European Heart Journal Advance Access published January 23, 2014

European Heart Journal
doi:10.1093/eurheartj/eht570

CLINICAL RESEARCH
Interventional cardiology

Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis

Si-Hyuck Kang[1†], Kyung Woo Park[1†], Do-Yoon Kang[1], Woo-Hyun Lim[1], Kyung Taek Park[1], Jung-Kyu Han[1], Hyun-Jae Kang[1], Bon-Kwon Koo[1], Byung-Hee Oh[1], Young-Bae Park[1], David E. Kandzari[2], David J. Cohen[3], Seung-Sik Hwang[4], and Hyo-Soo Kim[1*]

[1]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 28 Yeongeon-Dong, Chongno-gu, Seoul 110-744, Korea; [2]Piedmont Heart Institute, Altanta, GA, USA; [3]Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; and [4]Department of Social and Preventive Medicine, Inha University School of Medicine, Incheon, Korea

Received 26 June 2013; revised 10 November 2013; accepted 18 December 2013

Background The aim of this study was to compare the safety and efficacy of biodegradable-polymer (BP) drug-eluting stents (DES), bare metal stents (BMS), and durable-polymer DES in patients undergoing coronary revascularization, we performed a systematic review and network meta-analysis using a Bayesian framework.

Methods and results Study stents included BMS, paclitaxel-eluting (PES), sirolimus-eluting (SES), endeavor zotarolimus-eluting (ZES-E), cobalt–chromium everolimus-eluting (CoCr-EES), platinium–chromium everolimus-eluting (PtCr-EES), resolute zotarolimus-eluting (ZES-R), and BP biolimus-eluting stents (BP-BES). After a systematic electronic search, 113 trials with 90 584 patients were selected. The principal endpoint was definite or probable stent thrombosis (ST) defined according to the Academic Research Consortium within 1 year.

Results Biodegradable polymer-biolimus-eluting stents [OR, 0.56; 95% credible interval (CrI), 0.33–0.90], SES (OR, 0.53; 95% CrI, 0.38–0.73), CoCr-EES (OR, 0.34; 95% CrI, 0.23–0.52), and PtCr-EES (OR, 0.31; 95% CrI, 0.10–0.90) were all superior to BMS in terms of definite or probable ST within 1 year. Cobalt–chromium everolimus-eluting stents demonstrated the lowest risk of ST of all stents at all times after stent implantation. Biodegradable polymer-biolimus-eluting stents was associated with a higher risk of definite or probable ST than CoCr-EES (OR, 1.72; 95% CrI, 1.04–2.98). All DES reduced the need for repeat revascularization, and all but PES reduced the risk of myocardial infarction compared with BMS.

Conclusions All DESs but PES and ZES-E were superior to BMS in terms of ST within 1 year. Cobalt–chromium everolimus-eluting stents was safer than any DES even including BP-BES. Our results suggest that not only the biodegradability of polymer, but the optimal combination of stent alloy, design, strut thickness, polymer, and drug all combined determine the safety of DES.

Keywords Bare metal stents • Drug-eluting stents • Biodegradable polymer drug-eluting stents • Meta-analysis

† The first two authors contributed equally to the study.

* Corresponding author. Tel: +82 220722226, Fax: +82 27668904, Email: hyosoo@snu.ac.kr

Introduction

Drug-eluting stents (DESs) compared with bare metal stents (BMS) have reduced the need for repeat revascularization,[1–3] and have largely replaced BMS in the treatment of coronary artery disease. However, concerns have been raised regarding the potential for late stent thrombosis (ST) with DES related to delayed healing of vessel wall.[4,5] Studies have suggested that a reaction to the durable polymer (DP) containing the drug may trigger continued inflammation and late ST.[6–8] Therefore, developments in newer generation of DES have been focused on biocompatible polymer, biodegradable-polymer (BP) DESs, and polymer-free DESs.

Recent meta-analyses have shown improved safety as well as efficacy of newer-generation DESs.[9–11] However, the major limitations of the previous meta-analyses were that the proportion of patients with newer-generation DES were relatively small and thus comparisons had restricted statistical power. Furthermore, BP-DESs were not included in the analyses. Although BP-DESs have yet to receive approval in the USA, they are widely used across the world including Asia and Europe. In this study, we compared clinical outcomes of various types of coronary stents to assess their safety and efficacy. Specifically, we analysed (i) whether DES increases or decreases the risk of ST compared with BMSs, (ii) whether different DP-DESs are vulnerable to ST in the long-term clinical follow-up, (iii) the safety and efficacy of newer-generation DP-DESs and BP-DESs compared against each other and against BMS. A systematic literature review of randomized controlled trials (RCTs) comparing coronary stents was performed, and the data from the review were the basis of a multiple-treatments network meta-analysis using a Bayesian framework.[12]

Methods

Eligibility criteria

We included RCTs comparing two or more coronary stents in patients undergoing percutaneous coronary intervention. Study stents were restricted to those approved by regulatory bodies of both Korea (Ministry of Food and Drug Safety) and Europe (CE mark) and included the following stent types: (i) BMS, (ii) paclitaxel-eluting stents (PESs, Boston Scientific), (iii) sirolimus-eluting stent (SES, Cordis), (iv) endeavor zotarolimus-eluting stents (ZES-E, Medtronic), (v) cobalt–chromium everolimus-eluting stents (CoCr-EES, Abbott Vascular and Boston Scientific), (vi) platinum–chromium everolimus-eluting stents (PtCr-EES, Boston Scientific), (vii) resolute zotarolimus-eluting stents (ZES-R, Medtronic), (viii) BP biolimus A9-eluting stents (BP-BES, Biosensors and Terumo), and (ix) BP everolimus-eluting stents (BP-EES, Boston Scientific). After the initial analysis, the protocol was amended to exclude BP-EES from the study, because the sample size and the event numbers in the only study that tested BP-EESs were very small.[13] We excluded studies (i) comparing two stents with different stent design within the same category described above,[14] (ii) in which specific type of DESs was not predefined and the choice among available DES was left to the investigators' discretion (for example, BMSs vs. any DESs),[15,16] and (iii) published in a language other than English.[17] No restrictions were imposed on study period, sample size, or publication status as well as patient or lesion criteria. Thus, studies with exclusive enrollment of patients with acute myocardial infarction (MI) or with bypass grafts were also included in the meta-analysis.

Data sources and searches

We performed an electronic search of the PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and relevant websites (www.crtonline.org, www.clinicaltrialresults.com, www.tctmd.com, www.cardiosource.com, and www.pcronline.com) were also searched from the inception of each database to March 2013 (search terms described in Supplementary material online, *Table S1*). The electronic search strategy was complemented by manual review of reference lists of included articles. References of recent reviews, editorials, and meta-analyses were also examined. Two individual investigators (S.H.K. and W.H.L.) performed screening of titles and abstracts, identified duplicates, reviewed full articles, and determined their eligibility. Disagreement between reviewers was resolved by discussions. The most updated data for each study were searched manually, and chosen for abstraction. Data extraction was done by one reviewer (S.H.K.), and subsequently cross-checked by a second reviewer (W.H.L.).

Risk of bias assessment

The quality of eligible RCTs was assessed using the Cochrane Collaboration's tool for assessing the risk of bias.[18] Both manuscript and protocol, if available online, were reviewed for relevant information on quality. Risk of bias was assessed by one reviewer (K.P. or D.Y.K.), and cross-checked by a second reviewer (S.H.K.).

Study outcomes and definitions

The principal safety endpoint was definite or probable ST defined according to the Academic Research Consortium (ARC) within 1 year.[19] If a study reported the incidence of ST in a way other than the ARC consensus (such as protocol-defined ST), the results were not included in the analysis. Other safety endpoints included definite ST, all-cause death, cardiac death, and MI. Efficacy endpoints were target lesion revascularization (TLR) and target vessel revascularization (TVR). Outcomes within 1 year as well as long-term outcomes (>1 year) were evaluated. For each clinical outcome, the most inclusive definitions were abstracted if possible, e.g. all-cause MI rather than target vessel-related MI, all TLR rather than ischaemia-driven or clinically driven TLR.

