investigators. In the present analysis, outcomes were adjudicated according to the original authors' definitions. Outcomes were analyzed according to the intention-to-treat principle whenever possible. The internal validity and risk of bias of included trials were appraised by 2 independent investigators (U.B., M.R., M.K.) according to the "risk of bias assessment tool" developed by the Cochrane collaboration.[7] Briefly, for each trial, 7 domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data reporting, selective reporting, and presence of other bias. The presence of a possible source of bias in each domain was assessed, and a final judgment of low, moderate, or high risk of bias was assigned.

End Points

The primary end point was the commonly adopted composite of death, myocardial infarction (MI), or stroke (death/MI/stroke) at the longest follow-up available. Because second-generation stents are anticipated to reduce the risk of restenosis, repeat revascularization was also considered a primary end point. Secondary end points were mortality, MI, and stroke.

Data Synthesis and Analysis

The NMA was conducted using R (version 3.2.0, R Project for Statistical Computing) with the gemtc and rjags packages, which interface with Just Another Gibbs Sampler (JAGS) software (version 3.4.0). Two separate analyses were conducted. The first analysis compared different stent generations with CABG, and stents were categorized into 3 groups: BMS; DES of first generation, which included PES and SES; and DES of second-generation, which included Bio-ES, EES, and ZES. The second analysis compared individual stent types with CABG.

When modeling the clinical outcomes of interest, it is important to consider the different follow-up times of the various trials, because longer follow-up is likely to result in more reported events. To account for this, an underlying Poisson process with a constant event rate was assumed with the total number of events observed within a treatment group out of the total person-time of follow-up for that treatment group calculated from study follow-up. A log link function was used to model the incidence rate.[8]

Relative effect estimates from the NMA were calculated as log incidence rate ratios (IRRs) with 95% credible intervals (CrIs). For all practical purposes, incidence rates can be thought of as hazards, and thus the IRR can be roughly interpreted as the hazard ratio. Incidence of primary

end points observed in each treatment arm for each included trial was extracted and pooled using the Bayesian fixed effects model.[9] A fixed-effects model was chosen because it had a lower deviance information criterion compared with the random effects model, suggesting a better model fit. Noninformative prior distributions were chosen for model parameters so that results were driven entirely by the reported data. Analyses were performed using Markov-Chain Monte-Carlo methods, a method that estimates the effect of each treatment comparison by simulation, using 4 chains with 100,000 iterations and thinning interval of 10, after a burn-in of 50,000.[9] Convergence of the chains was assessed using the Gelman plot and diagnostic test.[10] Statistical significance was considered when the CrIs did not cross the line of no effect. The effect of SYNTAX score on treatment effect was investigated using meta-regression analysis as proposed by Gelman and colleagues.[11]

Consistency

An assumption of NMA models is that direct and indirect sources of evidence estimate the same true treatment effect. This was evaluated by conducting conventional pairwise meta-analyses and testing consistency by comparing the direct and indirect evidence results to see if a statistically significant difference existed. We applied the back-calculation method to check for consistency within the evidence networks.[12] On the basis of the back-calculation method, the difference between direct and indirect estimate was considered as an estimate of inconsistency. Our null hypothesis was that there was consistency between the direct and indirect evidence, and we would reject the null hypothesis if there was a statistically significant difference between the direct and indirect evidence comparison ($P < .05$).

For a secondary analysis, a pairwise meta-analysis was conducted to pool data from RCTs comparing PCI with CABG for primary end points, with subgroup analysis according to the type of stents used. We derived the log IRR and corresponding standard error from numbers of reported events and accumulated person-years of follow-up. Log IRRs were pooled using the generic inverse variance method with random and fixed model. Hypothesis of statistical heterogeneity was tested by means of Cochran Q test, with

statistical significance set at the 2-tailed 0.10 level, and extent of statistical consistency was measured with I^2, defined as $100\% \times (Q\text{-df})/Q$, where Q is Cochran's heterogeneity statistic and the degrees of freedom.

RESULTS

Of 2597 potentially relevant articles initially screened, 9 met the inclusion criteria and were included in the final analysis.[1-3,13-18] A flow diagram of study selection is reported in Figure E1. An overview of the study characteristics in individual RCTs is shown in Table 1, Table E1, and Table E2. Internal validity assessment for each trial is reported in Table E3. Overall, 6 studies[1-3,13-15] compared PCI and CABG (n = 4654) and 3 studies[16-18] compared different types of stents (n = 1360). Follow-up ranged from 6 months to 5 years.

For the analysis based on different stent generations, 7 studies[1-3,13-16] were included. Erglis and colleagues[16] did not report the stroke rate separately. For the analysis based on different stent generations, all 9 studies identified were included (Figure 1).

Network Meta-analysis

NMA estimates for primary and secondary end points are reported in Figures 2 and 3 for the analysis based on different stent generations and in Figures 4 and 5 for the analysis based on stents of different type. BMS (IRR, 0.63; 95% CrI, 0.27-1.4) and first-generation DES (IRR, 0.85; 95% CrI, 0.65-1.1) did not significantly differ from CABG for the composite of death/MI/stroke. Second-generation DESs were associated with a significantly

TABLE 1. Characteristics of randomized controlled trials included in the network meta-analysis

Trial	Year	Treatment received	euroSCORE (PCI)	euroSCORE (CABG)	SYNTAX (PCI)	SYNTAX (CABG)	Not isolated LMD, %	Distal LMD, %	Follow-up (y)
NOBLE	2016	CABG vs Bio-ES	2 (2, 4)	2 (2, 4)	22.5 ± 7.5	22.4 ± 8.0	NA	81	3.1
EXCEL	2016	CABG vs EES	NA	NA	26.9 ± 8.8	26.0 ± 9.8	82.2	79.2	3
LE MANS	2016	CABG vs BMS	3.3 ± 2.3	3.5 ± 2.3	25.2 ± 8.7	24.7 ± 6.8	94	60	1
PRECOMBAT	2015	CABG vs SES	2.6 ± 1.8	2.8 ± 1.9	24.4 ± 9.4	25.8 ± 10.5	NA	67	5
SYNTAX	2014	CABG vs PES	3.9 ± 2.8	3.9 ± 2.9	29.6 ± 13.5	30.2 ± 12.7	85.9	58.3	5
Boudriot and colleagues[14]	2011	CABG vs SES	2.4 (1.5, 3.7)	2.6 (1.7, 4.9)	24.0 (19.0, 29.0)	23.0 (14.8, 28.0)	71	69	1
Erglis and colleagues[16]	2007	BMS vs PES	NA	–	32.6 ± 11.7	–	49	75	0.5
ISAR-LEFT-MAIN	2009	PES vs SES	4.7 ± 3.4	–	NA	–	NA	64	1
ISAR-LEFT-MAIN 2	2013	ZES vs EES	5.1 ± 3.7		NA	–	NA	79	1

Values are mean, median (interquartile range), or %. *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial; *LMD*, left main disease; *NOBLE*, Nordic-Baltic-British left main revascularisation study; *Bio-ES*, biolimus-eluting stent; *NA*, not available; *EXCEL*, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; *EES*, everolimus-eluting stent; *LE MANS*, Study of Unprotected Left Main Stenting Versus Bypass Surgery; *BMS*, bare metal stents; *PRECOMBAT*, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; *SES*, sirolimus-eluting stents; *PES*, paclitaxel-eluting stents; *ISAR-LEFT-MAIN*, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions; *ZES*, zotarolimus-eluting stent.
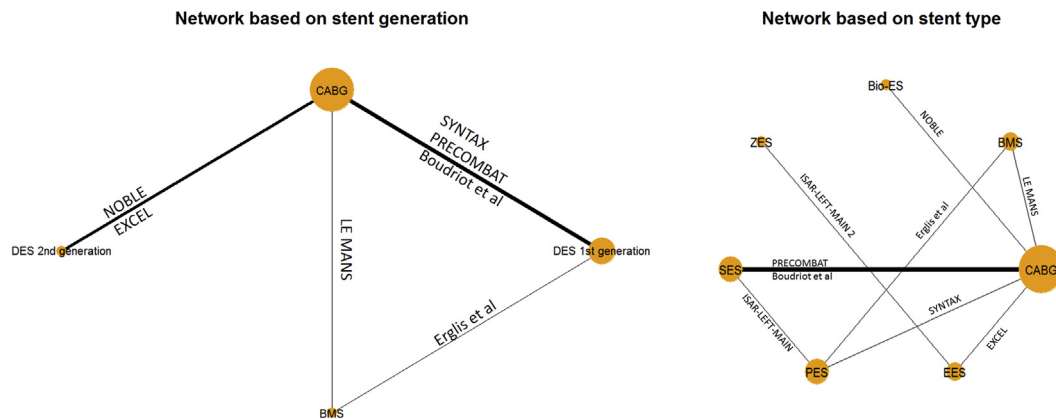
FIGURE 1. Network plots of relevant studies based on stent generation (*left*) and stent type (*right*). *Circles* represent each revascularization strategy as a node, and *lines* represent the direct comparisons. The extent of *circle* indicates the number of patients receiving each revascularization strategy, and the *line* thickness indicates the number of studies included in each comparison. DES first-generation include PES and SES; DES second-generation include Bio-ES, EES, and ZES. *DES*, Drug-eluting stents; *NOBLE*, Nordic-Baltic-British left main revascularisation study; *EXCEL*, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; *CABG*, coronary artery bypass grafting; *LE MANS*, Study of Unprotected Left Main Stenting Versus Bypass Surgery; *BMS*, bare metal stent; *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial; *PRECOMBAT*, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; *SES*, sirolimus-eluting stents; *ZES*, zotarolimus-eluting stent; *Bio-ES*, biolimus-eluting stent; *EES*, everolimus-eluting stent; *PES*, paclitaxel-eluting stents; *ISAR-LEFT-MAIN*, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions.

increased risk of death/MI/stroke when compared with CABG (IRR, 1.3; 95% CrI, 1.1-1.6). This result was driven by an increased risk of MI with Bio-ES (IRR, 3.0; 95% CrI, 1.5-6.4), a nonsignificant trend toward an increased risk of

FIGURE 2. NMA estimates for the primary end points at latest follow-up (expressed as IRR, with relative 95% CrI) for different stent generations (DES first-generation include PES and SES; DES second-generation include Bio-ES, EES, and ZES). CABG as comparator. *MI*, Myocardial infarction; *CABG*, coronary artery bypass grafting; *DES*, drug-eluting stents; *BMS*, bare metal stent; *PCI*, percutaneous coronary intervention; *IRR*, incidence rate ratio; *CrI*, credible interval.
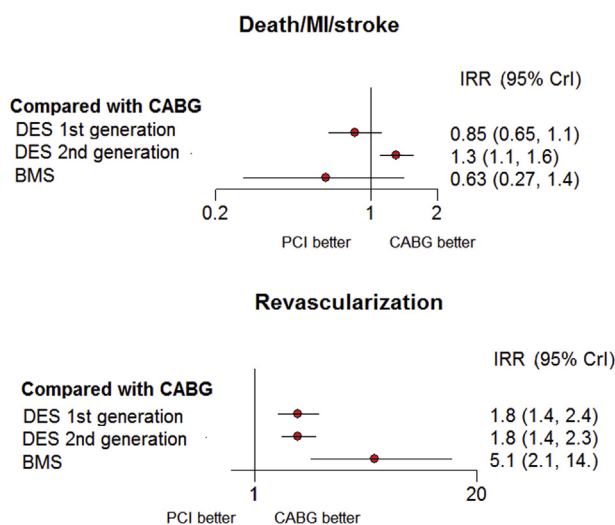
death and MI with ZES, and a marginally nonsignificant increased risk of death with EES (IRR, 1.4; 95% CrI, 0.97-1.9) (Table E4).

