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Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis

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Abstract

Objectives To investigate the safety and efficacy of durable polymer drug eluting stents (DES) and biodegradable polymer biolimus eluting stents (biolimus-ES).

Design Network meta-analysis of randomised controlled trials.

Data sources and study selection Medline, Google Scholar, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) database search for randomised controlled trials comparing at least two of durable polymer sirolimus eluting stents (sirolimus-ES) and paclitaxel eluting stents (paclitaxel-ES), newer durable polymer everolimus eluting stents (everolimus-ES), Endeavor and Resolute zotarolimus eluting stents (zotarolimus-ES), and biodegradable polymer biolimus-ES.

Primary outcomes Safety (death, myocardial infarction, definite or probable stent thrombosis) and efficacy (target lesion and target vessel revascularisation) assessed at up to one year and beyond.

Results 60 randomised controlled trials were compared involving 63 242 patients with stable coronary artery disease or acute coronary syndrome treated with a DES. At one year, there were no differences in mortality among devices. Resolute and Endeavor zotarolimus-ES, everolimus-ES, and sirolimus-ES, but not biodegradable polymer biolimus-ES, were associated with significantly reduced odds of myocardial infarction (by 29-34%) compared with paclitaxel-ES. Compared with everolimus-ES, biodegradable polymer biolimus-ES were associated with significantly increased odds of myocardial infarction (by 29%), while Endeavor zotarolimus-ES and paclitaxel-ES were

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associated with significantly increased odds of stent thrombosis. All investigated DES were similar with regards to efficacy endpoints, except for Endeavor zotarolimus-ES and paclitaxel-ES, which were associated with significantly increased the odds of target lesion and target vessel revascularisations compared with other devices. Direction of results beyond one year did not diverge from the findings for up to one year follow-up. Bayesian probability curves showed a gradient in the magnitude of effect, with everolimus-ES and Resolute zotarolimus-ES offering the highest safety profiles.

Conclusions The newer durable polymer everolimus-ES and Resolute zotarolimus-ES and the biodegradable polymer biolimus-ES maintain the efficacy of sirolimus-ES; however, for safety endpoints, differences become apparent, with everolimus-ES and Resolute zotarolimus-ES emerging as the safest stents to date.

Introduction

The first generation of coronary drug eluting stents (DES) has considerably reduced the need for repeat revascularisation compared with bare metal stents (BMS) and has led to their widespread use worldwide. Concerns have emerged, however, regarding late and very late thrombotic events, which in turn are associated with a high rate of death and myocardial infarction.[1][2] Such events have been attributed to incomplete re-endothelialisation caused by drug induced inhibition of endothelial cell proliferation, stent malapposition, accelerated neoatherosclerosis, and, importantly, polymer induced prolonged vessel wall inflammation.[3]

To improve the safety of first generation DES, new devices have been developed that use either biocompatible durable polymers combined with new metal alloys or biodegradable polymers combined with stainless steel platforms; both have been extensively tested in randomised controlled trials. The second generation durable polymer everolimus eluting stent (everolimus-ES) has been found to be safer than BMS and first generation DES.[4-6] On the other hand, two non-inferiority trials comparing the most investigated biodegradable polymer device, the biolimus eluting stent (biolimus-ES), with the first generation sirolimus eluting stent (sirolimus-ES) have provided contradictory results at one year,[7][8] with one trial showing non-inferiority and the other failing to do so. Two other trials have shown non-inferiority of biodegradable polymer biolimus-ES compared with everolimus-ES.[9][10] None of these trials was powered for separate safety and efficacy endpoints.

In light of these findings, the safety and efficacy of the biodegradable polymer devices compared with first generation paclitaxel-eluting stents (paclitaxel-ES) and sirolimus-ES, and with second generation durable polymer Endeavor and Resolute zotarolimus eluting stents (zotarolimus-ES) and everolimus-ES, are currently unclear. We performed a comprehensive network meta-analysis of all relevant data published and presented to date to gain an evidence based understanding of the impact of each of these devices compared with first generation DES and among each other on major safety and efficacy outcomes.

Methods

Study design and endpoint selection

We compared the safety and efficacy of DES currently approved by the Food and Drug Administration (FDA)—that is, first and second generation durable polymer DES and biodegradable polymer biolimus-ES. We selected biodegradable polymer biolimus-ES from among the different types of biodegradable polymer stents for two reasons: they have the most robust trial data, and all available biodegradable polymer biolimus-ES

prototypes share a stainless steel platform, similar strut thickness, and the same abluminal biodegradable polymer (poly-L-lactic acid) and therefore are generally considered equivalent. We limited our analysis to biodegradable polymer biolimus-ES as the other non-FDA approved biodegradable polymer devices are characterised by a limited number or absence of comparisons and by different stent designs (in terms of strut thickness, antiproliferative agents, and polymers), resulting in a large degree of heterogeneity among existing devices. Because of the conflicting one year outcome results, our primary pre-specified analyses were for up to one year follow-up, though we also analysed longer follow-ups. To provide the most robust evidence, we included randomised controlled trials enrolling at least 100 patients and with a minimum follow-up of six months.

To appreciate the comparative effect of different types of DES within their class, we did not include BMS. We included first generation durable polymer sirolimus-ES and paclitaxel-ES; second generation durable polymer everolimus-ES, Endeavor zotarolimus-ES, and Resolute zotarolimus-ES; and biodegradable polymer biolimus-ES. Prespecified safety endpoints comprised overall mortality, myocardial infarction, and definite or probable stent thrombosis according to the definition criteria of the Academic Research Consortium.[11] Efficacy endpoints were target lesion and target vessel revascularisation.

Although there were a limited number of trials comparing biodegradable polymer biolimus-ES with first and second generation DES that reported results beyond one year, we additionally performed such an analysis (see appendix).

Data source and search strategy

We adhered to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses in healthcare interventions.[12] Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and Embase databases and www.tctmd.com, www.clinicaltrials.gov, www.clinicaltrialresults.org, and www.cardiosource.com websites were searched until 15 May 2013 for relevant randomised controlled trials; documents accessible through the FDA website were also scrutinised. The following keywords were used: "randomised trials", "drug-eluting stent", "sirolimus stent", "paclitaxel stent", "everolimus stent", "zotarolimus stent", "Endeavor zotarolimus-stent", "Resolute zotarolimus-stent", "biodegradable polymer stent", "bioabsorbable polymer stent", "biolimus stent". No language, date, or publication status restrictions were imposed. For each trial, we used the most updated or most inclusive data.

Data collection and quality assessment

Four investigators (EPN, KT, BC, MK) critically and independently evaluated identified trials with regard to patient population, treatment, protocol, and endpoint selection. Divergences were resolved by consensus. Two investigators (BC, KT) independently appraised the potential risk of bias in trials according to the Cochrane Collaboration guidelines (adequate sequence generation, allocation concealment, blinded adjudication of events)[12]; discrepancies were resolved by discussion with a third investigator (EPN). EK supervised the data collection process. Trials with high or unclear risk of bias for any of these components were regarded as trials with a high risk of bias.