Data synthesis and analysis

A Bayesian random effects model for multiple treatment comparisons was constructed to compare clinical outcomes of different stent types. We used Bayesian extension of the hierarchical random-effects model proposed by Lumley for networks of multi-arm trials.[20] Odds ratios (ORs) with 95% credible intervals (CrIs) are presented as summary statistics. Non-informative prior distributions were selected so as to allow the data to dominate the final results. Data were analysed with WinBUGS v.1.4.3 (MRC Biostatistics Unit, Cambridge, UK) and R programming. We ran Markov chain Monte Carlo samplers in WinBUGS, running three chains with different starting values. A burn-in phase of 20 000 iterations was followed by 50 000 updates, where the number of burn-in iterations was chosen according to the Brooks–Gelman–Rubin method for convergence checks.[21] Pairwise ORs were estimated from the median of the posterior distribution with CrIs taken from the 2.5 and 97.5% percentiles. Results for which the CrIs of the ORs did not include 1 were considered significant. Sensitivity analysis was done excluding (i) studies with any potential risk of bias evaluated with the Cochrane Collaboration's tool, (ii) studies with exclusive enrollment of diabetic patients, (iii) studies with exclusive enrollment of ST-segment elevation myocardial infarction, and (iv) studies with mandatory angiographic follow-up.

Results

Study selection

Figure 1 shows the flow diagram of this study depicted according the statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Among 1649 potentially relevant items, 113 trials comprising 90 584 patients were finally selected for this meta-analysis. The network plot shows a polygonal network configuration with mixed connections (*Figure 2*). There were almost fully closed loops, while PtCr-EES and ZES-R had only limited comparisons.

Systematic review and study characteristics

Supplementary material online, *Table S2* briefly describes key features of the included trials. Six trials had a three-arm design, while one study had two-phase enrollment. Ten trials exclusively enrolled patients with diabetes, 21 with ST-segment elevation MI, 5 with chronic total occlusion, 3 with unprotected left main coronary artery disease, 3 with in-stent restenosis, and 2 with bypass graft. Estimated median duration of follow-up was 19.1 months ranging from 3 months to 5 years. Supplementary material online, *Table S3* further describes the patient and protocol characteristics of the included trials.

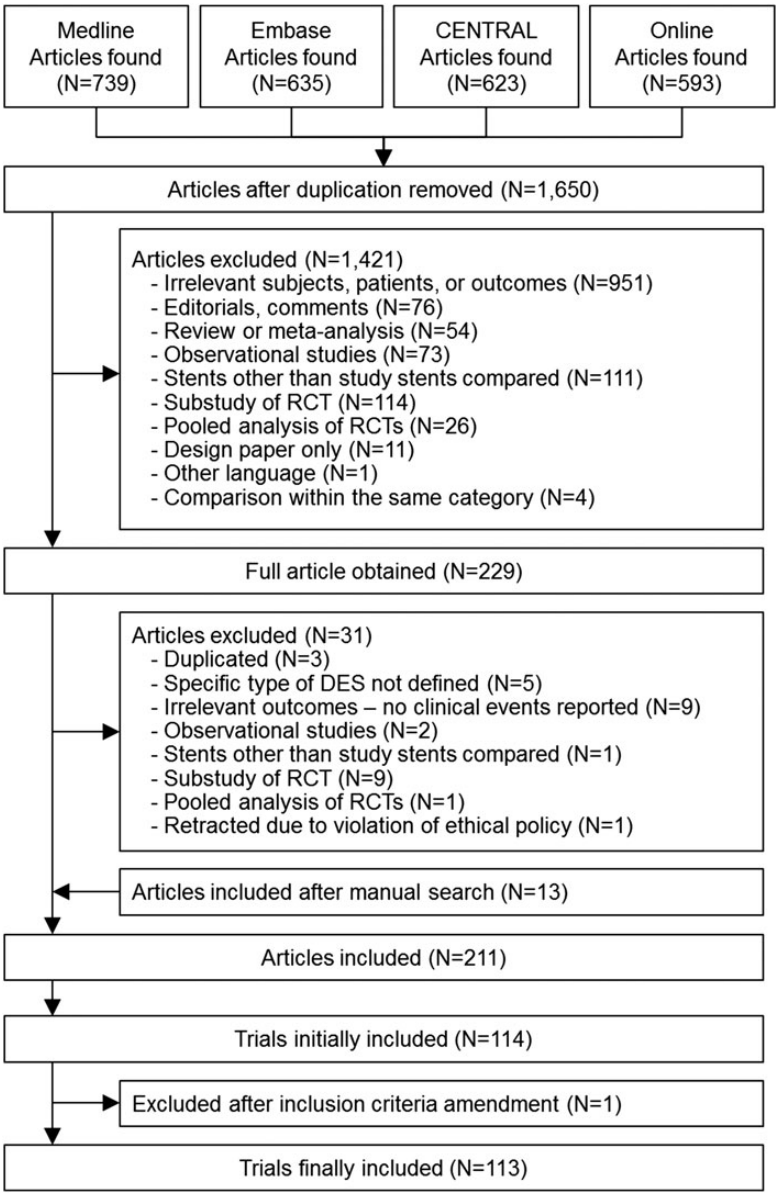

Figure 1 Flow diagram of systematic review. The study flow diagram was depicted following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement. RCT, randomized controlled trial; DES, drug-eluting stent.

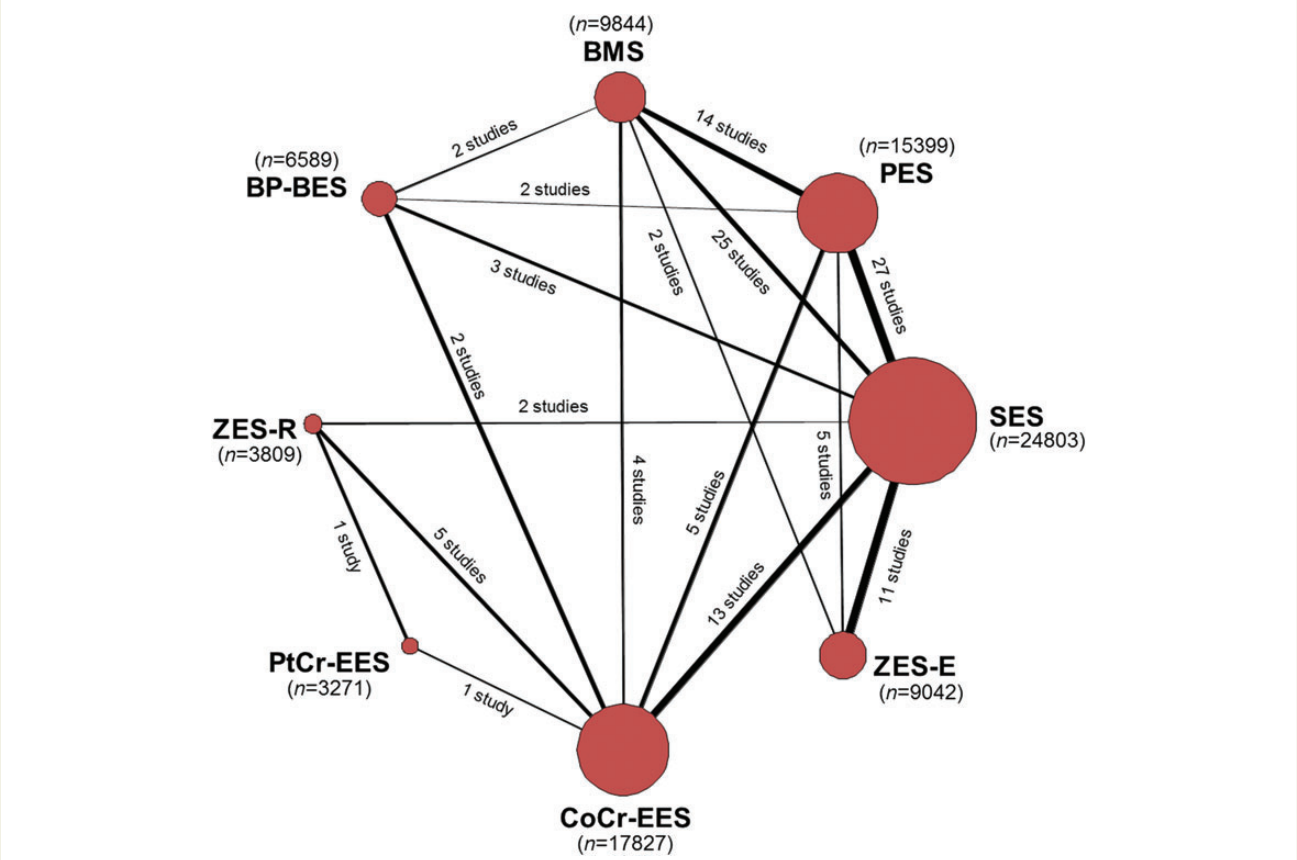

Figure 2 Network plot of included trials. Each stent is represented by a node. The size of the node is proportional to the sample size randomized to each stent, while the thickness of the line connecting the nodes is to the total randomized sample size in each pairwise treatment comparison. BMS, bare metal stents; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; ZES-E, endeavor zotarolimus-eluting stents; CoCr-EES, cobalt–chromium everolimus-eluting stents; PtCr-EES, platinum–chromium everolimus-eluting stents; ZES-R, resolute zotarolimus-eluting stents; BP-BES, biodegradable-polymer-biolimus-eluting stents.