When compared with CABG, the highest risk of repeat revascularization was observed for BMSs (hazard ratio, 5.1; 95% CI, 2.1-14), whereas such a risk was comparable between first-generation DES (IRR, 1.8; 95% CI, 1.4-2.4) and second-generation DES (IRR, 1.8; 95% CI, 1.4-2.4).

The comparison between CABG and different type of stents was constant across SYNTAX score values for both the composite of death/MI/stroke and repeat revascularization (Figures E2 and E3). No significant inconsistency was found between direct and indirect comparison within network loops for the analysis based on different stent generations (Figures E4 and E5) and different types of stents (Figures E6 and E7).

Pairwise Meta-analysis Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting

Pairwise comparison between PCI and CABG was based on 6 RCTs. Overall, PCI and CABG were comparable for death/MI/stroke (IRR, 0.99; 95% CI, 0.70-1.4). However, although first-generation DESs were associated with a nonsignificant 11% relative risk reduction of death/MI/stroke when compared with CABG, second-generation DESs were associated with a 33% relative risk increase (Figure E8). Pairwise comparison confirmed that first-generation DES (IRR, 1.82; 95% CI, 1.39-2.4) and
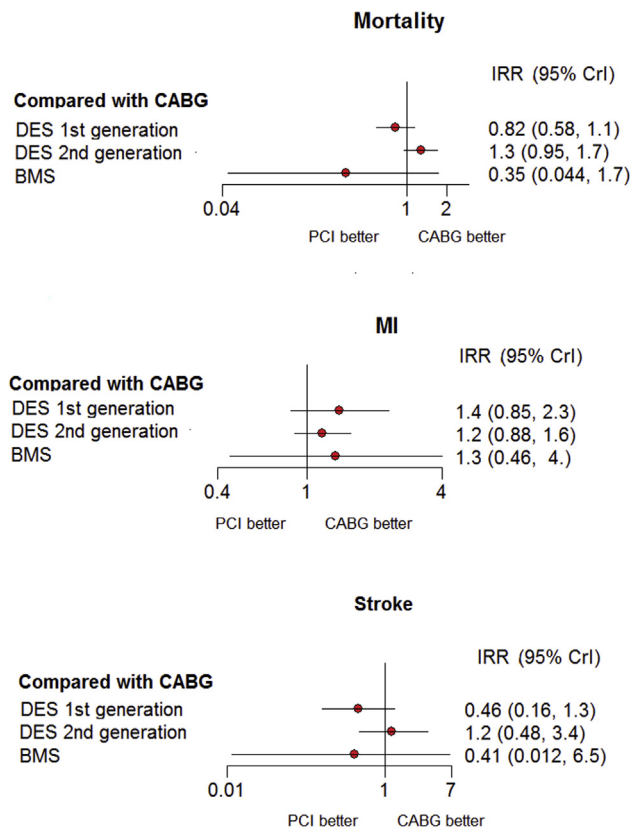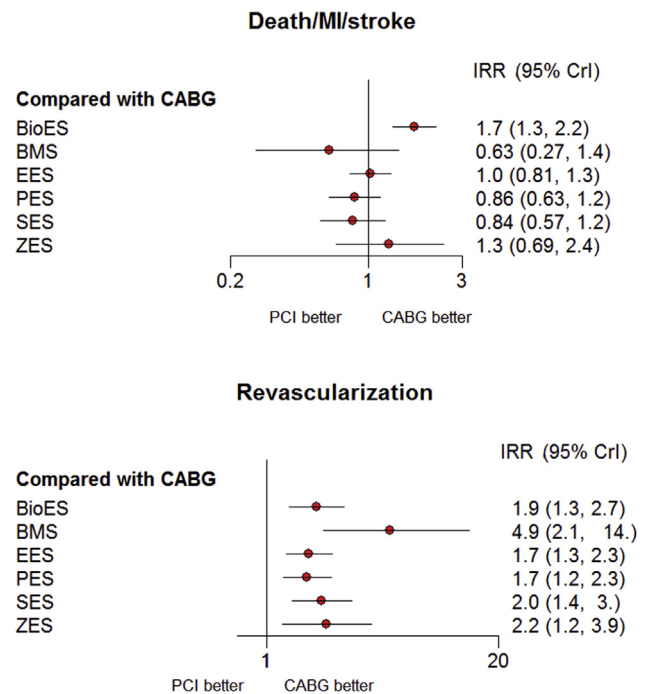
FIGURE 3. NMA estimates for individual component of death, MI, or stroke at latest follow-up (expressed as IRR, with relative 95% CrI) for different stent generations. DES first-generation include PES and SES; DES second-generation include Bio-ES, EES, and ZES. CABG as comparator. *CABG*, Coronary artery bypass grafting; *DES*, drug-eluting stents; *BMS*, bare metal stent; *PCI*, percutaneous coronary intervention; *IRR*, incidence rate ratio; *CrI*, credible interval; *MI*, myocardial infarction.

FIGURE 4. NMA estimates for the primary end points at latest follow-up (expressed as IRR, with relative 95% CrI) for different stent types CABG as comparator. *MI*, Myocardial infarction; *CABG*, coronary artery bypass grafting; *Bio-ES*, biolimus-eluting stent; *BMS*, bare metal stent; *EES*, everolimus-eluting stent; *PES*, paclitaxel-eluting stents; *SES*, sirolimus-eluting stents; *ZES*, zotarolimus-eluting stent; *PCI*, percutaneous coronary intervention; *IRR*, incidence rate ratio; *CrI*, credible interval.

second-generation DES (hazard ratio, 1.79; 95% CI, 1.42-2.2) presented comparable IRRs for repeat revascularization when compared with CABG (Figure E9).

DISCUSSION

NMA combines direct and indirect evidence for particular pairwise comparisons, thereby synthesizing a greater share of the available evidence than a traditional meta-analysis. The results from indirect evidence combined with the direct evidence may strengthen the assessment between treatments directly evaluated. Although the evidence networks underlying NMA typically include RCTs, randomization does not hold across trials and there is a residual risk of confounding bias, compromising internal validity.
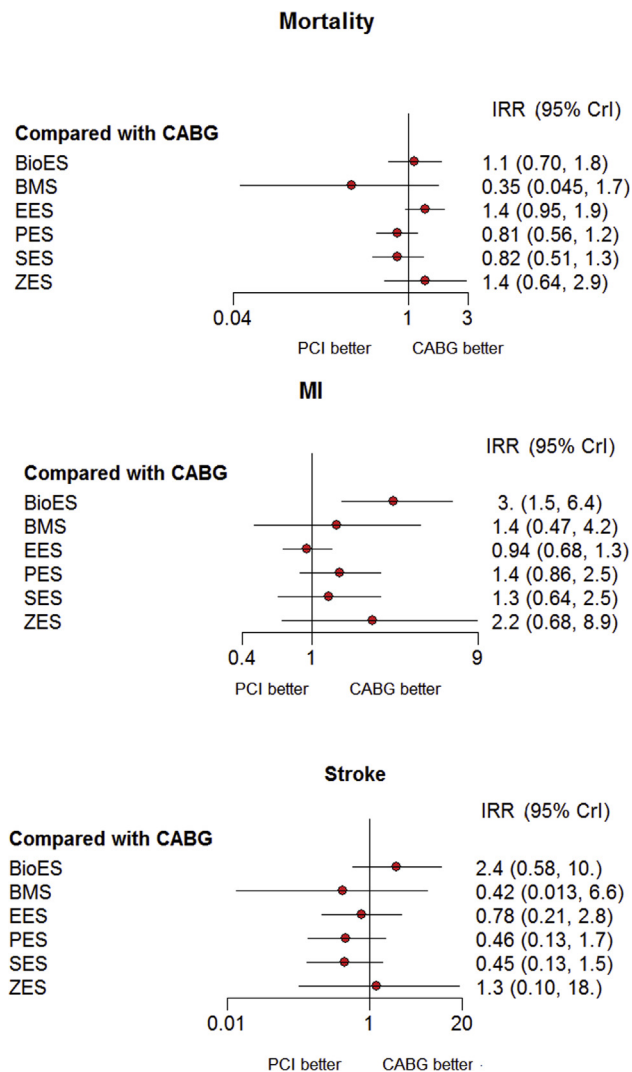
The main finding of the present NMA was that the introduction of second-generation DESs did not improve PCI outcomes when compared with CABG for unprotected LMD. Second-generation DESs (EES, ZES, and Bio-ES)

were associated with a significant trend toward an increased risk of death/MI/stroke when compared with CABG, although this was not observed with BMS or first-generation stents (SES and PES). When outcomes from individual stents were analyzed separately, we found that the Bio-ES was associated with a significant 3-fold increased risk of MI, ZES showed a nonsignificant trend toward an increased risk of mortality, and MI and EES showed a marginally nonsignificant increased risk of mortality.

Although the introduction of first-generation DESs narrowed the gap between CABG and PCI in terms of repeat revascularization when compared with BMS, the risk of a further reintervention did not further improve with second-generation DESs. Concern about the long-term safety of DESs for unprotected LMD has been raised in the past because of the observed risk of stent thrombosis, which may outweigh the benefits of DESs.[19-21] The SYNTAX trial[3] and PRECOMBACT trial[9] showed comparable results between first-generation DESs and CABG for unprotected LMD, but these studies were largely underpowered to detect differences in hard clinical end points such as death and MI. New-generation DES, including polymer Bio-ES and EES, have been introduced to replace first-generation DES with more biocompatible and thinner

Mortality

IRR (95% Crl)

Compared with CABG

BioES	1.1 (0.70, 1.8)
BMS	0.35 (0.045, 1.7)
EES	1.4 (0.95, 1.9)
PES	0.81 (0.56, 1.2)
SES	0.82 (0.51, 1.3)
ZES	1.4 (0.64, 2.9)

0.04   1   3

PCI better   CABG better

MI

IRR (95% Crl)

Compared with CABG

BioES	3. (1.5, 6.4)
BMS	1.4 (0.47, 4.2)
EES	0.94 (0.68, 1.3)
PES	1.4 (0.86, 2.5)
SES	1.3 (0.64, 2.5)
ZES	2.2 (0.68, 8.9)

0.4   1   9

PCI better   CABG better

Stroke

IRR (95% Crl)

Compared with CABG

BioES	2.4 (0.58, 10.)
BMS	0.42 (0.013, 6.6)
EES	0.78 (0.21, 2.8)
PES	0.46 (0.13, 1.7)
SES	0.45 (0.13, 1.5)
ZES	1.3 (0.10, 18.)

0.01   1   20

PCI better   CABG better

FIGURE 5. NMA estimates for individual component of death, MI, or stroke at latest follow-up (expressed as IRR, with relative 95% CrI) for different stent types. CABG as comparator. *CABG,* Coronary artery bypass grafting; *Bio-ES,* biolimus-eluting stent; *BMS,* bare metal stent; *EES,* everolimus-eluting stent; *PES,* paclitaxel-eluting stents; *SES,* sirolimus-eluting stents; *ZES,* zotarolimus-eluting stent; *PCI,* percutaneous coronary intervention; *IRR,* incidence rate ratio; *CrI,* credible interval; *MI,* myocardial infarction.

polymers to reduce stent thrombosis rates.[21] However, 2 recent large RCTs, NOBLE[1] and EXCEL,[2] compared Bio-ES and EES, respectively, with CABG, reaching conflicting conclusions about the noninferiority of PCI over CABG. Such a discrepancy can be partially related to different definitions adopted for MI. For the primary end point definition, the NOBLE trial included nonprocedural MI only, whereas EXCEL, SYNTAX, and PRECOMBAT included both procedural and subsequent spontaneous MI. However, PCI-related MI has a greater impact on long-term prognosis than CABG-related MI, and there is still

controversy on which unifying common definition for PCI-related and CABG-related MI should be adopted.[22] This aspect calls into question the validity of end point definitions, which include periprocedural MI in the comparison between PCI and CABG. Of note, in EXCEL, although the 2 strategies did not differ for the composite of procedural and spontaneous MI, PCI was associated with an increased risk of subsequent spontaneous MI when compared with CABG.