Statistical analyses

We used network meta-analysis methods on all available treatment comparisons to provide the most comprehensive evidence, incorporating direct comparisons within trials between two treatments (such as A *v* B) and indirect comparisons from trials having one treatment in common (such as A *v* C using trials comparing A *v* B and B *v* C).[13] Outcome analyses were compared by odds ratios and 95% credible intervals with a bayesian hierarchical random effects model that takes into account multi-arm trials. We adopted the random effects rather than the fixed effects model as the most appropriate and conservative analysis to account for differences among trials. Additional sensitivity analyses were conducted by repeating the main computations with the fixed effect method and by excluding trials with high risk of bias.

To further corroborate the robustness of the data and make probability inferences, we generated bayesian probability curves for each stent with sirolimus-ES as reference; rather than focusing on a single probability value, these curves provide a ranking of competing stent treatments with respect to overall safety and efficacy. Median rates of safety and efficacy outcomes, with corresponding credible intervals, were also calculated from the original trials in the network meta-analysis.

Heterogeneity was defined as the variability of results across trials over and above chance, with $\tau^2 < 0.04$ indicating low level and $\tau^2 > 0.4$ a high level. Potential inconsistency of the network, defined as the variability of results across the direct and indirect evidence comparisons, was evaluated by the node split method and the relative bayesian P value, measuring agreement between direct and indirect evidence for each split node.[14] Inconsistency was additionally evaluated by inspection of the goodness of fit of the model to the data with residual deviance; the model was considered to provide an adequate fit when the mean of the residual deviance was similar to the number of data points of the model.

For outcomes beyond one year, given the variable length of follow-up for each of these trials, we used the rate of outcome per 100 patient years to obtain the log rate ratios of one stent compared with another. Rates per unit of time, rather than number of events, were deemed the most appropriate outcome measure for long term analyses as they incorporate the duration of the trials, which was variable. A Poisson regression model was fitted because this analysis explicitly exploits differences in follow-up among studies, thus maximising precision.[15] We assessed the extent of small study effects/publication bias by visual inspection of funnel plots. All analyses were based on non-informative previous findings for effect sizes and precision, which yield results that are comparable with those obtained from conventional statistical analyses. Convergence and lack of autocorrelation were checked and confirmed. In the bayesian framework, we regarded as significant results for which the credible intervals of the odds ratios or rate ratios did not include the unit value. Data were analysed according to the intention to treat principle. All analyses were conducted with WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) and MIX 2.0. Pro for Microsoft Excel, version 2.0.1.2, (BiostatXL, California, USA).

Results

Study selection and patient population

The flow diagram of the analysis, the full electronic Medline database search, and the inclusion/exclusion criteria and risk of bias of the included randomised controlled trials are shown in the appendix (fig S1, table S1, table S2). Sixty trials,[7-10 16-88] comprising 63 242 randomised patients, met the inclusion criteria and entered the final analysis. Table 1 shows information on stent comparators, duration of follow-up, and investigated populations⇓. In general, the included populations were high risk groups, with most trials enrolling patients with stable coronary artery disease (53.7%) and acute coronary syndromes (46.3%). Nearly all included trials were multicentre, with a low risk of bias. We excluded trials testing two stents eluting the same drug but differing in their design,[89-91] trials with different stent metal platforms,[92-96] post hoc analyses or substudies,[97-103] the BMS arm or polymer free arm of six trials with three arms,[16 17 38 39 54 104] studies that did not report clinical outcomes,[105] and arms that did not include treatments in the network. Figure 1 shows the evidence network of direct comparisons⇓.

One year outcomes

Safety profile

A total of 46 studies (n=48 908) contributed to the analysis of one year mortality. Second generation durable polymer DES and biodegradable polymer biolimus-ES were associated with mortality outcomes that did not differ significantly from those of paclitaxel-ES and sirolimus-ES (fig 2⇓), although median one year rates varied almost twofold, ranging from 1.80% to 3.05% (numerical gradient: Resolute zotarolimus-ES < everolimus-ES < sirolimus-ES < biodegradable polymer biolimus-ES < paclitaxel-ES < Endeavor zotarolimus-ES) (table 2⇓).

Forty six studies (n=51 578) contributed to the analysis of myocardial infarction by one year. Compared with paclitaxel-ES, all DES except biodegradable polymer biolimus-ES significantly reduced the odds of myocardial infarction, particularly Resolute zotarolimus-ES and everolimus-ES (odds ratio 0.66 (95% credible interval 0.46 to 0.91) and 0.67 (0.53 to 0.81), respectively) (fig 3⇓). Compared with sirolimus-ES, the odds of myocardial infarction were not significantly reduced by second generation DES, although everolimus-ES and Resolute zotarolimus-ES, unlike biodegradable polymer biolimus-ES, showed numerical reductions (fig 3⇓). When new generation DES were compared among each other, biodegradable polymer biolimus-ES yielded a significant increase in the odds of myocardial infarction (1.29, 1.02 to 1.69) compared with everolimus-ES. Lowest median rates of myocardial infarction were observed with Resolute zotarolimus-ES and everolimus-ES (table 2⇓). There was no evidence of high heterogeneity among trials for either death ($\tau^2 = 0.007$) or myocardial infarction ($\tau^2 = 0.008$) outcomes (supplementary table S3).

Compared with paclitaxel-ES and Endeavor zotarolimus-ES, median rates of stent thrombosis were approximately halved with everolimus-ES, Resolute zotarolimus-ES, biodegradable polymer biolimus-ES, and sirolimus-ES (~1% *v* ~2.5%) (table 2⇓). Everolimus-ES provided significant reductions of the odds of stent thrombosis at one year compared with paclitaxel-ES (0.37, 0.18 to 0.65) and a numerical reduction compared with sirolimus-ES (0.63, 0.33 to 1.06) (fig 4⇓); compared with everolimus-ES, Endeavor zotarolimus-ES yielded a significant increase in the odds of stent thrombosis (3.13, 1.15 to 8.89). There was no evidence of high heterogeneity among trials for stent thrombosis ($\tau^2 = 0.21$; appendix table S3).

Efficacy profile

Forty four trials including 49 527 patients contributed to the analysis of target lesion revascularisation at one year. Sirolimus-ES, everolimus-ES, biodegradable polymer

biolimus-ES, and Resolute zotarolimus-ES significantly reduced the odds of target lesion revascularisation by 46% to 87% compared with paclitaxel-ES, and by 59% to 160% compared with Endeavor zotarolimus-ES (fig 5⇓). Compared with sirolimus-ES, the same devices (everolimus-ES, Resolute zotarolimus-ES, and biodegradable polymer biolimus-ES) showed a similar degree of efficacy, without significant differences between them (fig 5). The median target lesion revascularisation rate was ~3% with everolimus-ES, biodegradable polymer biolimus-ES, sirolimus-ES, and Resolute zotarolimus-ES versus 5.92% with paclitaxel-ES and 7.52% with Endeavor zotarolimus-ES (table 2).⇓

Target vessel revascularisation results at one year were consistent with target lesion revascularisation outcomes. Compared with sirolimus-ES, everolimus-ES, Resolute zotarolimus-ES, and biodegradable polymer biolimus-ES provided similar efficacy profiles, whereas Endeavor zotarolimus-ES and paclitaxel-ES were associated with higher odds of target vessel revascularisation (odds ratio 1.67 (95% credible interval 1.08 to 2.58) and 1.47 (1.14 to 1.90), respectively) (fig 6⇓). There was no evidence of high heterogeneity among trials for both target lesion revascularisation ($\tau^2 = 0.13$) and target vessel revascularisation ($\tau^2 = 0.12$) outcomes (appendix table S3).