Risk of bias within studies

Figure 3 shows the risk of bias graph illustrating the proportion of studies with each of the judgments ('Yes', 'No', 'Unclear') for each entry in the Cochrane Collaboration's tool. A full description of the summary of risk of bias judgments of each study is available in Supplementary material online, *Figure S1*. All of the included trials were RCTs. Allocation concealment was adequate in 86 out of 113 trials. A double-blind design was adopted in some studies, especially those done in early period (2003–06), while no studies since 2007 included double-blinding. Two-thirds of the studies described adequate blinding of clinical event adjudication.

Definite or probable stent thrombosis

The primary safety endpoint of this study, definite or probable ST within 1 year, was available from 77 studies including 75 484 patients. *Figure 4* shows the estimated OR of each stent compared with each other driven from Bayesian random effects model. All DESs showed significant or at least numerically lower risk of definite or probable ST compared with BMS, with significant reductions seen in BP-BES, SES, CoCr-EES, and PtCr-EES. In individual comparisons, SES was superior to PES, while CoCr-EES was superior to most other DES including PES, ZES-E, SES, and BP-BES. Although newer-generation DP DES such as ZES-R and PtCr-EES showed promising results, their credible intervals were wide and thus, none of the individual comparisons with other DES reached statistical significance. The rank of each stent was as follows (rankograms shown in Supplementary material online, *Figure S2*): (PtCr-EES ÷ CoCr-EES) > (ZES-R ÷ SES ÷ BP-BES) > (ZES-E ≥ PES ≥ BMS).

When the analysis was extended up to the longest follow-up available, a total of 84 studies comprising 79 239 patients were included. Seven studies that were not included in the 'within 1 year' analysis were added in this analysis since they reported clinical outcomes occurring beyond 1 year only in the literature. The results were mostly similar except for the superiority of ZES-E and BP-BES over PES, and CoCr-EES over ZES-E (*Figure 5*, Supplementary material online, *Figure S3*). The superiority of SES over BMS lost statistical significance in the long-term follow-up, as the risk of very late ST was significantly higher with SES. CoCr-EES maintained excellent performance with respect to any classification of ST relative to onset timing, while BP-BES was comparable with CoCr-EES in terms of late and/or very late ST (*Figure 5*, Supplementary material online, *Figure S4–S7*).

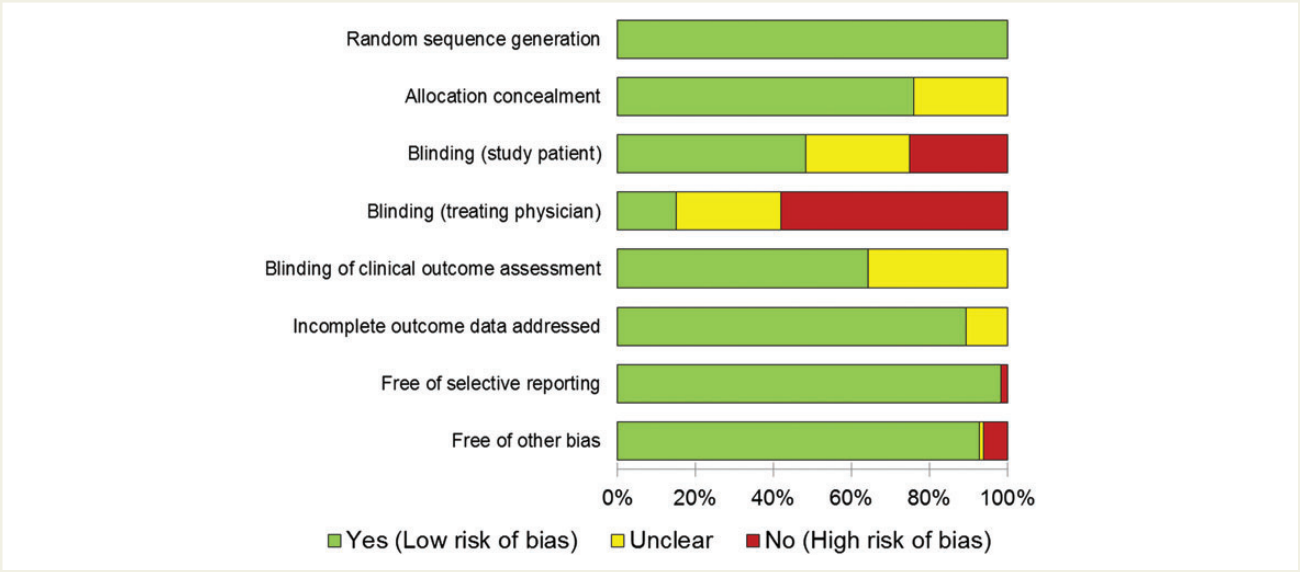

Figure 3 Risk of bias assessment. Risk of bias of each included trial was assessed with the Cochrane Collaboration's tool. This 'risk of bias graph' illustrates the proportion of studies with each of the judgements for each entry in the tool. Green represents 'yes (low risk of bias)'; yellow, 'unclear'; red, 'no (high risk of bias)'.

Definite stent thrombosis

A total of 77 studies with 73 255 contributed to the analysis of definite ST within 1 year. As shown in *Figure 6*, while SES was superior to BMS, CoCr-EES showed significantly lower risk of definite ST than most of the study stents including BMS, ZES-E, ZES-R, PES, BP-BES, and SES. The rank of each stent was as follows: CoCr-EES > (PtCr-EES ≥ SES ≥ BP-BES ≥ PES ≥ ZES-R ≥ ZES-E ≥ BMS). CoCr-EES showed the lowest risk of ST regardless of the timing of ST (early, late, and very late ST) and the duration of follow-up (longer-term analysis) (Supplementary material online, *Figure S8*).

Test for inconsistency

The superiority of BP-BES to BMS was consistently observed in both direct and indirect estimates of the comparison, and so was the superiority of CoCr-EES to BP-BES ($I^2 = 0\%$ for definite or probable ST, and definite ST) (*Figure 7*). All other pairwise estimates were consistent across direct and indirect evidence except for the comparison between BP-BES vs. SES ($I^2 = 58\%$ for definite or probable ST, 0% for definite ST). Inconsistency plot for triangular loops is shown in Supplementary material online, *Figure S9*.

Efficacy endpoints

Figure 8 shows the estimated pooled ORs with 95% credible intervals with regard to TLR within 1 year (87 studies including 68 234 patients). All DESs were associated with reduced risk of repeat revascularization compared with BMS. Biodegradable-polymer biolimus-eluting stents, CoCr-EES, and SES, in addition, were shown to have a lower risk of TLR than ZES-E, and PES. The efficacy rank of each stent was as follows: (BP-BES ≥ CoCr-EES ≥ SES ≥ PtCr-EES ≥ ZES-R) > (PES ≥ ZES-E) > BMS. Meta-analysis for TVR within 1 year is shown in Supplementary material online, *Figure S10*.