Although second-generation DESs have been reported to improve PCI outcomes achieved with first-generation DESs by reducing the risk of stent thrombosis and restenosis,[23] in most available comparisons, the distal targets were treated. We can speculate that the superiority of second-generation over first-generation DESs might not be reproducible in LMD. It has been shown that the risk of restenosis might be less relevant in case of coronary arteries with larger diameter (≥3.5 mm),[24] and this aspect can partially explain the lack of benefit in terms of repeat revascularization with second-generation DES observed in the present NMA.

On the other hand, the Bio-ES has been perceived as safer than the first-generation DES, mainly on the basis of results from individual trials powered only for composite end points of safety and efficacy.[25] However, a recent landmark NMA[26] concluded that the Bio-ES is associated with an excess of death and MI when compared with other stents. Biodegradable polymer DESs, such as Bio-ES, use polymers that dissolve after time and antiproliferative drug elution is needed. Once the degradation process of the polymer is completed in these devices, what remains is a bare-metal scaffold with a thick-strut design. This platform may provide lower elasticity than durable polymers, with an increased risk of fragility and micro-damage to the coating, and potential "jailing" of side branches. These factors explain the lower safety profile with biolimus biodegradable polymer stents.[26]

Study Limitations

As with any meta-analysis, our report shares the limitations of the original studies. By exploiting potentially complex evidence networks along with indirect and direct comparisons, NMA assumes that patients enrolled in the component studies were sampled from the same theoretical population and that similar comparators between different trials have a consistent risk–benefit ratio.

In the present analysis, some studies have a limited sample size, and there was a relatively small number of trials for the comparison of individual stents against CABG. As a consequence, few comparisons present relatively wide confidence interval (unaddressed uncertainty). However, no inconsistencies were apparent between the direct and indirect estimates for the end points considered across all comparisons, which provides strong scientific support for the reliability of the network. Results were analyzed on aggregate data, and therefore we could not assess whether

all baseline characteristics were balanced between the groups. Finally, several comparisons were of borderline statistical significance, and even greater numbers of patients with longer-term follow-up would add greater precision to the present results.

CONCLUSIONS

A word of caution should be noted on the current trend of preferring PCI with new-generation DESs over CABG for LMD in view of the present findings. We could not demonstrate the anticipated benefit from second-generation DESs in this population in terms of mortality, MI, and repeat revascularization. The routine use of new-generation DESs in the treatment of LMD still deserves further investigations. Current trials are largely underpowered to clarify whether DESs are as safe as CABG in terms of mortality, and the use of end points including procedural MI might have masked potential risks with DESs. Adequately powered and well-designed studies are needed to guide clinicians in decision-making. Finally, concerns remain because most clinical research studies are funded by manufacturers with the relative risk of bias in favor of new devices.

Conflict of Interest Statement
Authors have nothing to disclose with regard to commercial support.

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Key Words: coronary artery bypass grafting, percutaneous coronary intervention, coronary stenting, left main disease
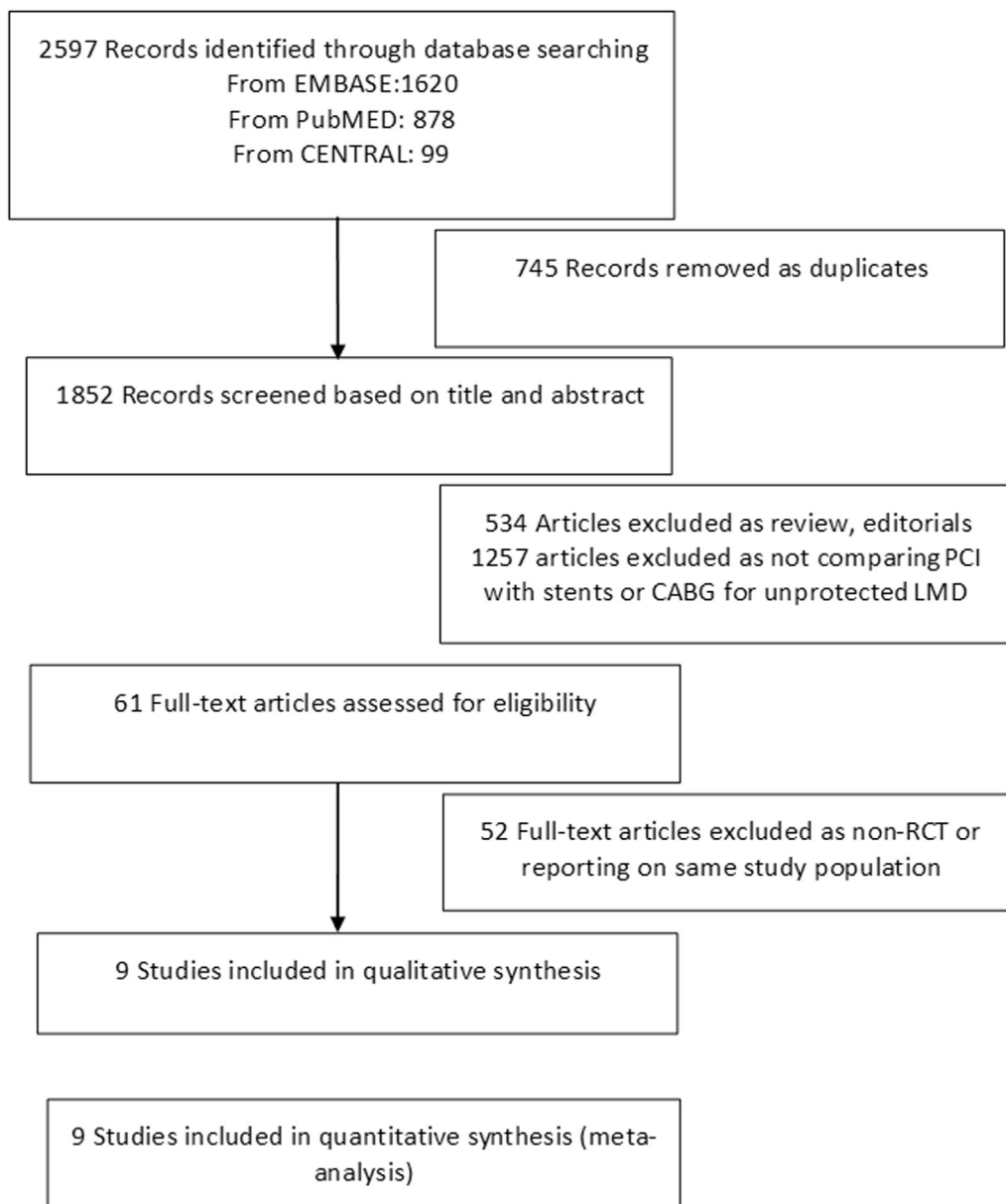
FIGURE E1. Flow diagram of study selection. *CENTRAL*, Cochrane Central Register of Controlled Trials; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *LMD*, left main disease; *RCT*, randomized controlled trial.
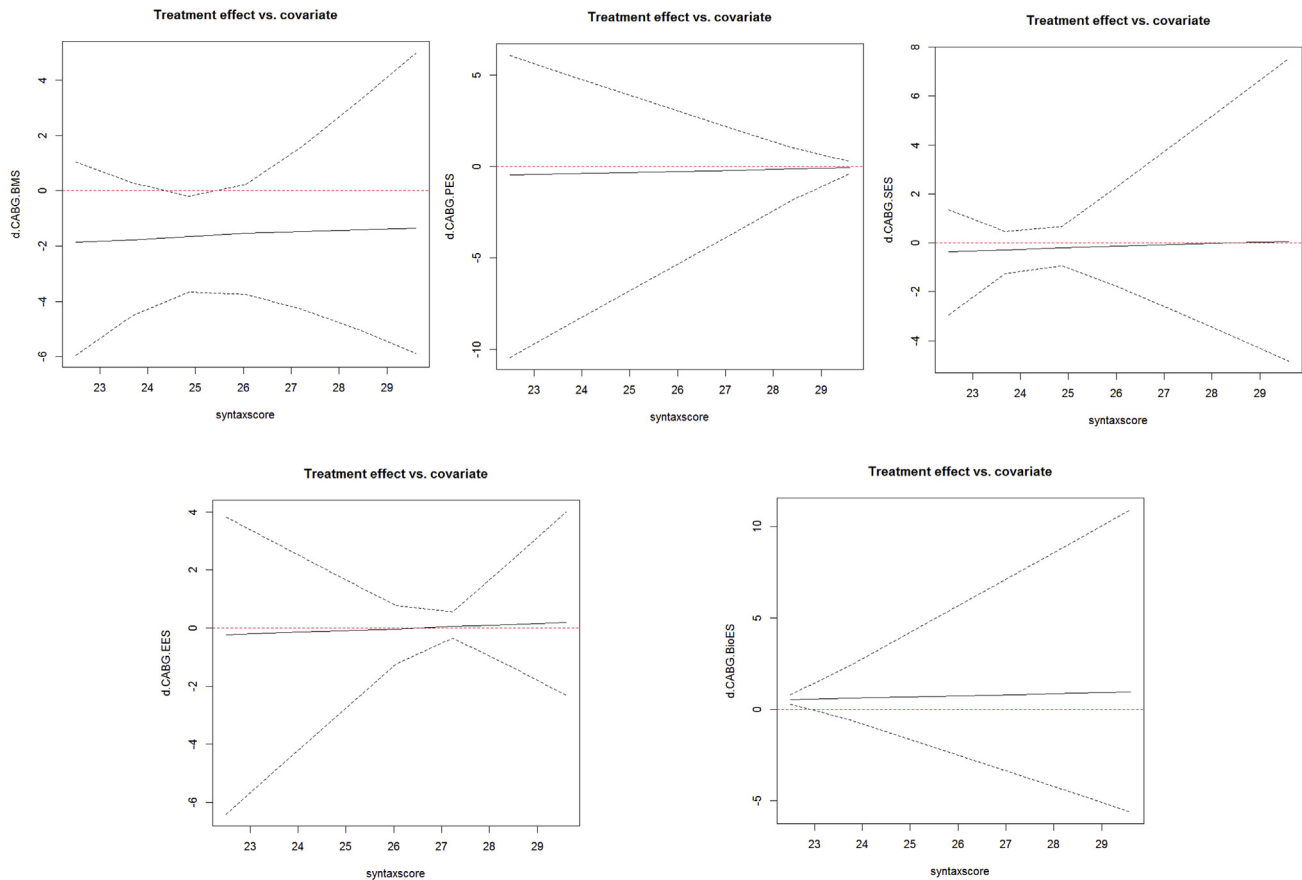
FIGURE E2. SYNTAX score has no effect on treatment effect (stents vs CABG) for the composite of death/MI/stroke (no variation across syntax score values). *CABG*, Coronary artery bypass grafting; *BMS*, bare metal stent; *PES*, paclitaxel-eluting stent; *SES*, sirolimus-eluting stent; *EES*, everolimus-eluting stent; *Bio-ES*, biolimus-eluting stent.
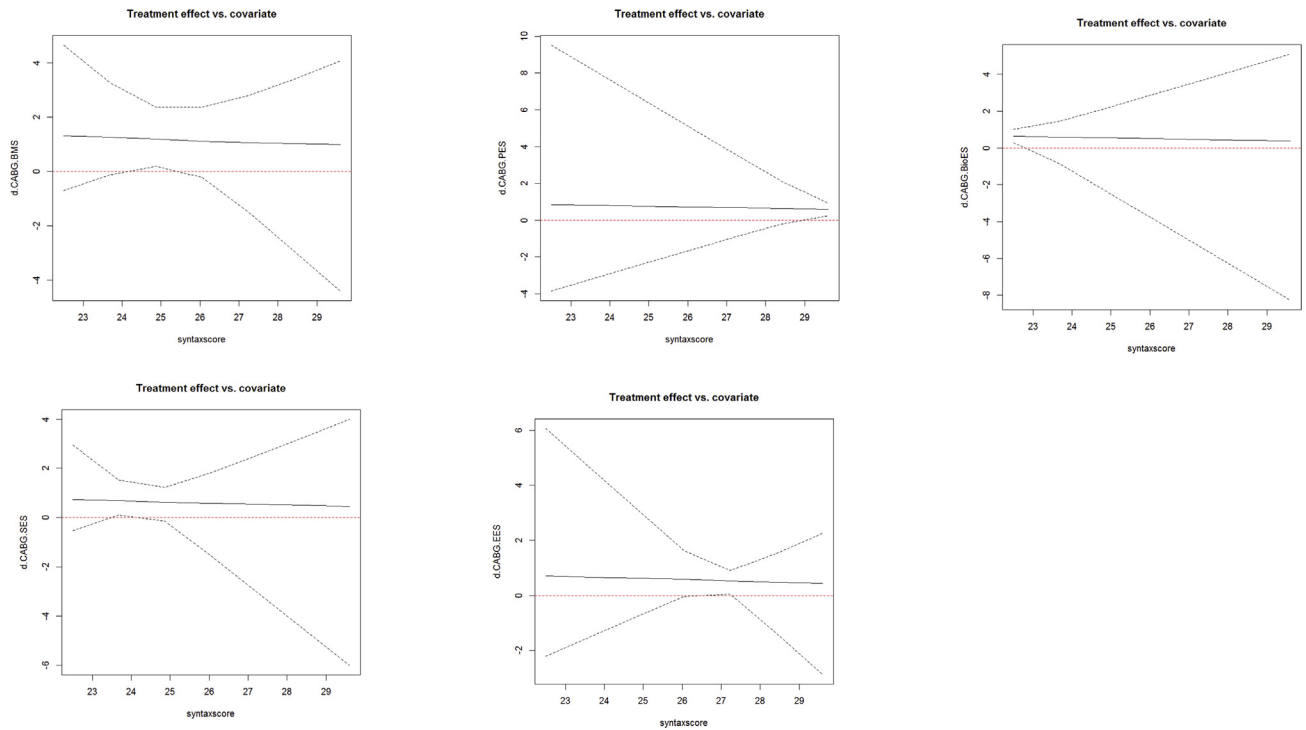
FIGURE E3. SYNTAX score has no effect on treatment effect (stents vs CABG) for repeat revascularization (no variation across syntax score values). *CABG*, Coronary artery bypass grafting; *BMS*, bare metal stent; *PES*, paclitaxel-eluting stent; *Bio-ES*, biolimus-eluting stent; *SES*, sirolimus-eluting stent; *EES*, everolimus-eluting stent.
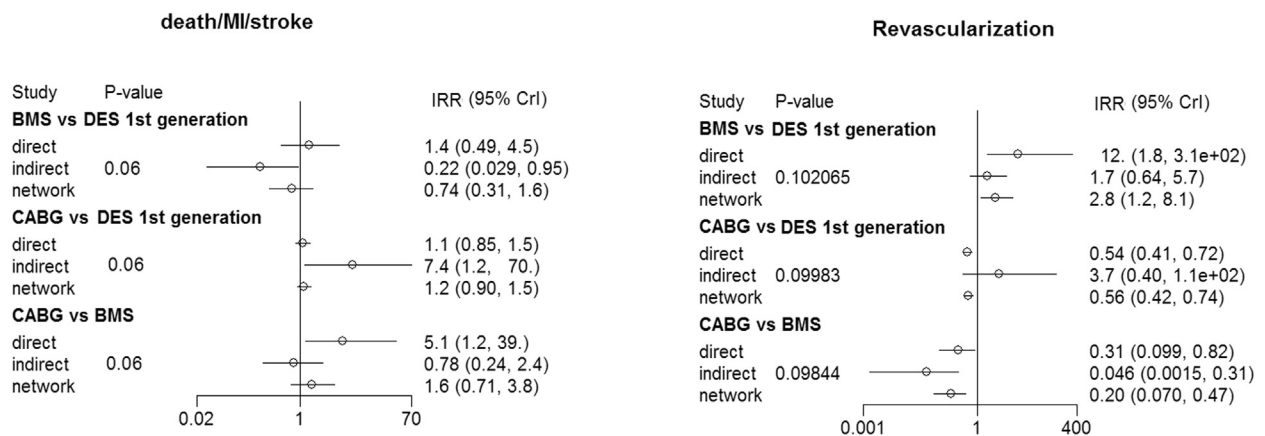
FIGURE E4. Comparison of direct and indirect estimates to assess inconsistency for the primary end points (expressed as IRR, with relative 95% CrI) for different stent generations (DES first-generation include PES and SES; DES second-generation include Bio-ES, EES, and ZES). *MI*, Myocardial infarction; *IRR*, incidence rate ratio; *CrI*, credible interval; *BMS*, bare metal stent; *DES*, drug-eluting stent; *CABG*, coronary artery bypass grafting.