Posterior probabilities

Figure 7⇓ shows the posterior probability curves for each DES and for each outcome, with sirolimus-ES as reference treatment. These curves allow probability inferences associated with a specific threshold of risk (odds ratio). Thus, compared with sirolimus-ES, the curves show a probability of 65% for Resolute zotarolimus-ES to reduce the odds of mortality by at least 20% (odds ratio 0.80); a probability of 56% and 49% for Resolute zotarolimus-ES and everolimus-ES, respectively, to reduce the odds of myocardial infarction by at least 10% (0.90); and a probability of 81% with everolimus-ES and 51% with Resolute zotarolimus-ES to reduce the odds of stent thrombosis by at least 20%.

Compared with sirolimus-ES, Resolute zotarolimus-ES showed a 30% probability to reduce target vessel revascularisation and a 21% probability to reduce target lesion revascularisation by at least 20% (odds ratio 0.80), which was comparable with the 17% probability seen with everolimus-ES and biodegradable polymer biolimus-ES.

Outcomes beyond one year

Twenty four trials (n=38 097) contributed to the analysis of follow-up after one year (table 1)⇓. As with the one year mortality results, long term mortality with first and second generation durable polymer DES and with biodegradable polymer biolimus-ES did not differ significantly among the different DES (appendix table S4).

As seen with the one year outcomes, in comparison with paclitaxel-ES, Endeavor zotarolimus-ES, everolimus-ES, and Resolute zotarolimus-ES (similarly to sirolimus-ES) provided a 31-37% significant decrease in myocardial infarction. Everolimus-ES was associated with a significant 56% reduction of the rate of definite or probable stent thrombosis against first generation sirolimus-ES. Again, similar to the one year outcomes, compared with first generation paclitaxel-ES, newer generation DES offered significantly lower rates of revascularisation, except for Endeavor zotarolimus-ES, which was associated with a 110% increase compared with everolimus-ES (appendix table S4).

Overall fit of the model and additional analyses

Evaluation of the goodness of fit for the models showed adequate fit for the various analyses. Heterogeneity among the trials was low to moderate for all outcomes (appendix table S3). Sensitivity analyses based on the fixed effect model did not significantly change the results of the meta-analysis (appendix table S5). Visual inspection of funnel plots did not suggest any small study effects or publication bias (appendix figs S2A-D). Exclusion of trials with high risk of bias (appendix table S6) yielded results largely consistent with the overall results. Finally, there was no evidence of inconsistency between direct and indirect estimates, with bayesian P values ranging from 0.06 to 1 (appendix table S7).

Discussion

This large meta-analysis, with 63 242 patients, examined the safety and efficacy profile of second generation durable polymer drug eluting stents (DES) and biodegradable polymer biolimus-ES compared with first generation DES and with each other. Second generation durable polymer everolimus-ES and Resolute zotarolimus-ES, the first generation sirolimus-ES, and the biodegradable polymer biolimus-ES were similar to each other with regards to their efficacy and significantly better than Endeavor zotarolimus-ES and paclitaxel-ES with regards to coronary revascularisations. There was a safety gradient, with everolimus-ES and Resolute zotarolimus-ES resulting in lowest rates of death and myocardial infarction and, conversely, biodegradable polymer biolimus-ES, Endeavor zotarolimus-ES, and paclitaxel-ES being associated with significantly increased odds of myocardial infarction or stent thrombosis compared with everolimus-ES.

Possibly one of our most important findings was the significant increase in the odds of myocardial infarction with biodegradable polymer biolimus-ES compared with durable polymer everolimus-ES. To date, biodegradable polymer biolimus-ES have been perceived as safer than first generation sirolimus-ES and non-inferior to second generation everolimus-ES, mainly on the basis of results from individual trials powered only for composite endpoints of safety and efficacy.[7 9 10] We analysed single (instead of composite) endpoints of safety and have provided new insights suggesting that biodegradable polymer biolimus-ES is associated with similar (not higher) safety compared with the first generation sirolimus-ES and with a significantly higher rate of myocardial infarction compared with everolimus-ES. Indeed, the second generation durable polymer everolimus-ES and Resolute zotarolimus-ES were associated with the most favourable safety profile compared with not only the first generation durable polymer paclitaxel-ES but also the second generation Endeavor zotarolimus-ES and biodegradable polymer biolimus-ES. In a wider perspective, this study shows that among all devices compared, the durable polymer second generation everolimus-ES and Resolute zotarolimus-ES are the safest DES to date.

Our findings agree with those of two previous network meta-analyses[4 5] that compared first and second generation DES with bare metal stents (BMS). The current meta-analysis, however, substantially differs from the others by incorporating the most recent evidence from head-to-head DES comparison trials and forming the largest DES database ever analysed, with a total of 63 242 patients. We also included biodegradable polymer biolimus-ES, which are used mainly in Europe and Asia, thus providing a comprehensive overview of the most widely used DES in current clinical practice worldwide, not

compared so far within their class in such a scale for single safety and efficacy endpoints.

Although our exclusion of BMS might be perceived as a limitation, methodological and conceptual reasons dictated such a choice. For a network meta-analysis to provide the highest degree of precision, robust direct and indirect evidence is required. This would not have been possible if we had included BMS as, to date, the direct comparison between biodegradable polymer biolimus-ES and BMS is limited to a single trial, making indirect comparisons through this "weak" common link imprecise and meaningful conclusions difficult.[106] Moreover, the safety and efficacy of durable polymer "limus"-ES compared with BMS has already been clarified.[4 5] Our study differs in design and in the number of included patients from a previous meta-analysis of three randomised controlled trials comparing biodegradable devices with sirolimus-ES, which found a reduction of stent thrombosis associated with biodegradable stents.[107] The devices pooled in the previous study under the biodegradable group were in fact three distinct types, only one of which is a biodegradable polymer biolimus-ES; all of them represent differences in terms of the biodegradable polymer used, the eluted drug, and stent strut thickness. To provide the most robust conclusions and avoid heterogeneity that might arise by pooling stents with different properties, we decided to include only biodegradable polymer biolimus-ES in this analysis.