Other safety endpoints

There was no statistical difference for any comparison between study stents in terms of all-cause death, or cardiac death (Supplementary material online, *Figure S11–S12*). In terms of MI within 1 year, PtCr-EES, ZES-R, CoCr-EES, ZES-E, SES, and BP-BES were shown to be superior to BMS, while PtCr-EES, ZES-R, CoCr-EES, ZES-E, and SES were to PES (*Figure 9*).

Sensitivity analysis

A sensitivity analysis was done for studies with low risk of bias. Entries of blinding of patients and physicians were not considered, since only 17 studies were designed double-blinded. After excluding studies with any potential risk of bias (unclear or no) in the other six entries assessed according the Cochrane Collaboration's tool, 49 trials with 61 411 patients contributed to the analysis (Supplementary material online, *Figure S13*). The results did not change to a significant degree except for the emergence of superiority of SES over ZES-E (Supplementary material online, *Figure S14*). Other sensitivity analyses after excluding studies with diabetic patients, studies with ST-segment elevation MI, or studies with mandatory angiographic follow-up with regard to any endpoints showed similar results with the main analysis (Supplementary material online, *Table S4*).

Discussion

To the best of our knowledge, this study is the most updated and comprehensive network meta-analysis comprising contemporary coronary stents including the biodegradable-polymer DES. The major findings of this study are as follows: (i) All DESs significantly or at least numerically reduced the risk of definite or probable ST up to 1 year compared with BMS. (ii) In individual comparisons,

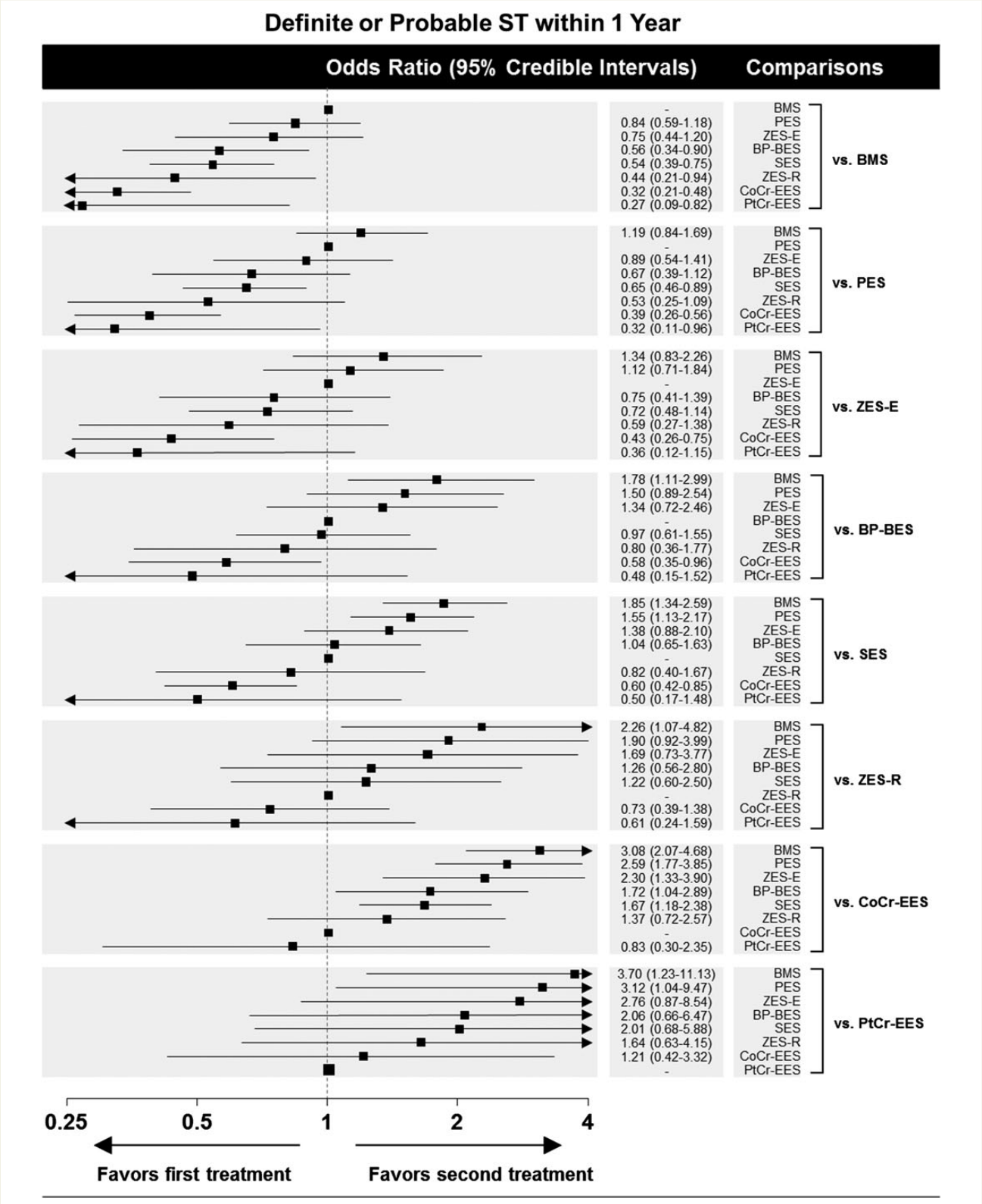

Figure 4 Definite or probable stent thrombosis within 1 year. The squares and horizontal lines indicate pairwise odds ratios and their 95% credible intervals for definite or probable stent thrombosis within 1 year estimated with multiple-treatment meta-analysis. BMS, bare metal stents; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; ZES-E, endeavor zotarolimus-eluting stents; CoCr-EES, cobalt–chromium everolimus-eluting stents; PtCr-EES, platinum-chromium everolimus-eluting stents; ZES-R, resolute zotarolimus-eluting stents; BP-BES, biodegradable-polymer-biolimus-eluting stents.