Inconsistency check: node split

Mortality

MI
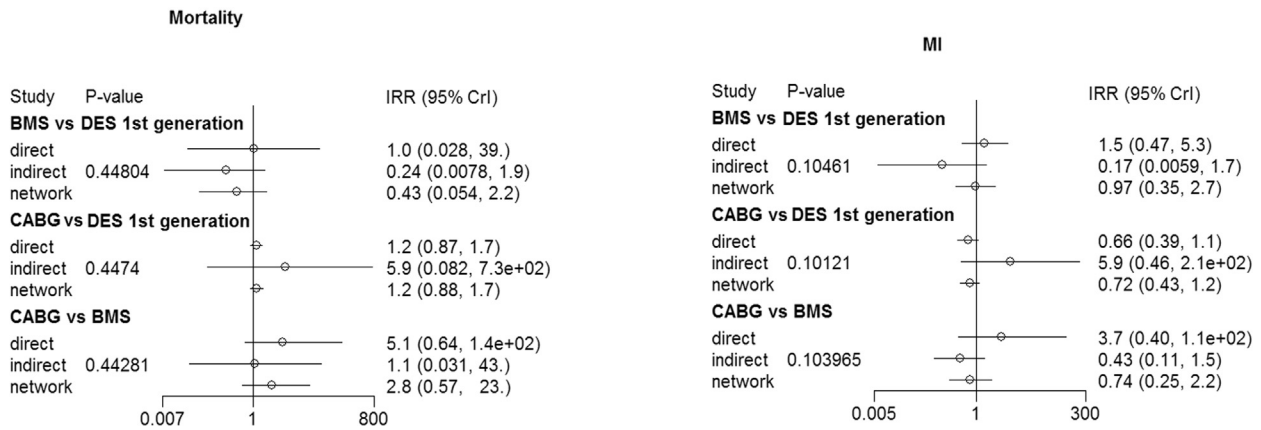
FIGURE E5. Comparison of direct and indirect estimates to assess inconsistency for individual component of death and MI (expressed as IRR, with relative 95% CrI) for different stent generations (DES first-generation include PES and SES; DES second-generation include Bio-ES, EES, and ZES). No computation for stroke because Erglis and colleagues[16] did not report stroke rate. *IRR,* Incidence rate ratio; *CrI,* credible interval; *BMS,* bare metal stent; *DES,* drug-eluting stent; *CABG,* coronary artery bypass grafting; *MI,* myocardial infarction.