Safety

The safety of first generation DES has been extensively debated. The relatively high rates of stent thrombosis associated with these devices, a phenomenon that translates into increased rates of death or myocardial infarction, raised concerns regarding their widespread use, despite the clear efficacy benefits over BMS.[1 2] Further studies showed that the mechanisms of stent thrombosis after DES implantation are complex, with factors related to device design being of paramount importance. Indeed, the inflammation induced by the durable polymers of first generation DES could result in delayed healing and incomplete covering of stent struts by new and functional endothelium, with uncovered stent struts serving as a source for future episodes of stent thrombosis.[3] Other factors such as stent malapposition and mechanical tissue injury caused by stent struts during implantation, however, also play a role in stent thrombosis.[20] New generation DES have dealt with the limitations observed with first generation devices in different ways; biodegradable polymer biolimus-ES use abluminal biodegradable polymers that dissolve within six to nine months, with the residual metal platform presumably regaining a safety profile similar to a BMS beyond this time frame.[108] Conversely, second generation durable polymer DES have replaced first generation polymers with more biocompatible and thinner polymers.[109-111] Interestingly, the design improvements of the new generation durable polymer DES have run in parallel with a reduction of definite stent thrombosis rates, compared with the first generation paclitaxel-ES and sirolimus-ES in both early and late and very late phases of follow-up.[4 79] Furthermore late stent thrombosis, with everolimus-ES being the first and most studied prototype, is reduced not only compared with first generation DES but also with BMS, suggesting that the durable fluoropolymer used in these devices might be "thromboresistant" and more biocompatible than BMS,[4-6] in turn generating a shift from the contention of an increased risk of stent thrombosis with DES compared with BMS towards the converse relation. In contrast, biodegradable polymer biolimus-ES have failed to provide a significant reduction in one year stent thrombosis rates compared with sirolimus-ES, with both available trials

showing a numerical advantage of sirolimus-ES.[7 8] Although the five year follow-up of LEADERS[44]—the only available trial with a long follow-up—shows a significant reduction of the one to five year rates of stent thrombosis compared with sirolimus-ES, the overall rate at five years was not significantly lower than for sirolimus-ES, pointing once more to the impact of first year outcomes. In our analysis, the stent thrombosis outcomes continue to favour the newer generation durable polymer DES, particularly everolimus-ES.

Stent thrombosis, however, remains a surrogate safety endpoint and needs to be interpreted in the context of objective safety endpoints such as death and myocardial infarction. We found that the durable polymer DES yielded lower odds of death and myocardial infarction compared with biodegradable polymer biolimus-ES, with everolimus-ES reaching a significant reduction in myocardial infarction. Of note, this finding is in line with the results of the NEXT and COMPARE II trials,[9 10] both of which showed a numerical reduction of myocardial infarction associated with everolimus-ES compared with biodegradable polymer biolimus-ES, which became significant for Q-wave myocardial infarction in the latter. The advantage with regards to myocardial infarction observed with thin strut devices such as everolimus-ES might be related not only to stent thrombosis but also to lower rates of periprocedural myocardial infarction resulting from side branch jailing, which in turn for mechanistic reasons might be more frequent with thick strut devices.[112] Higher degrees of re-endothelialisation achievable with these stents compared with the thick strut devices have been shown in preclinical[113] and optical coherence tomography studies[114] and might also play a role. Our findings on safety among different DES should also be viewed in the context of patients treated with DES who need to undergo non-cardiac surgery; surgery represents one of the most common reasons for premature discontinuation of antiplatelet therapy, which is associated with a significant increase in mortality and major adverse cardiac events.[115] Indeed, the favourable profile observed with second generation DES might become clinically relevant in this context, in light of recent studies suggesting the safety of shorter overall duration of dual antiplatelet therapy (three to six months) in patients treated with these devices.[116 117] In this perspective, newer thin strut biodegradable polymer DES recently introduced in the market might have the potential to enhance safety and efficacy outcomes after percutaneous coronary intervention (BIO-RESORT, TWENTE III (NCT01674803) and EVOLVE II QCA (NCT01787799)). Analyses beyond one year confirmed maintenance of the direction of the estimates observed at one year follow-up.

Efficacy

Factors related to design, such as strut thickness, type of antiproliferative agent, drug elution kinetics, and elution time, as well as type of polymer, could all affect efficacy outcomes.[118 119] We found that the new generation everolimus-ES, biodegradable polymer biolimus-ES, Resolute zotarolimus-ES, and the first generation sirolimus-ES were associated with reduced rates of target lesion and target vessel revascularisation compared with Endeavor zotarolimus-ES and/or first generation paclitaxel-ES. Our findings therefore confirm on a larger scale the comparable efficacy of biodegradable polymer biolimus-ES and second generation DES shown in the recent NEXT trial, powered for target lesion revascularisation as primary endpoint.[10]

Although not a new finding, in this analysis all "limus"-ES, with the exception of Endeavor zotarolimus-ES, were associated with significantly lower rates of target lesion and target vessel

revascularisation than the first generation paclitaxel-ES. This finding could derive from the differences in the healing process after implantation between paclitaxel and limus eluting stents. Indeed, the toxicity caused by the long lasting presence of paclitaxel in the vessel wall could give rise to acellular healing process, with prolonged fibrin deposition and inflammation, as shown in preclinical and postmortem studies.[3 120] On the other hand, with Endeavor zotarolimus-ES, short release kinetics could result in insufficient inhibition of neointimal hyperplasia. Indeed, the more recently introduced Resolute zotarolimus-ES, which has a much longer (up to 180 days) release curve of the same antiproliferative agent, zotarolimus, is associated with a significant reduction in target lesion and target vessel revascularisation compared with Endeavor zotarolimus-ES.

Limitations

As with any meta-analysis, our study shares the limitations of the original studies. Results were analysed on trial level data, and therefore we could not assess whether all baseline characteristics were balanced among groups (although for the most part they were balanced within each randomised controlled trial). Data for follow-up beyond a year were limited but seem to confirm the direction of the estimates at one year. The criteria for inclusion of patients of this meta-analysis were broad, more closely reflecting current practice, comprising both stable and unstable high risk patients. Potentially heterogeneous definitions of myocardial infarction used across the trials could represent another limitation. There was no evidence of significant statistical inconsistency among trials; heterogeneity among trials was found to be moderate for stent thrombosis and low to moderate for target lesion and target vessel revascularisation. On the other hand, the stability of the results in the sensitivity analyses confirms that the overall outcome effect is robust and justified. Another aspect is the duration of dual antiplatelet therapy (the combination of aspirin and a P2Y12 receptor blocker), which varied among the different trials. The variability of dual antiplatelet therapy, however, could be less important in the context of the present meta-analysis given that BMS were excluded and most trials used at least six months of dual antiplatelet therapy (a summary of current guideline recommendations[121] is in the appendix). Because of the limited number of trials that assessed Resolute zotarolimus-ES, the findings with this device should be viewed as exploratory but certainly deserve further attention.

Despite these limitations, this network meta-analysis provides the largest scale comparative information on the efficacy and safety profiles of different DES in current use.

Conclusions

Biodegradable polymer biolimus-ES show a similar efficacy and safety profile to first generation sirolimus-ES. Compared with second generation everolimus-ES and Resolute zotarolimus-ES, biodegradable polymer biolimus-ES again provide similar efficacy outcomes. Safety outcomes, however, favour both everolimus-ES and Resolute zotarolimus-ES, suggesting that these second generation durable polymer stents are the safest for current clinical practice.