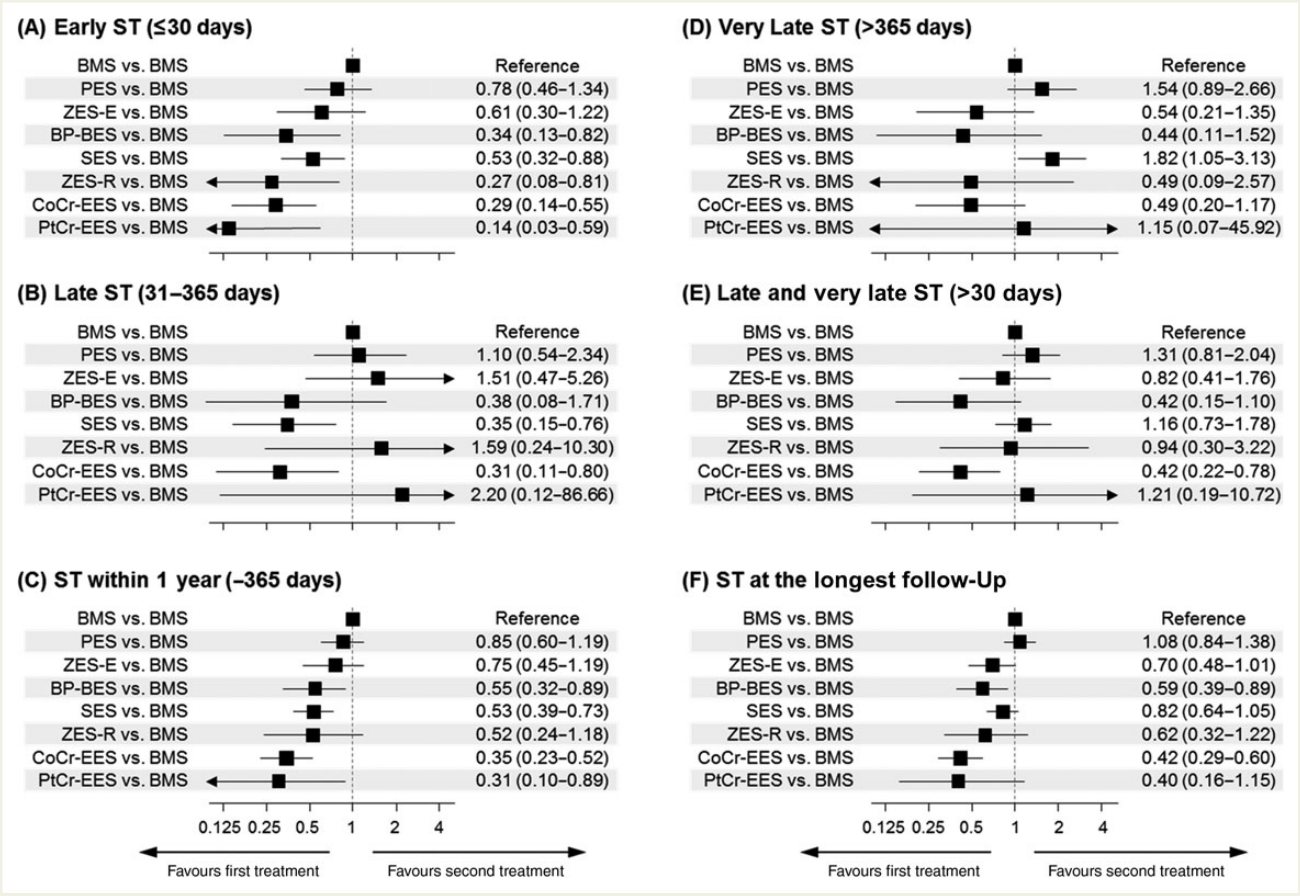

Figure 5 Definite or probable stent thrombosis with reference to bare metal stent. The squares and horizontal lines indicate odds ratios and their 95% credible intervals for definite or probable stent thrombosis estimated with multiple-treatment meta-analysis. All comparisons are presented with reference to bare metal stent. ST, stent thrombosis; BMS, bare metal stents; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; ZES-E, endeavor zotarolimus-eluting stents; CoCr-EES, cobalt–chromium everolimus-eluting stents; PtCr-EES, platinum–chromium everolimus-eluting stents; ZES-R, resolute zotarolimus-eluting stents; BP-BES, biodegradable-polymer-biolimus-eluting stents.

CoCr-EES was the safest stent regardless of the timing of ST or the duration of follow-up, showing significantly reduced risk of ST compared with BMS, PES, ZES-E, SES, and BP-BES. (iii) Biodegradable-polymer-biolimus-eluting stents also showed significantly reduced risk of definite or probable ST compared with BMS. However, BP-BES was not superior and in fact was inferior to CoCr-EES regarding risk of ST, mainly due to an increase in the risk of early ST. (iv) All DESs reduced the need for repeat revascularization compared with BMSs. In particular, all new generation stents, ZES-R, PtCr-EES, SES, CoCr-EES, and BP-BES, showed comparable performance.

Our finding that BMS was the worst among all stents in terms of ST may seem contrary to the common perception of increased thrombogenecity by polymer coatings of DES.[4,5] However, the mechanism behind ST may be different for short- vs. long-term events. In terms of outcomes within 1 year, all of the DES compared with BMS significantly reduced or at least tended to reduce the risk of definite or probable as well as definite ST. However, for very late ST occurring after 1 year, early-generation DP DES such as SES and PES were inferior to BMS, while newer-generation DES including CoCr-EES, ZES-R, ZES-E, and BP-BES maintained the tendency of superiority over BMS. These findings may be explained by a new concept on ST proposed by a recent study by Kolandaivelu *et al.*[22] They showed using an *ex vivo* model that strut thickness and geometry along with optimal positioning are critical factors in reducing thrombosis risk. It was also shown that well-designed drug/polymer coatings do not inherently increase acute ST, but rather serve as corrosive barriers and reduce thrombosis. A combination of stent geometry, thin strut, biocompatible polymer, and optimal drug coating may have contributed to the safety profile of newer-generation DES.

It has been shown in previous randomized trials that CoCr-EES reduced the risk of ST compared with PES and BMS.[23–25] Direct comparison meta-analyses suggested a risk reduction in definite ST with CoCr-EES compared with SES.[11,26] In this study, we showed that the reduction in the risk of ST occurs not only in the short term but is maintained through long-term follow-up for CoCr-EES. Platinium–chromium everolimus-eluting stents also showed promising results with significantly lower definite or probable ST within 1 year compared with BMS, but more data on very late ST are required.

The safety profile of BP-BES seen in the present analysis is interesting. Designed to improve long-term safety, BP-BES employed a

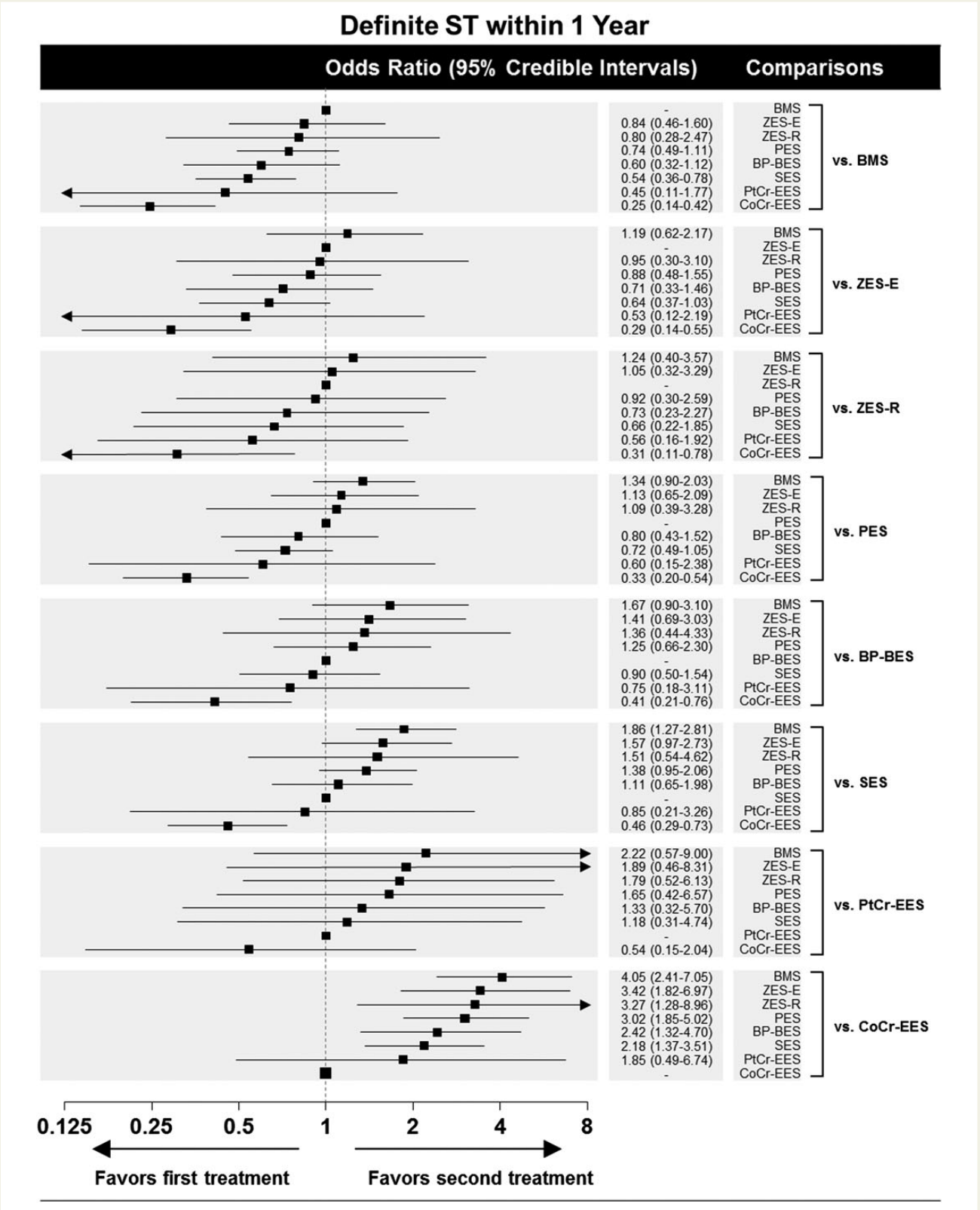

Figure 6 Definite stent thrombosis within 1 year. The squares and horizontal lines indicate pairwise odds ratios and their 95% credible intervals for definite stent thrombosis within 1 year estimated with multiple-treatment meta-analysis. BMS, bare metal stents; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; ZES-E, endeavor zotarolimus-eluting stents; CoCr-EES, cobalt–chromium everolimus-eluting stents; PtCr-EES, platinum–chromium everolimus-eluting stents; ZES-R, resolute zotarolimus-eluting stents; BP-BES, biodegradable-polymer-biolimus-eluting stents.