Inconsistency check: Node split

death/MI/stroke

Revascularization

FIGURE E6. Comparison of direct and indirect estimates to assess inconsistency for the primary end points (expressed as IRR, with relative 95% CrI) for different stent types. *MI,* Myocardial infarction; *IRR,* incidence rate ratio; *CrI,* credible interval; *CABG,* coronary artery bypass grafting; *BMS,* bare metal stent; *PES,* paclitaxel-eluting stent; *SES,* sirolimus-eluting stent.
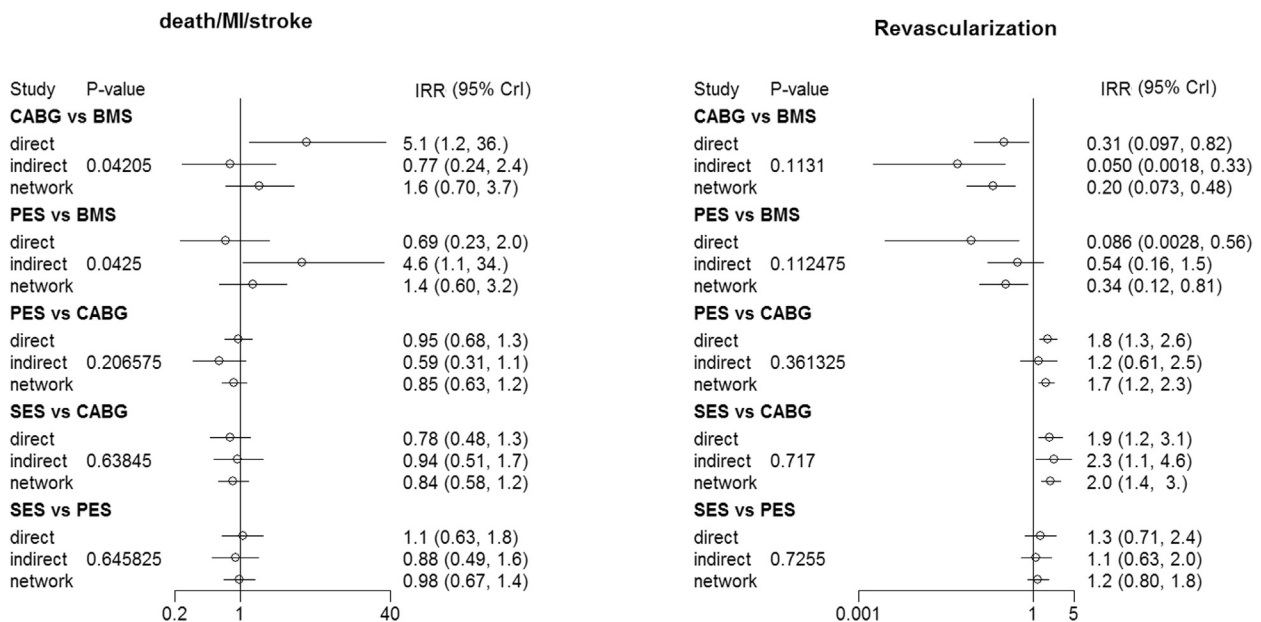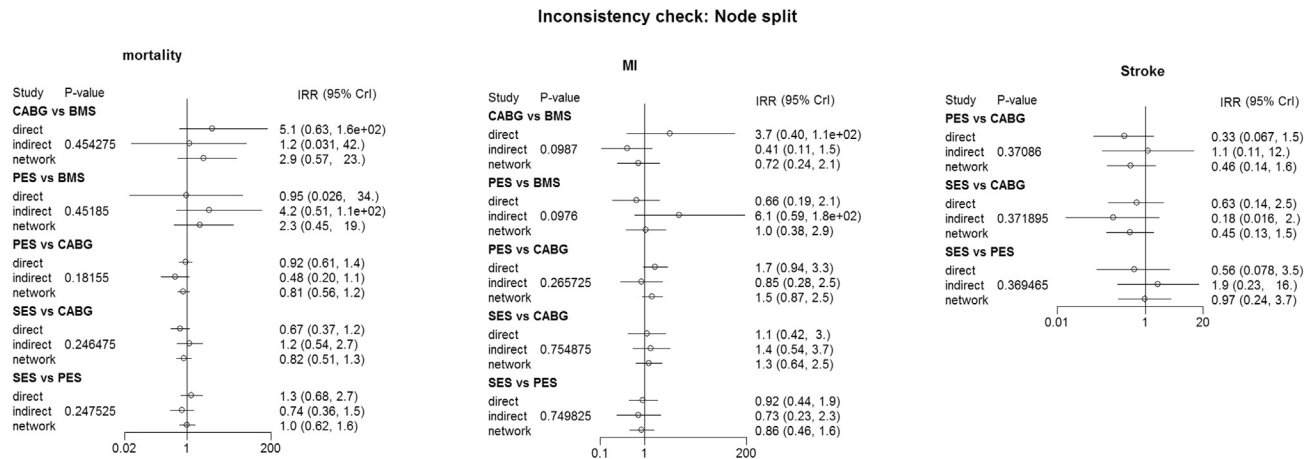
FIGURE E7. Comparison of direct and indirect estimates to assess inconsistency for individual component of death, MI, or stroke at latest follow-up (expressed as IRR, with relative 95% CrI) for different stent types. *IRR*, Incidence rate ratio; *CrI*, credible interval; *CABG*, coronary artery bypass grafting; *BMS*, bare metal stent; *PES*, paclitaxel-eluting stent; *SES*, sirolimus-eluting stent; *MI*, myocardial infarction.
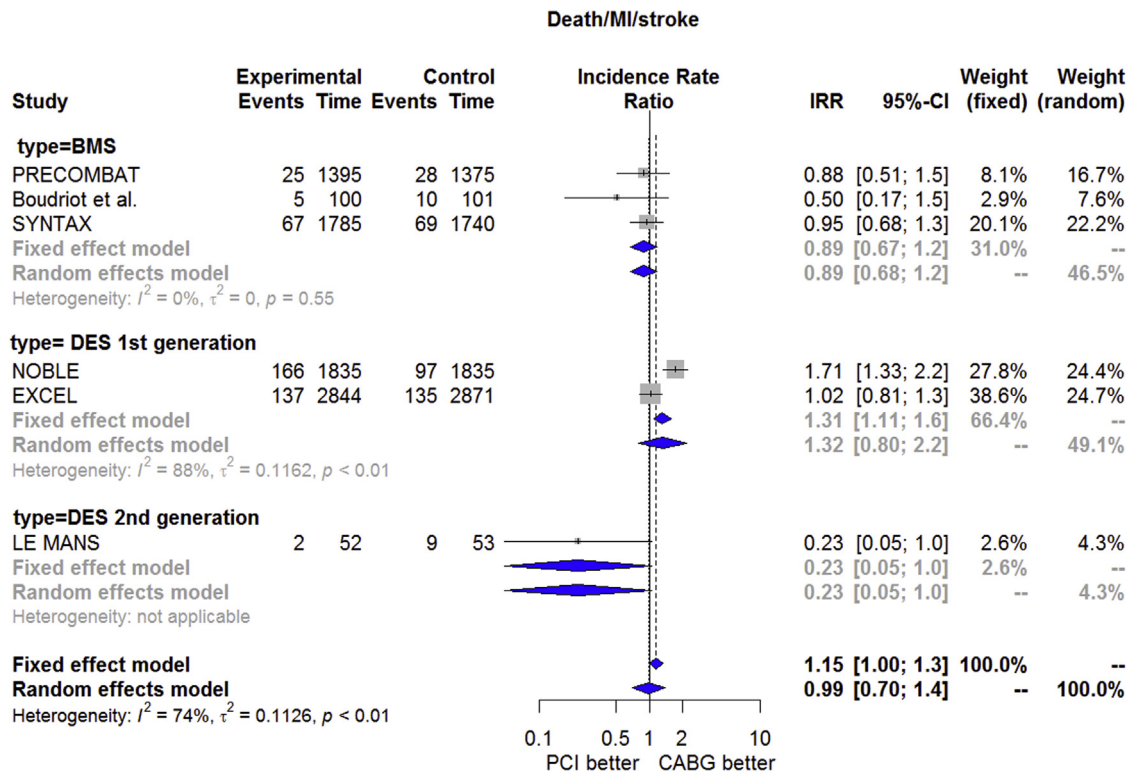
FIGURE E8. Pairwise pooled and subgroup meta-analysis for the composite of death/MI/stroke with BMS and first- and second-generation DESs (first-generation DESs include PES and SES; second-generation DESs include Bio-ES, EES, and ZES). CABG as comparator. *MI*, Myocardial infarction; *IRR*, incidence rate ratio; *CI*, confidence interval; *BMS*, bare metal stent; *PRECOMBAT*, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial; *DES*, drug-eluting stent; *NOBLE*, Nordic-Baltic-British left main revascularisation study; *EXCEL*, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; *LE MANS*, Study of Unprotected Left Main Stenting Versus Bypass Surgery; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.
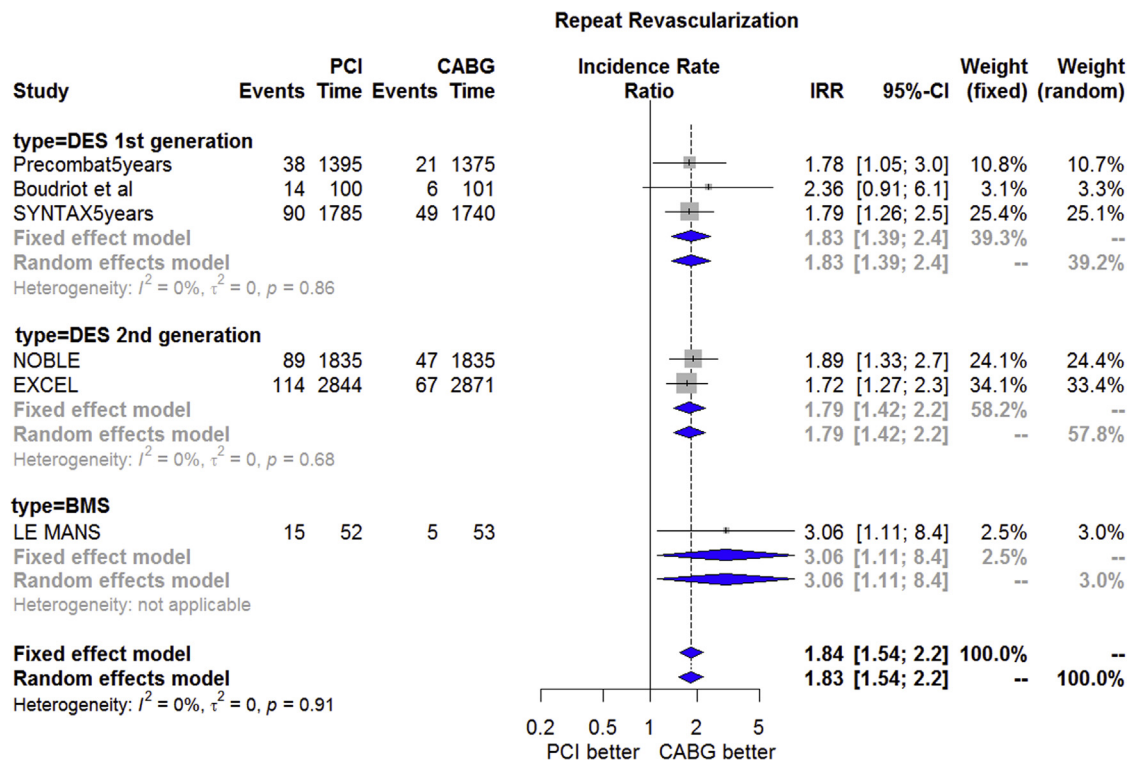
FIGURE E9. Pairwise pooled and subgroup meta-analysis for repeat revascularization with BMS and first- and second-generation DESs (first-generation DESs include PES and SES; second-generation DESs include Bio-ES, EES, and ZES). CABG as comparator. *PCI*, Percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *IRR*, incidence rate ratio; *CI*, confidence interval; *DES*, drug-eluting stent; *PRECOMBAT*, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial; *NOBLE*, Nordic-Baltic-British left main revascularisation study; *EXCEL*, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; *BMS*, bare metal stent; *LE MANS*, Study of Unprotected Left Main Stenting Versus Bypass Surgery.

TABLE E1. Main inclusion and exclusion criteria, primary and secondary end points of randomized controlled trials

Trial	Main inclusion criteria	Main exclusion criteria	Primary end point	Secondary end point
NOBLE	Stable angina pectoris, unstable angina pectoris, or acute coronary syndrome, together with a lesion with visually assessed stenosis diameter ≥50% or fractional flow reserve ≤0.80 in the left main coronary artery ostium, mid-shaft, or bifurcation, with no more than 3 additional noncomplex lesions.	ST-elevation infarction within 24 h, being considered too high risk for CABG or PCI, or expected survival of <1 y.	Composite of MACCE; death from any cause, nonprocedural MI, repeat revascularization, or stroke.	The individual component of the primary MACCE end point, definite stent thrombosis, and symptomatic graft occlusion. Procedural MIs were documented (post hoc). Repeat revascularizations.
EXCEL	Stenosis of the left main coronary artery of ≥70%, as estimated visually, or stenosis of 50% to <70% if determined by means of noninvasive or invasive testing to be hemodynamically significant, and a consensus among the members of the heart team regarding eligibility for revascularization with PCI or CABG. In addition, participants were required to have low-to-intermediate anatomic complexity of coronary artery disease, as defined by a site-determined SYNTAX score of ≤32 (the SYNTAX score reflects a comprehensive angiographic assessment of the coronary vasculature, with 0 as the lowest score and higher scores [no upper limit] indicating more complex coronary anatomy).	Prior PCI of the left main trunk at any time before randomization, PCI of any other (nonleft main) coronary artery lesions within 1 y before randomization, CABG at any time before randomization. Need for any concomitant cardiac surgery other than CABG. Angiographic exclusion criteria: a. Left main diameter stenosis <50%, unless left main equivalent disease is present; b. SYNTAX score ≥33, as determined by the local Heart Team; c. Visually estimated left main reference vessel diameter <2.25 mm or >4.25 mm; d. The presence of specific coronary lesion characteristics or other cardiac conditions that lead the participating interventional cardiologist or cardiac surgeon to believe that clinical equipoise is not present	The primary composite end point of death from any cause, stroke, or MI	A composite of death from any cause, stroke, or MI at 30 d and the rate of a composite of death, stroke, MI, or ischemia-driven revascularization at 3 y. Additional secondary end points included the components of the primary end point, revascularization, stent thrombosis, symptomatic graft stenosis or occlusion, bleeding complications, and a prespecified composite of periprocedural MAEs.
LE MANS	Patients with >50% narrowing of ULMCA, with or without multivessel coronary artery disease suitable for equal revascularization both with PCI and CABG. All patients had to be symptomatic with documented myocardial ischemia.	Acute MI, total occlusion of left main, comorbid conditions, or coronary anatomic considerations that increased the surgical risk to a euroSCORE of ≥8, stroke or transient ischemic attack within 3 mo, renal dysfunction, or contraindication to antiplatelet therapy.	The change in LVEF assessed by 2-dimensional echocardiography 12 mo	MACCE, other MAE, length of hospitalization, exercise tolerance measured with an electrocardiographic treadmill stress test along with angina severity according to the Canadian Cardiovascular Society classification after 1 y, total survival, TVF, and TVR.