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What is already known on this topic

Coronary stents are widely used to treat patients with coronary artery disease, with drug eluting stents (DES) being more efficacious than bare metal stents

Among DES, the second generation durable polymer stents (with everolimus eluting being the most studied prototype) are safer than first generation durable polymer DES and bare metal stents

The efficacy and safety profile of biodegradable polymer stents (with biolimus eluting being the most widely used) compared with first and second generation durable polymer DES is controversial

What this study adds

This large network meta-analysis of randomised trials on DES compares durable with biodegradable polymer stents and provides a clear visual ranking of the efficacy and safety of all of the most used DES

The newer durable polymer everolimus and Resolute zotarolimus eluting stents, as well as the biodegradable polymer biolimus eluting stents, provide similar efficacy to first generation sirolimus eluting stents. Everolimus and Resolute zotarolimus eluting stents are the safest devices to date

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Tables

Table 1 Randomised controlled trials included in network meta-analysis of safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents

Trial	Total sample size	Stent comparators	Trial design	Maximum follow-up (months)	Clinical setting (%)
BASKET, 2005[16]	525 (826)	SES v PES (v BMS)	Superiority (cost effectiveness)/single centre	6	Stable coronary artery disease/ACS (42/58)
BASKET-PROVE, 2010[17]	1549 (2314)	EES v SES (v BMS)	Superiority (cost effectiveness)/multicentre	24	Stable coronary artery disease/ACS (35/65)
CATOS, 2012[18]	160	ZES-E v SES	Parallel/multicentre	12	Stable coronary artery disease
CIBELES, 2013[19]	207	EES v SES	Non-inferiority/multicentre	12	Stable coronary artery disease
COMPARE, 2010-11[20 21]	1800	EES v PES	Superiority/single centre	24	Stable coronary artery disease/ACS (40/60)
COMPARE II, 2013[9]	2707	BP-BES v EES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (42/58)
CORPAL, 2005[22]	515	SES v PES	Parallel/multicentre	6	Stable coronary artery disease
CREST MI, 2011[23]	875	ZES-E v SES	Parallel/multicentre	6	STEMI
DES-diabetes, 2008-11[24 25]	400	SES v PES	Superiority/multicentre	48	Stable coronary artery disease/ACS (42/58)
DiabeDES, 2009[26]	153	SES v PES	Superiority/multicentre	8	Stable coronary artery disease/ACS (67/33)
ENDEAVOR III, 2006-11[27 28]	436	ZES-E v SES	Non-inferiority/multicentre	60	Stable coronary artery disease
ENDEAVOR IV, 2010-13[29 30]	1548	ZES-E v PES	Non-inferiority/multicentre	60	Stable coronary artery disease/ACS (53/47)
ESSENCE-Diabetes, 2011[31]	300	EES v SES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (58/42)
EXCELLENT, 2010[32]	1443	EES v SES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (48/52)
Hong et al, 2010[33]	169	SES v PES	Parallel/multicentre	36	Stable coronary artery disease/ACS (39/61)
ISAR-DIABETES, 2005[34]	250	SES v PES	Non-inferiority/multicentre	9	Stable coronary artery disease/ACS (60/40)
ISAR-Left-Main, 2009[35]	607	SES v PES	Non-inferiority/multicentre	24	Stable coronary artery disease
ISAR-Left-Main 2, 2012[36]	650	ZES-R v EES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (64/36)
ISAR-SMART 3, 2006[37]	360	SES v PES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (69/31)
ISAR-TEST-2, 2009-10[38 39]	674 (1007)	ZES-E v SES (v polymer free dual DES)	Superiority/multicentre	24	Stable coronary artery disease/ACS (58/42)
Juwana et al, 2009[40]	397	SES v PES	Superiority/single centre	12	STEMI
Kamoi et al, 2011[41]	100	SES v PES	Parallel/single centre	12	Stable coronary artery disease
Kim et al, 2008[42]	169	SES v PES	Superiority/multicentre	6	Stable coronary artery disease/ACS (39/61)
KOMER, 2011[43]	611	ZES-E v SES v PES	Parallel/multicentre	18	STEMI
LEADERS, 2008-13[7 44]	1707	BP-BES v SES	Non-inferiority/multicentre	60	Stable coronary artery disease/ACS (45/55)
Long DES II, 2006[45]	500	SES v PES	Superiority/multicentre	9	Stable coronary artery disease/ACS (45/55)
LONG-DES III, 2011[46]	450	EES v SES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (58/42)
LONG-DES V, 2012[47]	500	ZES-R v SES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (64/36)
Naples diabetes, 2010[48]	226	ZES-E v SES v PES	Superiority single-centre	36	Stable coronary artery disease/ACS (86/14)

(continued)

Trial	Total sample size	Stent comparators	Trial design	Maximum follow-up (months)	Clinical setting (%)
NEXT, 2013[10]	3235	BP-BES *v* EES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (84/16)
NOBORI 1-Phase 1, 2007[49]	120	BP-BES *v* PES	Non-inferiority/multicentre	9	Stable coronary artery disease/ACS (80/20)
NOBORI 1-Phase 2, 2009[50]	243	BP-BES *v* PES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (72/28)
NOBORI Japan, 2012[51 52]	335	BP-BES *v* SES	Non-inferiority/multicentre	36	Stable coronary artery disease/ACS (86/14)
Pan et al, 2007[53]	205	SES *v* PES	Superiority/multicentre	24	Stable coronary artery disease/ACS (40/60)
PASEO, 2009[54]	180 (270)	SES *v* PES (*v* BMS)	Superiority/single centre	48	STEMI
Petronio et al, 2007[55]	100	SES *v* PES	Superiority/single centre	9	Stable coronary artery disease/ACS (52/48)
PRISON III, 2013[56]	304	SES *v* ZES-E + SES *v* ZES-R	Superiority/multicentre	12	Stable coronary artery disease
PROSIT, 2008-11[57 58]	308	SES *v* PES	Superiority/multicentre	36	STEMI
PROTECT, 2012[59]	8709	ZES-E *v* SES	Superiority/multicentre	36	Stable coronary artery disease/ACS (55/45)
R-CHINA RCT, 2013[60]	400	ZES-R *v* PES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (9/91)
REALITY, 2006[61]	1386	SES *v* PES	Superiority/multicentre	12	Stable coronary artery disease/ACS (70/30)
RESET, 2011[62]	3197	EES *v* SES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (82/18)
Separham et al, 2011[66]	200	BP-BES *v* EES	Parallel/single centre	12	Stable coronary artery disease/ACS (29/71)
SIRTAX, 2005-11[67 68]	1012	SES *v* PES	Superiority/multicentre	60	Stable coronary artery disease/ACS (49/51)
SORT OUT II, 2008[69]	2098	SES *v* PES	Superiority/multicentre	18	Stable coronary artery disease/ACS (45/55)
SORT OUT III, 2010-12[70 71]	2332	ZES-E *v* SES	Superiority/multicentre	36	Stable coronary artery disease/ACS (55/45)
SORT OUT IV, 2012[72 73]	2774	EES *v* SES	Non-inferiority/multicentre	24	Stable coronary artery disease/ACS (58/42)
SORT OUT V, 2013[8]	2468	BP-BES *v* SES	Non-inferiority/multicentre	9	Stable coronary artery disease/ACS (51:49)
SPIRIT II, 2006-12[74 75]	300	EES *v* PES	Non-inferiority/multicentre	60	Stable coronary artery disease/ACS (62/38)
SPIRIT III, 2008-11[76 77]	1001	EES *v* PES	Non-inferiority/multicentre	36	Stable coronary artery disease/ACS (80/20)
SPIRIT IV, 2010-11[78 79]	3717	EES *v* PES	Superiority/multicentre	24	Stable coronary artery disease/ACS (72/28)
SPIRIT V, 2012[80]	324	EES *v* PES	Non-inferiority/multicentre	12	Stable coronary artery disease/ACS (64/36)
TAXI-LATE, 2005-07[81 82]	202	SES *v* PES	Superiority/single centre	36	Stable coronary artery disease/ACS (84/16)
TWENTE, 2012-13[83 84]	1391	ZES-R *v* EES	Non-inferiority/single centre	24	Stable coronary artery disease/ACS (49/51)
XAMI, 2012[85]	625	EES *v* SES	Non-inferiority/multicentre	12	STEMI
ZEST, 2010[86]	2645	ZES-E *v* SES *v* PES	Superiority (ZES-E *v* PES)/non-inferiority (ZES-E *v* SES)/multicentre	12	Stable coronary artery disease/ACS (45/55)
ZEST-AMI, 2009[87]	328	ZES-E *v* SES *v* PES	Superiority/multicentre	12	STEMI
Zhang et al, 2006[88]	673	SES *v* PES	Superiority/single centre	12	Stable coronary artery disease/ACS (45/55)