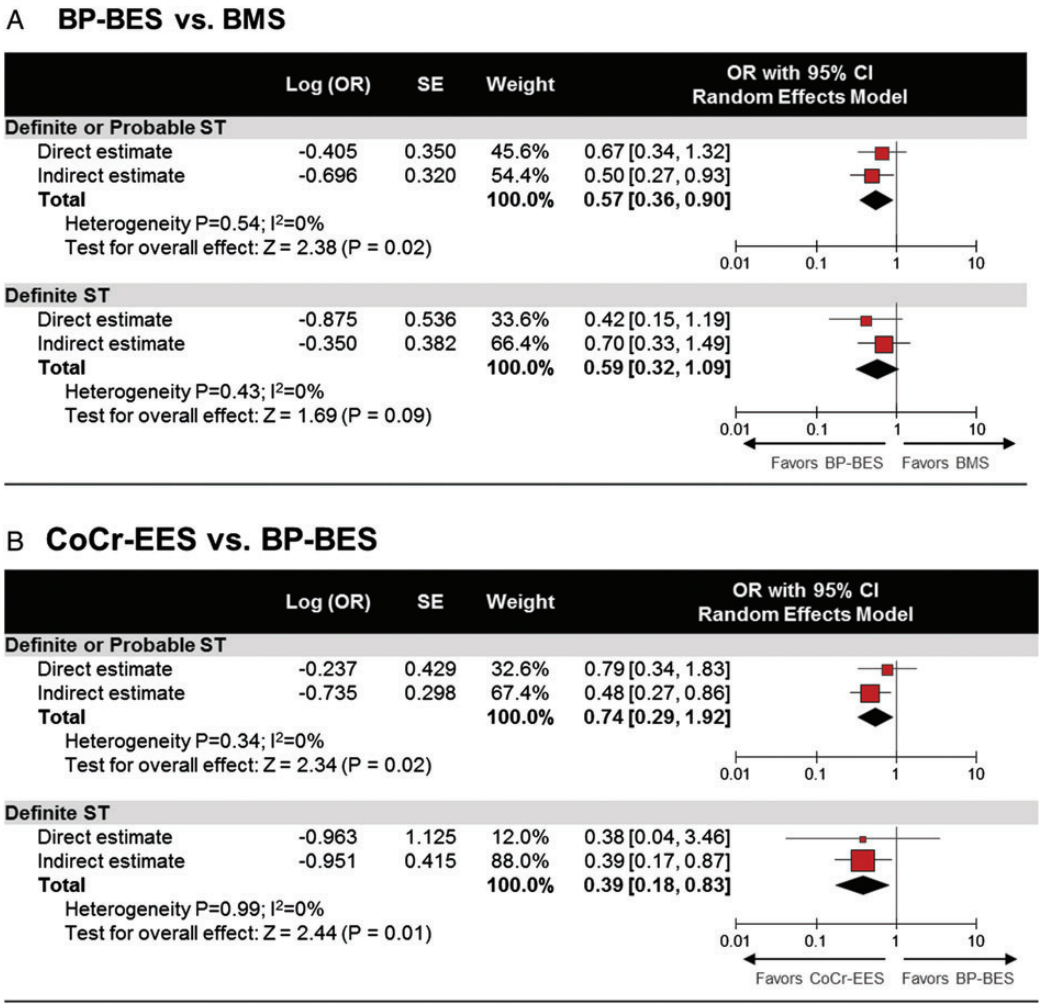

Figure 7 Consistency between direct and indirect estimates of stent thrombosis comparing (*A*) BP-BES vs. BMS and (*B*) CoCr-EES vs. BP-BES. BMS, bare metal stents; CoCr-EES, cobalt–chromium everolimus-eluting stents; BP-BES, biodegradable-polymer-biolimus-eluting stents; OR, odds ratio; SE, standard error.

bioabsorbable polymer (poly-lactic acid), which is known to be absorbed in the body within a few months.[27,28] In this study, BP-BES reduced the risk of definite or probable ST compared with BMS. In the COMFORTABLE-AMI trial, in which patients with ST-segment elevation MI were randomized to BP-BES or BMS with an identical design (Gazelle), the occurrence of ST at 1 year was numerically lower in the BP-BES arm than in the BMS arm, although the difference did not reach statistical significance.[29] In the present analysis, the combination of the indirect and direct evidences consistently showed statistically significant differences in safety compared with BMS. The safety feature of BP-BES was prominent especially in the long-term period: the point estimates of late and very late ST compared against BMS were almost comparable with those of CoCr-EES. As most trials comparing BP-BES were done recently and data on very late ST was mostly derived from a single study,[31] long-term outcomes from other studies are needed.

When comparing the individual stents, BP-BES was not superior and was in fact inferior to CoCr-EES in terms of definite or probable ST as well as definite ST. These findings are contradictory to a recent meta-analysis that showed a trend towards lower risk of ST of BP-DES compared with DP-DES.[30] However, in that study, the BP-DES was not only BP-BES, but also included two different types of BP-SES, and the DP-DES arm consisted of mostly first-generation DES. We believe for a fair comparison only the BP-BES should be compared against the best DP-DES, the CoCr-EES. In our analysis, when ST was analysed separately according to the time classification, it was obvious that the difference was mostly due to increase in early ST (within 30 days). The finding can be also be explained by the new concepts on ST as described above.[22] Biodegradable-polymer-biolimus-eluting stents (BioMatrix®, Biosensors; Nobori®, Terumo), whose platform is made of stainless steel, has relatively thick strut (120 μm), and the abluminal polymer coating is 10 μm thick. In comparison, CoCr-EES has thinner strut thickness of 81 μm, and a polymer coating as thin as 7.8 μm. This study suggests that rather than the biodegradability of the polymer itself, the optimal combination of stent geometry, strut thickness, polymer coating