(Continued)

TABLE E1. Continued

Trial	Main inclusion criteria	Main exclusion criteria	Primary end point	Secondary end point
PRECOMBAT	Age >18 y and had received a diagnosis of stable angina, unstable angina, silent ischemia, or non–ST-segment elevation MI. All patients had newly diagnosed ULMCA stenosis (>50% diameter stenosis by visual angiographic estimation) and had been judged to be suitable candidates for PCI or CABG.	Systemic (IV) sirolimus use within 12 mo. Any previous PCI within 1 y. Previous bypass surgery. Any previous PCI of a ULMCA or ostial left circumflex artery or ostial left anterior descending artery lesion within 1 y. Acute MI within 1 wk. Ejection fraction <30%. Cardiogenic shock.	Composite of death from any cause, MI, stroke, or ischemia-driven TVR	The individual components of the primary end point; a composite of death, MI, or stroke, and clinically driven TVR.
SYNTAX	De novo lesions, ≥50% target vessel stenosis with stable/ unstable angina or atypical chest pain. If asymptomatic, positive evidence of myocardial ischemia was required.	Previous PCI or CABG, acute MI, or the need for concomitant cardiac surgery.	Composite of MACCE (ie, death from any cause, stroke, MI, or repeat revascularization)	The individual component of the primary MACCE end point, quality of life, and cost-effectiveness.
Boudriot and colleagues[14]	Patients aged 18-80 y with stenosis (>50%) of the ULM with or without additional multivessel coronary artery disease were included in this multicenter study. Patients had to be symptomatic or have documented myocardial ischemia.	MI 48 h requiring immediate intervention, additional valvular heart disease requiring surgery, previous surgical treatment for coronary artery or valvular disease, severe peripheral arterial disease, significant carotid stenosis requiring treatment, renal dysfunction requiring dialysis, any disease with limited life expectancy, overt congestive heart failure, and contraindication to antiplatelet therapy. Angiographic exclusion criteria were total occlusions, extreme left-dominant coronary artery perfusion, and distal lesion length >30 mm in a single lesion	MACCE, which included death from any cause, MI, and the need for repeat revascularization	Each individual component of the composite end point.
Erglis and colleagues[16]	Eligible patients were those with clinically symptomatic LM disease with angiographic evidence of >50% diameter stenosis of LM suitable for stent implantation. All patients were good candidates for CABG.	CABG to LAD artery branches or LCX branches	Neointimal growth (volume, square, luminal diameter, and late lumen loss) evaluated by IVUS at 6 mo, or earlier if clinically indicated.	MACE were defined as death, MI, and target lesion revascularization

(Continued)

TABLE E1. Continued

Trial	Main inclusion criteria	Main exclusion criteria	Primary end point	Secondary end point
ISAR-LEFT-MAIN	Patients aged >18 y with ischemic symptoms or evidence of myocardial ischemia in the presence of >50% de novo stenosis located in the left main stem	ST-segment elevation MI within 48 h of symptom onset; prior bypass graft surgery; in-stent restenosis; cardiogenic shock; malignancies or other comorbid conditions with life expectancy <1 y or that might result in protocol noncompliance; left main size >4.5 mm; planned staged PCI procedure within 30 d from index PCI; planned elective surgical procedure necessitating interruption of clopidogrel during the first 6 mo after enrollment; known allergy to the study medications: clopidogrel, rapamycin, paclitaxel, stainless steel, or cobalt alloy; pregnancy; or previous enrollment in this trial	The combined incidence of death, MI, and target lesion revascularization at 1 y	Angiographic restenosis on the basis of the LMCA area analysis at follow-up angiography
ISAR-LEFT-MAIN 2	Patients aged >18 y with ischemic symptoms or evidence of myocardial ischemia in the presence of >50% de novo stenosis located in the left main stem	ST-segment elevation MI within <48 h of symptom onset; prior CABG surgery; in-stent restenosis; cardiogenic shock; malignancies or other comorbid conditions with a life expectancy <1 y; planned staged PCI procedure within 30 d of index PCI; planned elective surgical procedure necessitating interruption of P2Y12-receptor inhibitors during the first 6 mo postenrollment; known allergy to the study medications: everolimus, zotarolimus, or cobalt alloy; pregnancy; or previous enrollment in this trial	Combined incidence of death, MI, and target lesion revascularization	Definite or probable stent thrombosis at 1 y and angiographic restenosis based on analysis of the left main coronary artery area at follow-up angiography

NOBLE, Nordic-Baltic-British left main revascularisation study; *CABG*, coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *MACCE*, major adverse cardiac and cerebrovascular events; *MI*, myocardial infarction; *EXCEL*, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial; *MAE*, major adverse event; *LE MANS*, Study of Unprotected Left Main Stenting Versus Bypass Surgery; *ULMCA*, unprotected left main coronary artery; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *LVEF*, left ventricular ejection fraction; *TVF*, target vessel failure; *TVR*, target vessel revascularization; *PRECOMBAT*, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; *IV*, intravenous; *LM*, left main; *LAD*, left anterior descending; *LCX*, left circumflex; *IVUS*, intravascular ultrasound; *MACE*, major adverse cardiac event; *ISAR-LEFT-MAIN*, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions; *LMCA*, left main coronary artery.

TABLE E2. Outcome definition in randomized controlled trials

NOBLE

All-cause mortality: Death from any cause.

Cardiac death: Cardiac death was defined as any death due to a suspected cardiac cause (MI, low-output heart failure, fatal arrhythmia), unwitnessed death, and death of unknown cause. All procedure-related deaths, including those related to concomitant treatment, were classified as cardiac death. The end point was included post hoc. (Modified from Cutlip et al. *Circulation*. 2007;115:2344-51.) The information on cause of death was obtained from hospital patient files, general practitioners, or families if no other source was available.

Vascular death: Death caused by noncoronary vascular causes, including cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases. The end point was included post hoc. (Modified from Cutlip et al. *Circulation*. 2007;115:2344-51.)

Nonprocedure-related MI: A increase in biochemical markers exceeding the decision limit for MI with at least 1 of the following; (1) ischemic symptoms, (2) ECG changes indicative of ischemia (ST-segment elevation or depression), and (3) development of a pathologic Q-wave with no relation to a PCI procedure.

Repeat revascularization: Any new PCI or CABG operation performed during follow-up. If an index revascularization was attempted or successful, any subsequent revascularization was counted as repeat revascularization. Attempted PCI was defined as an advancement of a wire in the coronary tree at least. Attempted CABG was defined as at least initiation of an index operation.

Procedure-related biomarker release: The diagnosis of a procedure-related biomarker increase required an increase in total CK or troponin–T/I. Because of the heterogeneity of biomarkers and various assays used during the study in participating centers, this comparison was omitted from the final analysis.

Procedural MI: Diagnosis of procedural MI for both PCI and CABG cases was based on CK-MB elevations when available. Patients needed to have stable angina pectoris as the clinical indication OR a normal baseline CK-MB, TnI, TnT, or highly sensitive TnT, to be assessable for procedural MI. Diagnosis required a CK-MB value >10 × URL or ULN to establish the diagnosis. The diagnosis could also be placed by the combination of a CK-MB value above 5 × URL or ULN, AND 1 or more of the following: (1) new pathologic Q waves in at least 2 contiguous leads or new persistent non–rate-related left bundle branch block or (2) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. The end point of procedural MI was included post hoc, and the definition was adapted to match the definition applied in the EXCEL trial on PCI versus CABG for LMCA stenosis. Periprocedural MI due to repeat revascularization during follow-up were assessed applying the 3rd Universal definition because CK-MB was not available in all event patients. A procedural MI according to this definition was counted as a nonindex procedural MI.

Nonprocedural myocardial infarction: Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020-35.

Target lesion revascularization: Repeat revascularization by PCI of any target segment treated during the index procedure. A target lesion segment was defined as a stented or balloon treated segment and its 5-mm margins.

LMCA revascularization: Any subsequent revascularization by PCI of the segments within 5 mm of any treated segment related to the LMCA or the LMCA bifurcation. Any revascularization by CABG of native LMCA including the LMCA bifurcation, or revascularization of a graft supplying the left anterior descending artery or circumflex arteries.

Definite stent thrombosis: Stent thromboses were categorized as acute, subacute, late, and very late and as definite, probable, and possible according to Academic Research Consortium criteria. (Cutlip et al. *Circulation*. 2007;115:2344-51.)

Symptomatic graft occlusion: Diagnosis of symptomatic graft occlusion required it to be detected during a clinically indicated coronary angiography.

Stroke: Ischemic or hemorrhagic cerebrovascular event verified by brain CT or MRI.

Pulmonary embolus: The diagnosis of pulmonary embolus required verification by an appropriate CT scan.

EXCEL

Death: The cause of death will be adjudicated as being due to cardiovascular causes, noncardiovascular causes, or undetermined causes.

Cardiovascular death includes sudden cardiac death, death due to acute MI, heart failure or cardiogenic shock, stroke, other cardiovascular causes, or bleeding.

- Noncardiovascular death is defined as any death with known cause not of cardiac or vascular causes.
- Undetermined cause of death refers to a death not due to 1 of the above categories of cardiovascular death or to a noncardiovascular cause. For this trial, all deaths of undetermined cause will be included in the cardiovascular category

MI (protocol definition):

Postprocedure MI: Defined as the occurrence within 72 h after PCI or CABG of CK-MB >10× URL*, OR

- CK-MB >5× URL*, PLUS
  - New pathologic Q waves in at least 2 contiguous leads or new persistent nonrated-related LBBB, or
  - Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Spontaneous MI: Defined as the occurrence >72 h after any PCI or CABG of:

The increase or decrease of cardiac biomarkers (CK-MB or troponin) >1× URL* PLUS:

(Continued)

TABLE E2. Continued

- ECG changes indicative of new ischemia (ST-segment elevation or depression, in the absence of other causes of ST-segment changes such as left ventricular hypertrophy or bundle branch block), or
- Development of pathologic Q waves ($\geq$0.04 sec in duration and $\geq$1 mm in depth) in $\geq$2 contiguous precordial leads or $\geq$2 adjacent limb leads) of the ECG, or
- Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis or diminished epicardial flow, or
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Each MI will also be adjudicated as:
- ST-segment elevation MI
- Non–ST-segment elevation MI
- Each ST-segment elevation MI and non–ST-segment elevation MI will be subcategorized as
    - Q-wave
    - Non–Q-wave
    - Unknown (no ECG or ECG not interpretable)

Stroke: The rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent nonvascular cause (eg, trauma, tumor, or infection). A vascular neurologist or stroke specialist will determine whether a stroke has occurred and determine the stroke severity using the National Institutes of Health Stroke Scale Transient Ischemia Attack/Stroke questionnaire. Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown. Four criteria must be fulfilled to diagnosis stroke:

1. Rapid onset of a focal/global neurologic deficit with at least 1 of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphasia/aphasia, hemianopia, amaurosis fugax, other new neurologic sign(s)/symptom(s) consistent with stroke; and
2. Duration of a focal/global neurologic deficit $\geq$24 h or <24 h if any of the following conditions exist:
    i. At least 1 of the following therapeutic interventions:
        a. Pharmacologic (ie, thrombolytic drug administration)
        b. Nonpharmacologic (ie, neurointerventional procedure such as intracranial angioplasty)
    ii. Available brain imaging clearly documents a new hemorrhage or infarct
    iii. The neurologic deficit results in death
3. No other readily identifiable nonstroke cause for the clinical presentation (eg, brain tumor, trauma, infection, hypoglycemia, other metabolic abnormality, peripheral lesion, or drug side effect). Patients with nonfocal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
4. Confirmation of the diagnosis by a neurology or neurosurgical specialist and at least 1 of the following:
    a. Brain imaging procedure (at least 1 of the following):
        i. CT scan
        ii. MRI scan
        iii. Cerebral vessel angiography
    b. Lumbar puncture (ie, spinal fluid analysis diagnostic of intracranial hemorrhage)

All strokes with stroke disability of modified Rankin Scale $\geq$1 (increase from baseline assessment) will be included in the primary end point. All diagnosed strokes (even with modified Rankin Scale 0) will also be tabulated.