(continued)

Trial	Total sample size	Stent comparators	Trial design	Maximum follow-up (months)	Clinical setting (%)

SES=sirolimus eluting stents; PES=paclitaxel eluting stents; BMS=bare metal stent; ZES-E=Endeavor zotarolimus stent; ZES-R=Resolute zotarolimus stent; EES=Everolimus eluting stent; BP-BES=biodegradable polymer biolimus-eluting stent; DES=drug eluting stent; ACS=acute coronary syndrome; STEMI=ST-elevation myocardial infarction.

Trial	Total sample size	Stent comparators	Trial design	Maximum follow-up (months)	Clinical setting (%)

Table 2| One year event rates with different types of drug eluting stent (DES). Numbers are rates (95% credible intervals)

	SES	PES	EES	ZES-E	BP-BES	ZES-R
Death	2.45 (1.86 to 3.14)	2.68 (1.88 to 3.75)	2.27 (1.59 to 3.17)	3.05 (1.96 to 4.62)	2.48 (1.64 to 3.67)	1.80 (1.04 to 3.00)
Myocardial infarction	2.58 (1.98 to 3.30)	3.44 (2.53 to 4.61)	2.32 (1.68 to 3.16)	2.47 (1.67 to 3.58)	3.00 (2.07 to 4.27)	2.28 (1.52 to 3.39)
Stent thrombosis	1.42 (0.98 to 1.96)	2.38 (1.27 to 4.30)	0.89 (0.44 to 1.66)	2.74 (1.01 to 6.91)	1.38 (0.57 to 3.03)	1.11 (0.33 to 3.01)
Target revascularisation:						
Lesion	3.25 (2.57 to 4.04)	5.92 (4.30 to 8.05)	3.03 (2.06 to 4.40)	7.52 (4.97 to 11.29)	3.18 (1.95 to 4.97)	3.25 (1.77 to 5.71)
Vessel	4.91 (4.07 to 5.86)	7.05 (5.21 to 9.41)	4.30 (3.11 to 5.87)	7.93 (5.11 to 12.19)	4.93 (3.27 to 7.43)	4.59 (2.45 to 8.36)

SES=sirolimus eluting stent; PES=paclitaxel eluting stent; EES=everolimus eluting stent; ZES-E=Endeavor zotarolimus eluting stent; BP-BES=biodegradable polymer biolimus eluting stent; ZES-R=Resolute zotarolimus eluting stent.
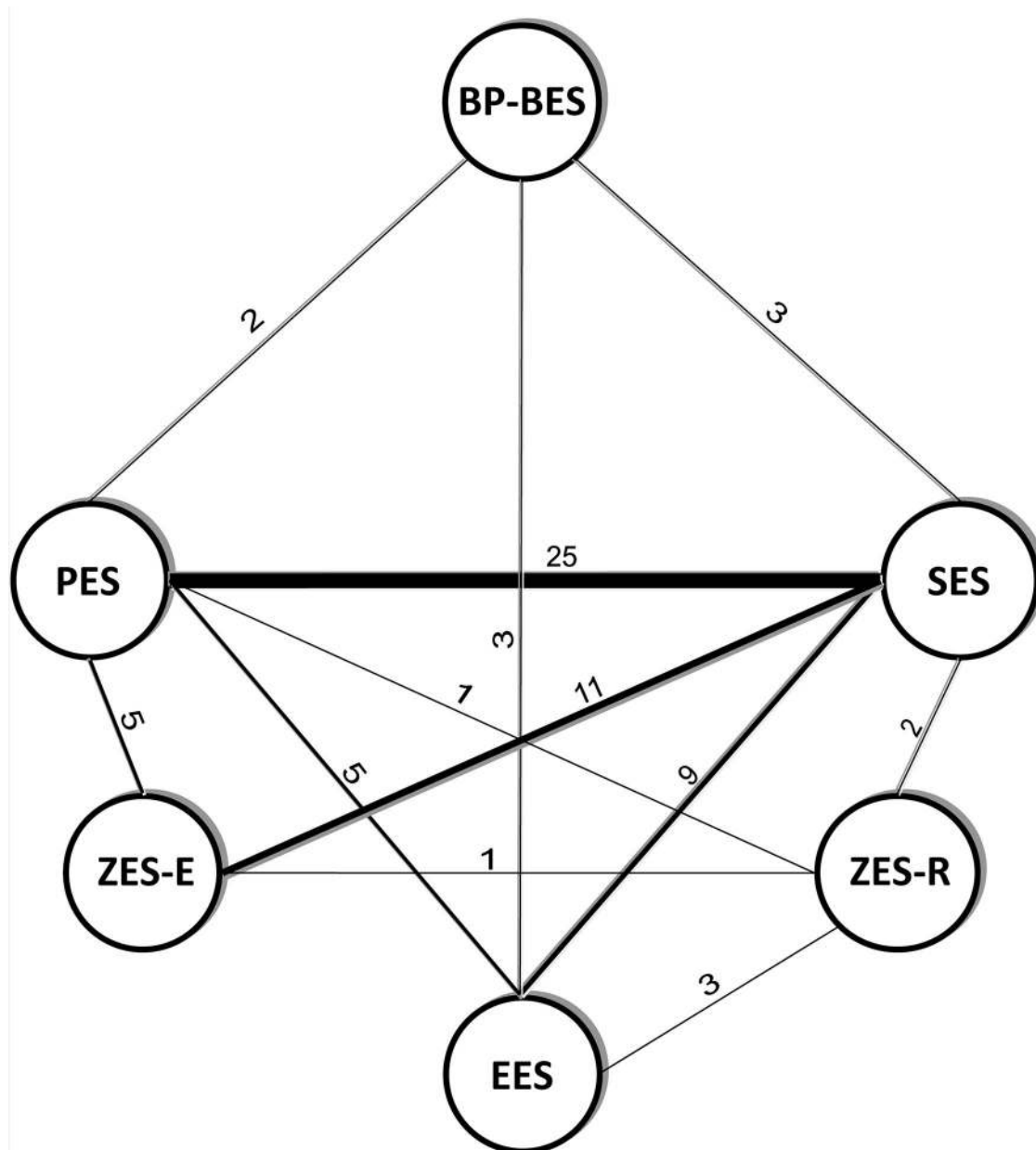
Figures