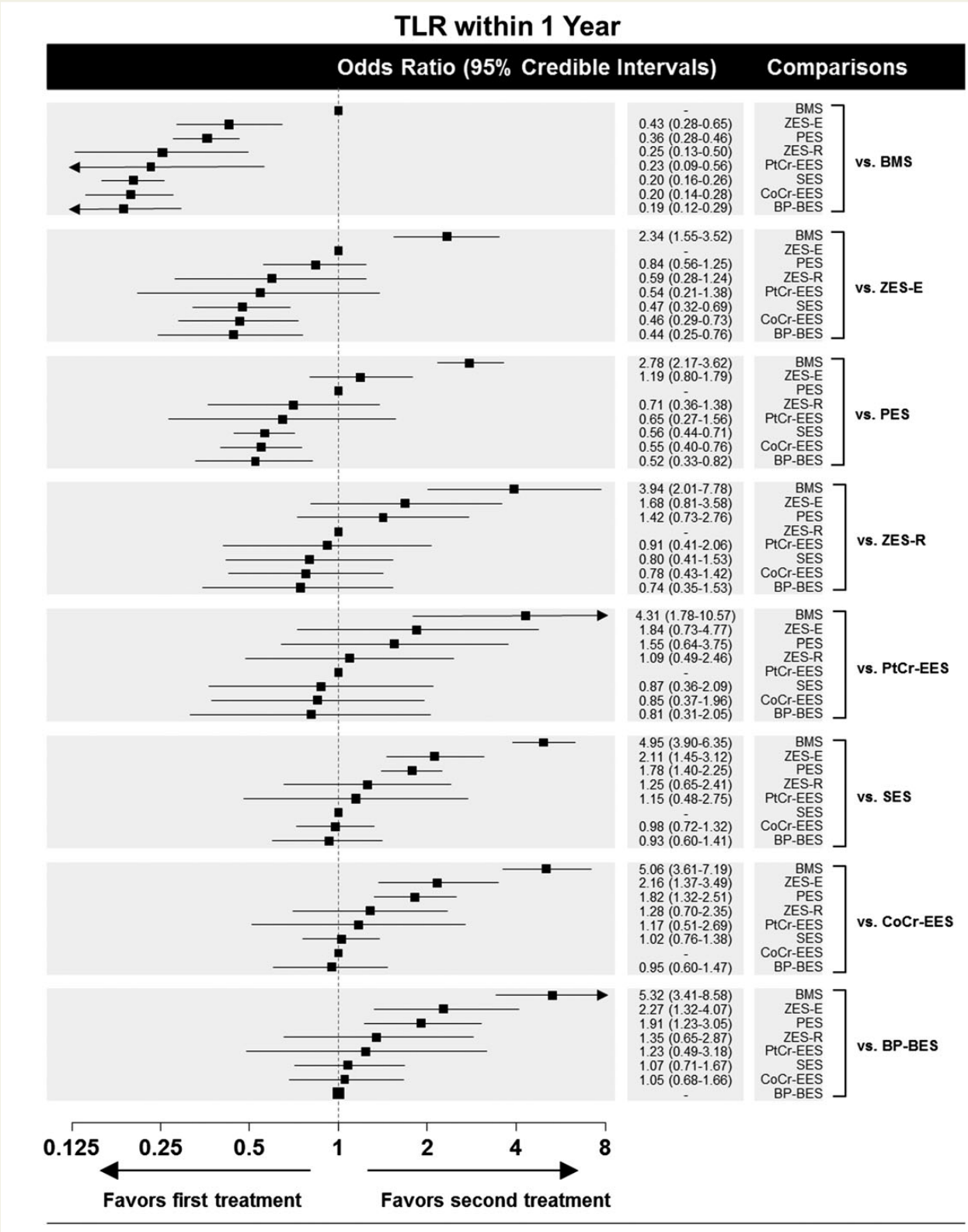

Figure 8 Target lesion revascularization within 1 year. The squares and horizontal lines indicate pairwise odds ratios and their 95% credible intervals for target lesion revascularization within 1 year estimated with multiple-treatment meta-analysis. BMS, bare metal stents; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; ZES-E, endeavor zotarolimus-eluting stents; CoCr-EES, cobalt–chromium everolimus-eluting stents; PtCr-EES, platinum–chromium everolimus-eluting stents; ZES-R, resolute zotarolimus-eluting stents; BP-BES, biodegradable-polymer-biolimus-eluting stents.

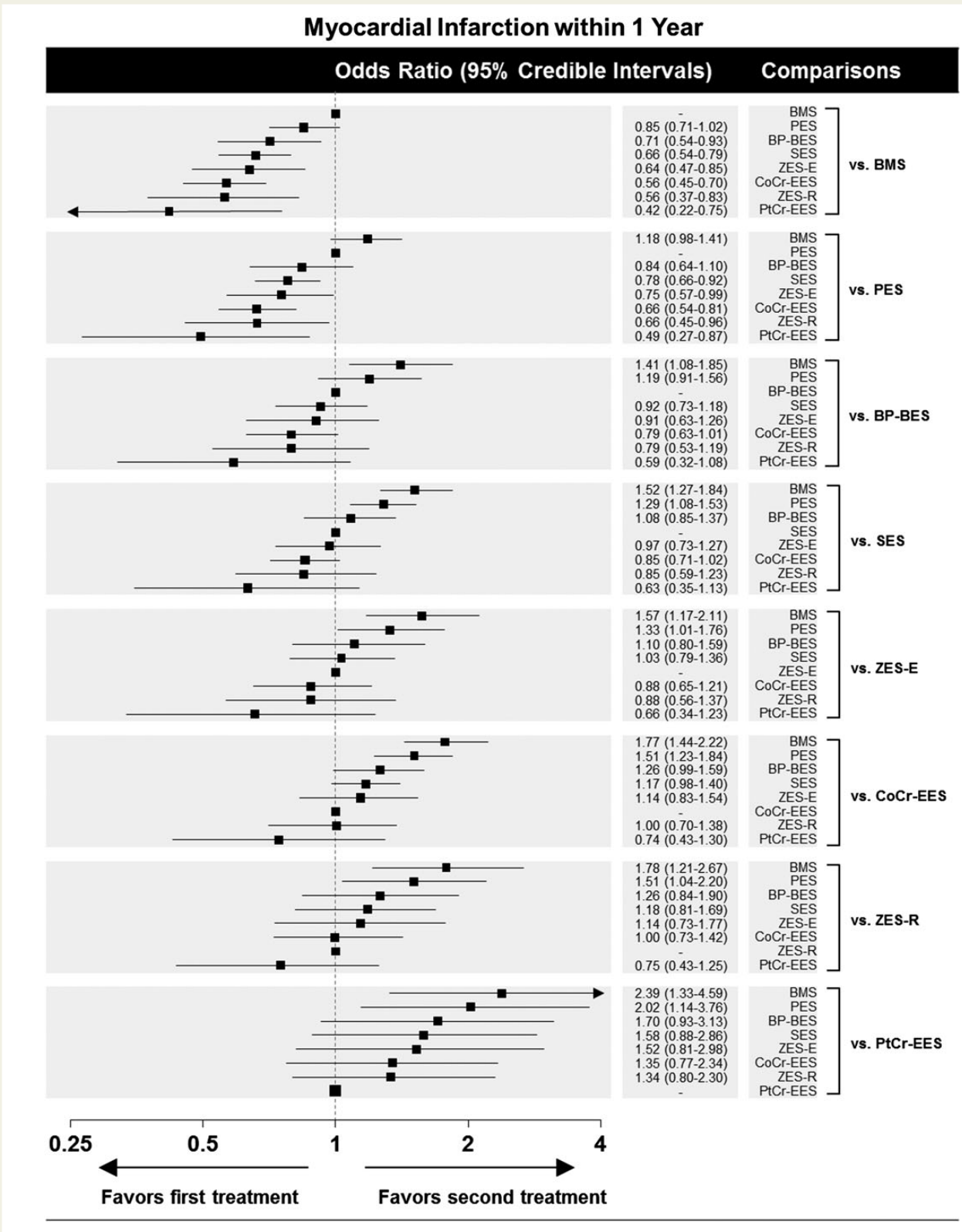

Figure 9 Myocardial infarction within 1 year. The squares and horizontal lines indicate pairwise odds ratios and their 95% credible intervals for myocardial infarction within 1 year estimated with multiple-treatment meta-analysis. BMS, bare metal stents; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; ZES-E, endeavor zotarolimus-eluting stents; CoCr-EES, cobalt–chromium everolimus-eluting stents; PtCr-EES, platinum–chromium everolimus-eluting stents; ZES-R, resolute zotarolimus-eluting stents; BP-BES, biodegradable-polymer-biolimus-eluting stents.

technology, and drug may play the pivotal role in the occurrence of early-phase ST. Future efforts to achieve better safety of BP-DES need to be focused on reducing the stent strut and polymer thickness.

Unfortunately, newly developed BP-DESs, such as BP-EES (SYNERGY™, Boston Scientific) and BP-SES (OSIRO®, BIOTRONIK), were not included in this meta-analysis because of their limited data.[13,32] SYNERGY has improved stent platform with thinner strut thickness and lighter polymer coating. More recently, the OSIRO stent, whose stent strut is even thinner (60 μm), also showed promising results. It will be interesting to see whether the combination of improvements in stent design combined with biodegradable polymer would lead to better short- and long-term safety.

A network meta-analysis with a similar design has been published recently by Palmerini *et al.*[9] One of the major differences is that in the present analysis, data regarding BP-BES were included, and that the statistical power regarding newer-generation DESs such as PtCr-EES and ZES-R is significantly increased. Superiority of PtCr-EES over BMS in terms of definite or probable ST was not seen in the previous work. In addition, the findings regarding BP-BES provide important insights on future stent design. Another merit of this study is that a variety of clinical outcomes were comprehensively analysed along with ST. In particular, we confirmed the comparable efficacy of all of the newer generation DES.