Ischemia-driven revascularization:

A coronary revascularization procedure may be a CABG or PCI. The coronary segments revascularized will be subclassified as:
- Target Lesion: A lesion revascularized in the index procedure (or during a planned or provisional staged procedure). The LM target lesion extends from the left main stem ostium to the end of the 5-mm proximal segments of the left anterior descending and left circumflex arteries as well as the ramus intermedius if the latter vessel has a vessel diameter of $\geq$2 mm.
- Target Vessel: The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main and any vessel originating from the left main coronary artery or its major branches is, by definition, considered a target vessel for the purposes of this trial (unless the LAD or LCX are occluded at baseline and no attempt was made to revascularize these territories by PCI or CABG).
- Target Vessel Nontarget Lesion: The target vessel nontarget lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography.
- Nontarget Vessel: For the purposes of this trial, the only possible nontarget vessel would be the right coronary artery and its major branches that were not treated by PCI or CABG at the index procedure (unless the LAD or LCX are occluded at baseline and no attempt was made to revascularize these territories by PCI or CABG).

(Continued)

TABLE E2. Continued

All revascularization events will be adjudicated as ischemia driven or nonischemia driven. Revascularization will be considered ischemia driven if the diameter stenosis of the revascularized coronary segment is ≥50% by quantitative coronary angiography and any of the following criteria for ischemia are met:

- A positive functional study corresponding to the area served by the target lesion; or
- Ischemic ECG changes at rest in a distribution consistent with the target vessel; or
- Typical ischemic symptoms referable to the target lesion; or
- IVUS of the target lesion with a minimal lumen area of ≤4 mm^2 for nonleft main lesions or ≤6 mm^2 for left main lesions. If the lesions are de novo (ie, not restenotic), the plaque burden must also be ≥60%; or
- Fractional flow reserve of the target lesion ≤0.80

A target lesion revascularization for a diameter stenosis <50% might be considered ischemia-driven by the Clinical Events Committee if there was a markedly positive functional study or ECG changes corresponding to the area served by the target lesion.

Periprocedural major adverse events:

The composite rate of any of the following, occurring within 30 d postprocedure

- Death
- Stroke
- MI
- Ischemia-driven revascularization
- TIMI major or minor bleeding
- Transfusion ≥2 units of blood
- Major arrhythmia (supraventricular tachycardia requiring cardioversion, ventricular tachycardia or fibrillation requiring treatment, or bradyarrhythmia requiring temporary or permanent pacemaker)
- Any unplanned surgery or therapeutic radiologic procedure
- Renal failure (serum creatinine increase by ≥0.5 mg/dL from baseline or need for dialysis)
- Sternal wound dehiscence
- Infection requiring antibiotics
- Prolonged intubation (>48 h)
- Postpericardiotomy syndrome

LE MANS

The major adverse events were defined as all-cause mortality, acute MI (defined as an increase in creatine phosphokinase-MB to >3 times the upper limit of normal after PCI and 5 times after CABG), repeat revascularization, acute heart failure (eg, pulmonary edema, cardiogenic shock), or low output syndrome requiring intravenous inotropic agents and/or intra-aortic balloon pump support, postprocedural complications leading to reintervention, stroke, arrhythmia (ventricular fibrillation, ventricular tachycardia, or atrial fibrillation), major bleeding requiring additional blood transfusion, and infections compromising postprocedural rehabilitation. Any cardiac mortality, acute MI, stroke, repeat intervention, and/or acute/ subacute in-stent thrombosis were considered MACCE.

Target vessel failure was defined as any MACCE related to insufficient flow through the LMCA, and TVR as any repeat intervention (PCI or CABG) caused by a narrowing of the LMCA. The incidence of stent thrombosis was evaluated in accordance with the Academic Research Consortium Definitions of Stent Thrombosis

SYNTAX

Deaths were considered cardiac unless an unequivocal, noncardiac cause was established.

Cerebrovascular accident was defined as a focal, central neurologic deficit lasting >72 h that resulted in irreversible brain damage or body impairment.

Repeat revascularization was defined as any repeat PCI or CABG. Complete revascularization was defined as the successful treatment of all eligible lesions identified during the Heart Team conference and estimated postprocedure by the investigator.

MI was based on previous studies, MI was defined in relation to intervention status as follows i) after allocation but before treatment: Q -wave (new pathologic Q-waves in ≥2 leads lasting ≥0.04 sec with CK-MB levels elevated above normal), and non–Q–wave MI (elevation of CK levels >2× the ULN with positive CK-MB or elevation of CK levels to >2× ULN without new Q-waves if no baseline CK-MB was available); ii) <7 d after intervention: new Q-waves and peak CK-MB/total CK >10% or plasma level of CK-MB 5× ULN; iii) 7d after intervention: new Q waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5× ULN or plasma level of CK 5× ULN. The CK/CK-MB enzyme levels were obtained and measured by a core laboratory for all randomized patients.

Per protocol graft occlusion and ST were considered acute if occurring ≤24 h after the study procedure, subacute if occurring >24 h to ≤30 d after the study procedure, and late after 30 d. Per protocol graft occlusion and stent thrombosis were defined as i) clinical presentation of an acute coronary syndrome with documentation of a flow limiting thrombus or occlusion within a bypass graft or adjacent to the anastomosis of a previously bypassed coronary artery (for CABG cases) or within or adjacent to a previously successfully treated artery (for PCI cases); ii) a Q-wave MI in the territory of ≥1 treated vessels within first 30 d.

(Continued)

TABLE E2. Continued

Boudriot and colleagues[14]

MI was defined as an increase in creatine kinase-MB activity >3× the upper limit of normal after PCI and >5× after CABG. In addition, standard electrocardiographic criteria were applied.

The incidence of stent thrombosis was evaluated in accordance with the Academic Research Consortium definitions.

Repeat revascularization was defined as any revascularization by CABG or PCI within 12 mo and was subdivided into target lesion revascularization of the ULM and distally located lesions or those of the right coronary artery.

Erglis and colleagues[16]

MACE were defined as death, MI, and TLR. Patients with >1 event were assigned the highest rank event.

All deaths were considered to be of cardiac origin unless a noncardiac origin was diagnosed.

MI was diagnosed by elevation of myocardial damage biomarkers: 3-fold in troponin I and 5-fold in MB fraction of creatine kinase.

Target lesion revascularization was defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis in the stent or within the 5-mm segments adjacent to the stent, including the ostium of the LAD or LCX artery.

ISAR-LEFT-MAIN

The diagnosis of MI required the presence of new significant Q waves on the electrocardiogram and/or elevation of CK-myocardial band isoform (or CK if the latter was not available) at least 2× the upper limit of normal in no fewer than 2 blood samples.

The TLR was defined as any repeat PCI involving the left main area or CABG involving at least 1 of the main left coronary vessels due to luminal renarrowing in the presence of symptoms or objective signs of ischemia.

Stent thrombosis was defined according to Academic Research Consortium criteria (Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.).

Angiographic binary restenosis was defined as diameter stenosis >50%, measured by quantitative coronary angiography, in the left main area.

ISAR-LEFT-MAIN 2

The diagnosis of MI required the presence of new significant Q waves on electrocardiography or elevation of CK-MB isoform (or creatine kinase if the latter was not available) to at least 2 times the upper limit of normal in no fewer than 2 blood samples.

Target lesion revascularization was defined as any repeat PCI involving the left main area or CABG surgery involving at least 1 of the main left coronary vessels due to luminal renarrowing in the presence of symptoms or objective signs of ischemia.

Stent thrombosis was defined according to Academic Research Consortium criteria (Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.).

Angiographic binary restenosis was defined as diameter stenosis >50%, measured by quantitative coronary angiography, in the left main area.

NOBLE, Nordic-Baltic-British left main revascularisation study; *MI*, myocardial infarction; *ECG*, electrocardiogram; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *CK*, creatine kinase; *CK-MB*, creatine-kinase MB form; *Tn*, troponin; *URL*, upper reference limit; *ULN*, upper limit of normal; *EXCEL*, the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; *LBBB*, left bundle branch block; *LMCA*, left main coronary artery; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *EXCEL*, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; *LM*, left main; *LAD*, left anterior descending; *LCX*, left circumflex; *IVUS*, intravascular ultrasound; *TIMI*, Thrombolysis in Myocardial Infarction; *LE MANS*, Study of Unprotected Left Main Stenting Versus Bypass Surgery; *MACCE*, major adverse cardiac and cerebrovascular events; *TVR*, target vessel revascularization; *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial; *TLR*, target lesion revascularization; *MACE*, major adverse cardiac event; *ISAR-LEFT-MAIN*, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions.

TABLE E3. Risk of bias of included randomized controlled trials

NOBLE

Risk of bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer-generated using permuted random blocks
Allocation concealment (selection bias)	Low risk	Web-based computer randomization
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Unclear risk	>20% losses (31% losses to follow-up)
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Unclear risk	Primary end point timing changed

EXCEL

Risk of bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Variable block random allocation
Allocation concealment (selection bias)	Low risk	Interactive voice-based or Web-based system
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Low risk	8% of participants were lost to follow-up; reasons reported
Selective reporting (reporting bias)	Low risk	Study protocol is available, all expected outcomes included
Other bias	Low risk	Free of other sources of bias

LE MANS

Risk of bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Randomization stated to have been done but no method reported
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Blinded outcome assessors
Incomplete outcome data (attrition bias)	Low risk	11.4% of participants were lost to follow-up; reasons reported
Selective reporting (reporting bias)	Low risk	Include all expected outcomes
Other bias	Low risk	Free of other sources of bias

PRECOMBAT

Risk of bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Low risk	Sealed envelopes concealed the allocation
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Low risk	6.8% of participants were lost to follow-up; reasons reported
Selective reporting (reporting bias)	Low risk	Study protocol is available, all Expected outcomes included
Other bias	Low risk	Free of other sources of bias

SYNTAX

Risk of bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Variable block random allocation
Allocation concealment (selection bias)	Low risk	Central allocation (Interactive Voice Response System)
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Low risk	5.2% of participants were lost to follow-up; reasons reported
Selective reporting (reporting bias)	Low risk	Study protocol is available, all expected outcomes included
Other bias	Low risk	Free of other sources of bias

TABLE E3. Continued

Boudriot and colleagues[14]		
Risk of bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Computerized randomization program
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation was not reported
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Blinded outcome assessors
Incomplete outcome data (attrition bias)	Low risk	0.5% of participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Low risk	Free of other sources of bias
Erglis and colleagues[16]		
Risk of bias		
Random sequence generation (selection bias)	Unclear	No sufficient information to allow judgment
Allocation concealment (selection bias)	Unclear	No sufficient information to allow judgment
Blinding of participants and personnel (performance bias)	Unclear	No sufficient information to allow judgment
Blinding of outcome assessment (detection bias)	Unclear	No sufficient information to allow judgment
Incomplete outcome data (attrition bias)	Low risk	No patient lost to follow-up
Selective reporting (reporting bias)	Unclear	No sufficient information to allow judgment
Other bias	Low risk	There is no evidence of other bias
ISAR-LEFT-MAIN		
Risk of bias		
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias)	High risk	The article does not report information about the blinding of participants and personnel. We assume this is an open-label study
Blinding of outcome assessment (detection bias)	Low risk	An events committee blinded to treatment allocation adjudicated all adverse clinical events.
Incomplete outcome data (attrition bias)	Low risk	No patient lost to follow-up
Selective reporting (reporting bias)	Unclear	No sufficient information to allow judgment
Other bias	High risk	The ISAR-LEFT-MAIN study was supported in part by an unrestricted grant from Cordis (Milpitas, Calif).
ISAR-LEFT-MAIN 2		
Risk of bias		
Random sequence generation (selection bias)	Low risk	Randomization was done by a web-based computer randomization system
Allocation concealment (selection bias)	Low risk	Patients were assigned to the allocated treatment according to Randomization by the local research team
Blinding of participants and personnel (performance bias)	High- risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study
Incomplete outcome data (attrition bias)	High risk	17 patients lost to follow-up, unlikely to have influenced results
Selective reporting (reporting bias)	Unclear	No sufficient information to allow judgment
Other bias	Low risk	Aarhus University Hospital was the main sponsor of the trial. Biosensors provided an institutional research grant for the trial but had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of this report; or in the decision to submit the paper for publication.