Fig 1 Evidence network among stents included in meta-analysis. Links between stent types represent direct (lines) comparison studies. Nodes denote stent type; thickness of link indicates number of direct comparisons. SES=sirolimus eluting stent; PES=paclitaxel eluting stent; EES=everolimus eluting stent; ZES-E=Endeavor zotarolimus eluting stent; BP-BES=biodegradable polymer biolimus eluting stent; ZES-R=Resolute zotarolimus eluting stent
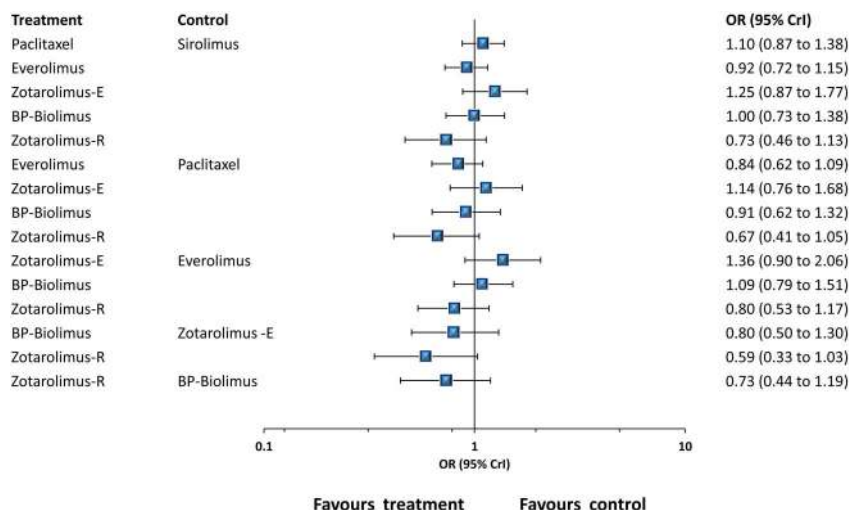
Fig 2 Pooled odds ratio and 95% credible intervals determined by network meta-analysis for mortality. BP=biodegradable polymer; E=Endeavor; R=Resolute
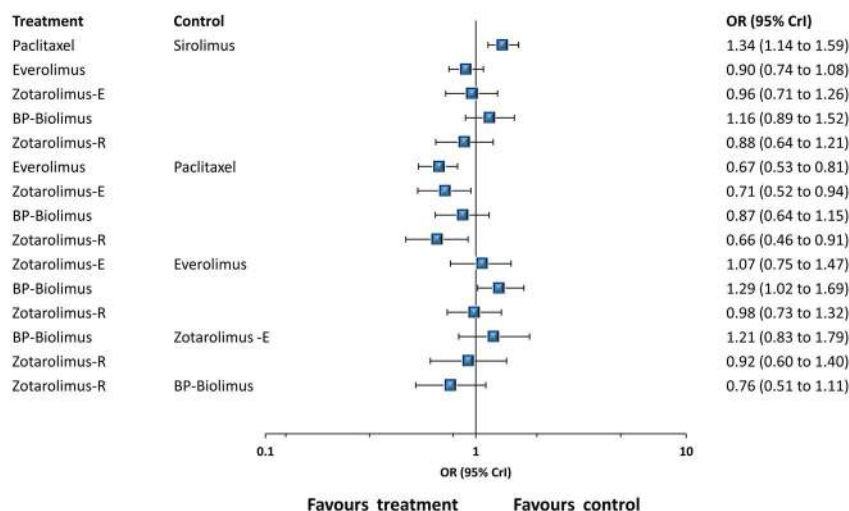
Fig 3 Pooled odds ratio and 95% credible intervals determined by network meta-analysis for myocardial infarction. BP=biodegradable polymer; E=Endeavor; R=Resolute
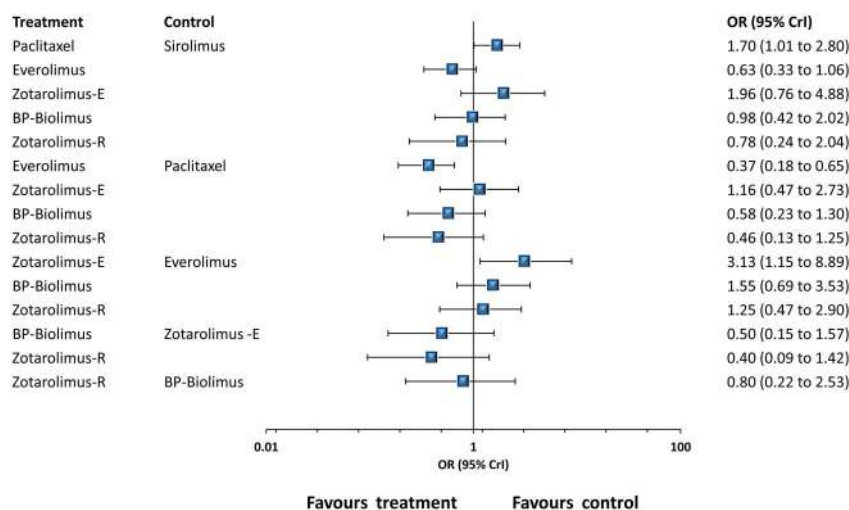