Limitations

First, this meta-analysis comprising 112 randomized trials inherently shares the limitations of each trial. However, sensitivity analysis excluding studies with any potential risk of bias showed consistent results with the main analysis. In addition, no remarkable inconsistency was found between direct and indirect evidence for most of the comparisons. Secondly, each study had different designs including enrolment criteria, follow-up protocols, and recommendations on medications. While earlier studies recommended short-term dual antiplatelet treatment and mandatory angiographic follow-up, dual antiplatelet therapy for at least 6–12 months and no mandatory follow-up angiography were common in recent trials. In addition, more potent antiplatelet agents, such as prasugrel and ticagrelor, were widely used in recent trials. However, we still lack evidence that longer and more potent antiplatelet treatment has an interaction with the performance any specific stent type. In addition, sensitivity analyses excluding studies with specific enrollment criteria or mandatory angiographic follow-up also showed consistent results. Thirdly, many different types of BMS were regarded as a single domain of comparator in this meta-analysis. Fourthly, each study had different durations of clinical follow-up. For this reason, we performed separate analyses with outcomes within 1 year, and with longer-term follow-up. In addition, we reported the risk of ST in detail according to the classification relative to the onset timing. Fifthly, newer-generation DESs such as ZES-R, and PtCr-EES had restricted sample size, limiting full appreciation of their relative efficacy and safety.

Conclusion

All existing DESs reduced the risk of repeat revascularization compared with BMS, and all but PES reduced the risk of MI. SES, PtCr-EES, BP-BES, and CoCr-EES significantly reduced the risk of definite or probable ST up to 1 year compared with BMS. While PtCr-EES compared with BMS reduced the risk of early ST only, SES was superior within 1 year but inferior after 1 year to BMS regarding the risk of ST. In contrast, CoCr-EES reduced or tended to reduce the risk of ST, regardless of time after DES implantation, showing the lowest risk of ST of all stents. Our results suggest that not only the biodegradability of polymer, but the optimal combination of stent alloy, design, strut thickness, polymer, and drug all combined determine the safety of DES.

Supplementary material

Supplementary Material is available at *European Heart Journal* online.

Funding

This study was supported by a grant from the Seoul National University Hospital Research Fund, a grant from the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean Government (2010-0020258).

Conflict of interest: K.H.S. reports receiving research grants and honorarium for lectures from Boston Scientific Korea and Medtronic Korea. None of the other authors has any conflict of interest to declare. The funding source of the study had no role in study design, data collection, monitoring, analysis, interpretation, or writing of the manuscript.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;**346**:1773–1780.
2. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;**350**:221–231.
3. Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J* 2010;**31**:2501–2555.
4. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;**364**:1519–1521.
5. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C, Investigators B-L. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;**48**:2584–2591.
6. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004;**109**:701–705.
7. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;**48**:193–202.
8. Nakazawa G, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation* 2008;**118**:1138–1145.
9. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabate M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012;**379**:1393–1402.

10. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, Bhatt DL, Slater J. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117,762 patient-years of follow-up from randomized trials. *Circulation* 2012;**125**:2873–2891.
11. Park KW, Kang SH, Velders MA, Shin DH, Hahn S, Lim WH, Yang HM, Lee HY, Van Boven AJ, Hofma SH, Kang HJ, Koo BK, Oh BH, Park YB, Kandzari DE, Kim HS. Safety and efficacy of everolimus- versus sirolimus-eluting stents: a systematic review and meta-analysis of 11 randomized trials. *Am Heart J* 2013;**165**:241–250 e4.
12. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;**17**:279–301.
13. Meredith IT, Verheye S, Dubois CL, Dens J, Fajadet J, Carrie D, Walsh S, Oldroyd KG, Varenne O, El-Jack S, Moreno R, Joshi AA, Allocco DJ, Dawkins KD. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. *J Am Coll Cardiol* 2012;**59**:1362–1370.
14. Kereiakes DJ, Cannon LA, Feldman RL, Popma JJ, Magorien R, Whitbourn R, Dauber IM, Rabinowitz AC, Ball MW, Bertolet B, Kabour A, Foster MC, Wang JC, Underwood P, Dawkins KD. Clinical and angiographic outcomes after treatment of de novo coronary stenoses with a novel platinum chromium thin-strut stent: primary results of the PERSEUS (Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System) trial. *J Am Coll Cardiol* 2010;**56**:264–271.
15. Kelbaek H, Thuesen L, Helqvist S, Clemmensen P, Klovgaard L, Kaltoft A, Andersen B, Thuesen H, Engstrom T, Botker HE, Saunamaki K, Krusell LR, Jorgensen E, Hansen HH, Christiansen EH, Ravkilde J, Kober L, Kofoed KF, Terkelsen CJ, Lassen JF, Investigators D. Drug-eluting versus bare metal stents in patients with st-segment-elevation myocardial infarction: eight-month follow-up in the Drug Elution and Distal Protection in Acute Myocardial Infarction (DEDICATION) trial. *Circulation* 2008;**118**:1155–1162.
16. Mehilli J, Pache J, Abdel-Wahab M, Schulz S, Byrne RA, Tiroch K, Hausleiter J, Seyfarth M, Ott I, Ibrahim T, Fusaro M, Laugwitz KL, Massberg S, Neumann FJ, Richardt G, Schomig A, Kastrati A, Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts I. Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomised controlled superiority trial. *Lancet* 2011;**378**:1071–1078.
17. Wang B, Han YL, Jing QM, Wang SL, Ma YY, Wang G, Luan B, Li Y, Wang ZL, Wang DM. Therapeutic effect and safety of drug eluting stent for patients with acute ST-elevation anterior wall myocardial infarction by left anterior descending artery occluded abruptly. *Zhonghua Yi Xue Za Zhi* 2010;**90**:2099–2102.
18. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaborations 2011, available from http://www.cochrane-handbook.org/.
19. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research C. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344–2351.
20. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;**23**:3105–3124.
21. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Stat Sci* 1992;**7**:457–472.
22. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, Coleman L, Wong GK, Edelman ER. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation* 2011;**123**:1400–1409.
23. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010;**362**:1663–1674.
24. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 2010;**375**:201–209.
25. Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tespili M, den Heijer P, Bethencourt A, Vazquez N, Gomez-Hospital JA, Baz JA, Martin-Yuste V, van Geuns RJ, Alfonso F, Bordes P, Tebaldi M, Masotti M, Silvestro A, Backx B, Brugaletta S, van Es GA, Serruys PW. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012;**380**:1482–1490.
26. de Waha A, Cassese S, Park DW, Burzotta F, Byrne RA, Tada T, King LA, Park SJ, Schomig A, Kastrati A. Everolimus-eluting versus sirolimus-eluting stents: an updated meta-analysis of randomized trials. *Clin Res Cardiol* 2012;**101**:461–467.
27. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008;**372**:1163–1173.
28. Chevalier B, Serruys PW, Silber S, Garcia E, Suryapranata H, Hauptmann K-E, Wijns W, Schuler G, Fath-Ordoubadi F, Worthley S, Thuesen L, Meredith IT, Bressers M, Nagai H, Paunovic D. Randomised comparison of Nobori™, biolimus A9-eluting coronary stent with a Taxus®, paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the Nobori 1 trial. *EuroIntervention* 2007;**2**:426–434.
29. Raber L, Kelbaek H, Ostojic M, Baumbach A, Heg D, Tuller D, von Birgelen C, Roffi M, Moschovitis A, Khattab AA, Wenaweser P, Bonvini R, Pedrazzini G, Kornowski R, Weber K, Trelle S, Luscher TF, Taniwaki M, Matter CM, Meier B, Juni P, Windecker S. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA* 2012;**308**:777–787.
30. Lupi A, Rognoni A, Secco GG, Lazzero M, Nardi F, Fattori R, Bongo AS, Agostoni P, Sheiban I. Biodegradable versus durable polymer drug eluting stents in coronary artery disease: Insights from a meta-analysis of 5834 patients. *Eur J Prev Cardiol* 2012; [Epub ahead of print].
31. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, van Es GA, Meier B, Windecker S, Juni P. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011;**378**:1940–1980.
32. Windecker S, Witzenbichler B, Stangl K, Slagboom T, Neumann F-J, Lefévre T, Ruiz-Salmeron R, Sabaté M, Piot C, Richardt G, Merkely B, Goicolea J, Bilger J, Schneider H, Barragan P, Cook S, Erne P, Waksman R, Haude M. Safety and clinical performance of the drug- eluting orsiro stent in the treatment of subjects with single de novo coronary artery lesions-II (BIOFLOW-II). *EuroPCR* 2013; Paris; 2013.