NOBLE, Nordic-Baltic-British left main revascularisation study; *EXCEL*, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; *LE MANS*, Study of Unprotected Left Main Stenting Versus Bypass Surgery; *PRECOMBAT*, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial; *ISAR-LEFT-MAIN*, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions.

TABLE E4. Full network meta-analytic estimates (expressed as log incidence rate ratio, and 95% credible interval; statistical significance in bold)

Outcome	Bio-ES	BMS	CABG	EES	PES	SES	ZES
Mortality	Bio-ES	−1.166 (−3.262, 0.5108)	−0.1185 (−0.6011, 0.3578)	0.1858 (−0.4146, 0.7829)	−0.3287 (−0.9366, 0.2736)	−0.3186 (−0.9935, 0.3468)	0.192 (−0.7034, 1.083)
	1.166 (−0.5108, 3.262)	BMS	1.042 (−0.5564, 3.093)	1.348 (−0.2925, 3.43)	0.833 (−0.7845, 2.895)	0.843 (−0.8156, 2.939)	1.363 (−0.4249, 3.532)
	0.1185 (−0.3578, 0.6011)	−1.042 (−3.093, 0.5564)	CABG	0.3038 (−0.05129, 0.6653)	−0.2084 (−0.5795, 0.1597)	−0.1997 (−0.6654, 0.2652)	0.311 (−0.4428, 1.063)
	−0.1858 (−0.7829, 0.4146)	−1.348 (−3.43, 0.2925)	−0.3038 (−0.6653, 0.05129)	EES	−0.514 (−1.029, 0.0007923)	−0.505 (−1.093, 0.08261)	0.007237 (−0.659, 0.6691)
	0.3287 (−0.2736, 0.9366)	−0.833 (−2.895, 0.7845)	0.2084 (−0.1597, 0.5795)	0.514 (−0.0007923, 1.029)	PES	0.009336 (−0.4756, 0.4963)	0.5207 (−0.3156, 1.358)
	0.3186 (−0.3468, 0.9935)	−0.843 (−2.939, 0.8156)	0.1997 (−0.2652, 0.6654)	0.505 (−0.08261, 1.093)	−0.009336 (−0.4963, 0.4756)	SES	0.512 (−0.371, 1.397)
	−0.192 (−1.083, 0.7034)	−1.363 (−3.532, 0.4249)	−0.311 (−1.063, 0.4428)	−0.007237 (−0.6691, 0.659)	−0.5207 (−1.358, 0.3156)	−0.512 (−1.397, 0.371)	ZES
MI	Bio-ES	−0.7653 (−2.094, 0.5427)	**−1.087 (−1.864, −0.3979)**	**−1.148 (−1.983, −0.3826)**	−0.7197 (−1.647, 0.1613)	−0.8682 (−1.881, 0.1073)	−0.2824 (−1.7, 1.26)
	0.7653 (−0.5427, 2.094)	BMS	−0.3304 (−1.433, 0.7578)	−0.3903 (−1.537, 0.7464)	0.04066 (−0.9842, 1.073)	−0.107 (−1.285, 1.074)	0.4879 (−1.154, 2.221)
	1.087 (0.3979, 1.864)	0.3304 (−0.7578, 1.433)	CABG	−0.05837 (−0.3818, 0.264)	0.3709 (−0.1532, 0.9082)	0.2247 (−0.4473, 0.9072)	0.8076 (−0.3876, 2.188)
	1.148 (0.3826, 1.983)	0.3903 (−0.7464, 1.537)	0.05837 (−0.264, 0.3818)	EES	0.4306 (−0.1877, 1.057)	0.2832 (−0.4617, 1.04)	0.8652 (−0.2814, 2.211)
	0.7197 (−0.1613, 1.647)	−0.04066 (−1.073, 0.9842)	−0.3709 (−0.9082, 0.1532)	−0.4306 (−1.057, 0.1877)	PES	−0.1469 (−0.7678, 0.4729)	0.4399 (−0.8755, 1.905)
	0.8682 (−0.1073, 1.881)	0.107 (−1.074, 1.285)	−0.2247 (−0.9072, 0.4473)	−0.2832 (−1.04, 0.4617)	0.1469 (−0.4729, 0.7678)	SES	0.5882 (−0.7967, 2.112)
	0.2824 (−1.26, 1.7)	−0.4879 (−2.221, 1.154)	−0.8076 (−2.188, 0.3876)	−0.8652 (−2.211, 0.2814)	−0.4399 (−1.905, 0.8755)	−0.5882 (−2.112, 0.7967)	ZES
Revascularization	Bio-ES	**0.9567 (0.01152, 2.033)**	**−0.641 (−1.003, −0.293)**	−0.0982 (−0.5659, 0.3653)	−0.1277 (−0.6017, 0.3418)	0.0608 (−0.4646, 0.59)	0.1264 (−0.5473, 0.8067)
	−0.9567 (−2.033, −0.01152)	BMS	**−1.596 (−2.623, −0.7295)**	**−1.054 (−2.118, −0.1309)**	**−1.082 (−2.116, −0.1973)**	−0.8956 (−1.975, 0.04512)	−0.832 (−1.994, 0.224)
	0.641 (0.293, 1.003)	**1.596 (0.7295, 2.623)**	CABG	**0.5432 (0.2455, 0.8497)**	**0.514 (0.2072, 0.8272)**	**0.7023 (0.3189, 1.097)**	**0.7689 (0.1983, 1.353)**
	0.0982 (−0.3653, 0.5659)	1.054 (0.1309, 2.118)	**−0.5432 (−0.8497, −0.2455)**	EES	−0.02982 (−0.4618, 0.4039)	0.1596 (−0.3316, 0.654)	0.2256 (−0.2644, 0.7221)
	0.1277 (−0.3418, 0.6017)	1.082 (0.1973, 2.116)	**−0.514 (−0.8272, −0.2072)**	0.02982 (−0.4039, 0.4618)	PES	0.1886 (−0.225, 0.6081)	0.2553 (−0.3963, 0.9129)
	−0.0608 (−0.59, 0.4646)	0.8956 (−0.04512, 1.975)	**−0.7023 (−1.097, −0.3189)**	−0.1596 (−0.654, 0.3316)	−0.1886 (−0.6081, 0.225)	SES	0.06595 (−0.6265, 0.7658)
	−0.1264 (−0.8067, 0.5473)	0.832 (−0.224, 1.994)	**−0.7689 (−1.353, −0.1983)**	−0.2256 (−0.7221, 0.2644)	−0.2553 (−0.9129, 0.3963)	−0.06595 (−0.7658, 0.6265)	ZES
Stroke	Bio-ES	−1.752 (−5.447, 1.362)	−0.8569 (−2.321, 0.5531)	−1.115 (−3.055, 0.7876)	−1.63 (−3.525, 0.2809)	−1.673 (−3.549, 0.2075)	−0.6292 (−3.531, 2.364)
	1.752 (−1.362, 5.447)	BMS	0.8718 (−1.88, 4.328)	0.6285 (−2.407, 4.272)	0.1115 (−2.902, 3.776)	0.06921 (−2.946, 3.726)	1.157 (−2.635, 5.375)
	0.8569 (−0.5531, 2.321)	−0.8718 (−4.328, 1.88)	CABG	−0.2518 (−1.538, 1.021)	−0.7692 (−2.008, 0.5028)	−0.805 (−2.035, 0.4157)	0.2288 (−2.285, 2.902)
	1.115 (−0.7876, 3.055)	−0.6285 (−4.272, 2.407)	0.2518 (−1.021, 1.538)	EES	−0.5174 (−2.266, 1.308)	−0.5585 (−2.292, 1.229)	0.4776 (−1.689, 2.855)
	1.63 (−0.2809, 3.525)	−0.1115 (−3.776, 2.902)	0.7692 (−0.5028, 2.008)	0.5174 (−1.308, 2.266)	PES	−0.04 (−1.415, 1.31)	0.9973 (−1.835, 3.913)
	1.673 (−0.2075, 3.549)	−0.06921 (−3.726, 2.946)	0.805 (−0.4157, 2.035)	0.5585 (−1.229, 2.292)	0.04 (−1.31, 1.415)	SES	1.037 (−1.765, 3.959)
	0.6292 (−2.364, 3.531)	−1.157 (−5.375, 2.635)	−0.2288 (−2.902, 2.285)	−0.4776 (−2.855, 1.689)	−0.9973 (−3.913, 1.835)	−1.037 (−3.959, 1.765)	ZES
Death/MI/Stroke	Bio-ES	**−1.001 (−1.895, −0.1452)**	**−0.5382 (−0.7923, −0.2897)**	**−0.5147 (−0.8634, −0.1697)**	**−0.6938 (−1.086, −0.3051)**	**−0.7158 (−1.17, −0.2634)**	−0.2929 (−0.9653, 0.3897)
	1.001 (0.1452, 1.895)	BMS	0.4615 (−0.3563, 1.319)	0.4848 (−0.3656, 1.374)	0.3071 (−0.5049, 1.154)	0.285 (−0.5917, 1.191)	0.7091 (−0.3203, 1.772)
	0.5382 (0.2897, 0.7923)	−0.4615 (−1.319, 0.3563)	CABG	0.02384 (−0.2147, 0.2622)	−0.1551 (−0.4557, 0.1429)	−0.1771 (−0.5554, 0.199)	0.2453 (−0.3767, 0.8807)
	0.5147 (0.1697, 0.8634)	−0.4848 (−1.374, 0.3656)	−0.02384 (−0.2622, 0.2147)	EES	−0.1792 (−0.5603, 0.2039)	−0.2009 (−0.6472, 0.2449)	0.2222 (−0.3544, 0.8121)
	0.6938 (0.3051, 1.086)	−0.3071 (−1.154, 0.5049)	0.1551 (−0.1429, 0.4557)	0.1792 (−0.2039, 0.5603)	PES	−0.02207 (−0.4051, 0.3617)	0.401 (−0.2901, 1.101)
	0.7158 (0.2634, 1.17)	−0.285 (−1.191, 0.5917)	0.1771 (−0.199, 0.5554)	0.2009 (−0.2449, 0.6472)	0.02207 (−0.3617, 0.4051)	SES	0.4237 (−0.3051, 1.162)
	0.2929 (−0.3897, 0.9653)	−0.7091 (−1.772, 0.3203)	−0.2453 (−0.8807, 0.3767)	−0.2222 (−0.8121, 0.3544)	−0.401 (−1.101, 0.2901)	−0.4237 (−1.162, 0.3051)	ZES

Bio-ES, Biolimus-eluting stent; *BMS*, bare metal stent; *CABG*, coronary artery bypass grafting; *EES*, everolimus-eluting stent; *PES*, paclitaxel-eluting stent; *SES*, sirolimus-eluting stent; *ZES*, zotarolimus-eluting stent; *MI*, myocardial infarction.