Fig 4 Pooled odds ratio and 95% credible intervals determined by network meta-analysis for definite or probable stent thrombosis. BP=biodegradable polymer; E=Endeavor; R=Resolute
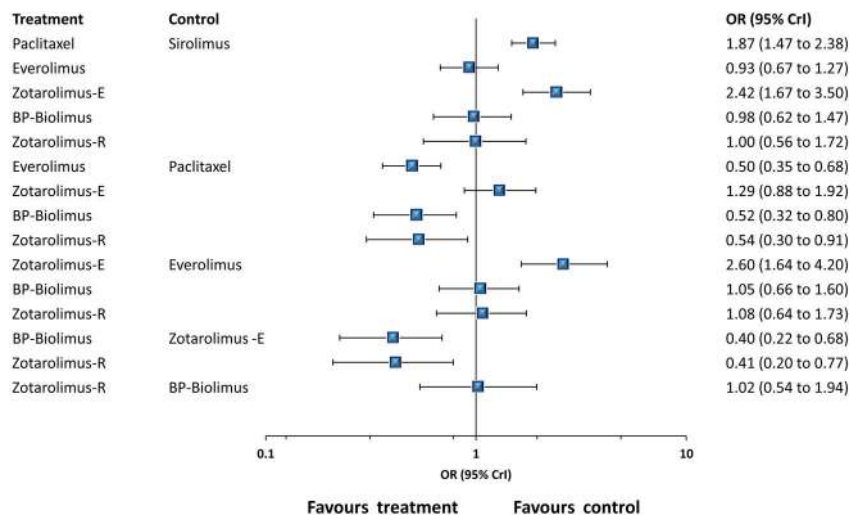
Fig 5 Pooled odds ratio and 95% credible intervals determined by network meta-analysis for target lesion revascularisation. BP=biodegradable polymer; E=Endeavor; R=Resolute
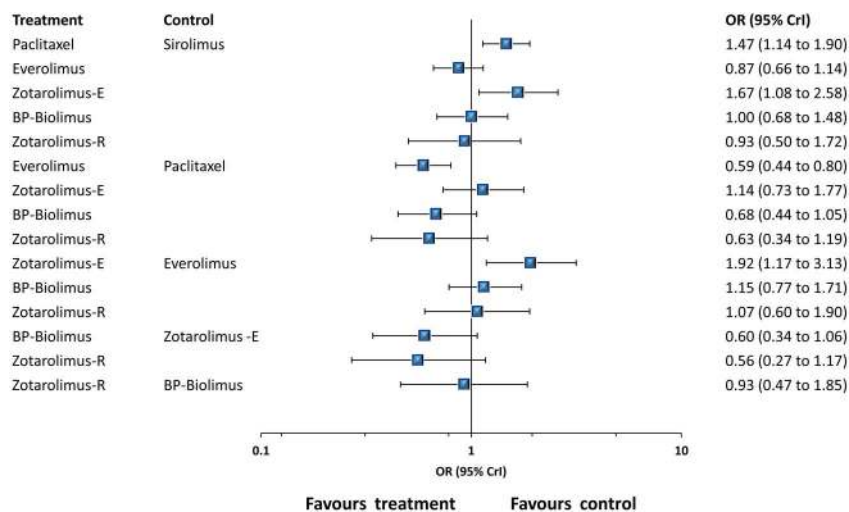

Fig 6 Pooled odds ratio and 95% credible intervals determined by network meta-analysis for target vessel revascularisation. BP=biodegradable polymer; E=Endeavor; R=Resolute
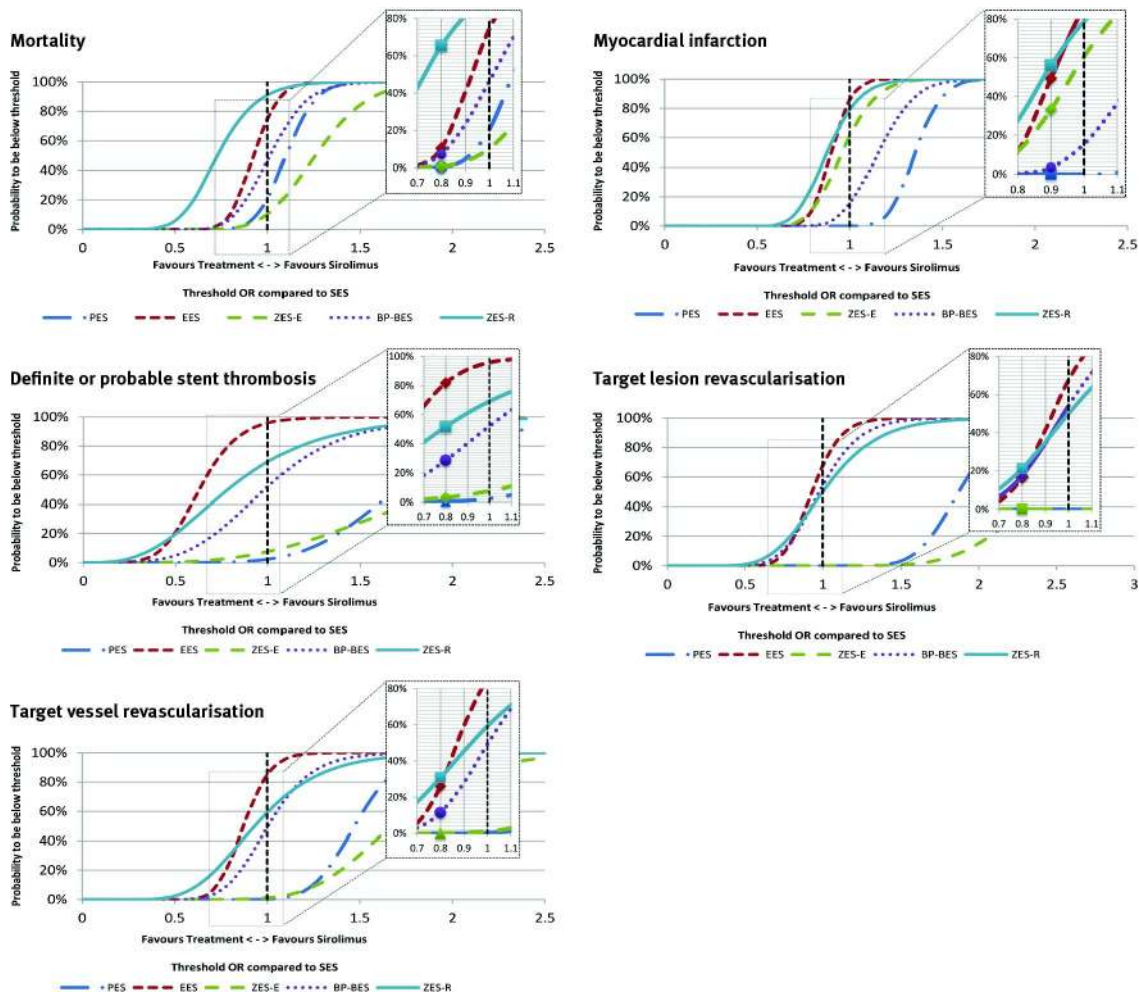
Fig 7 Posterior probabilities of different risk thresholds (odds ratios) for each stent compared with sirolimus eluting stent (reference treatment). Curves can be used to examine overall safety and efficacy profile of specific DES compared with reference treatment sirolimus-ES (SES) (identity line=unit value); improved safety and efficacy profiles indicated by highest leftward shift of curve, as shown with Resolute zotarolimus-ES (ZES-R) and everolimus-ES (EES) with regard to mortality and myocardial infarction; curves allow inferences to extract probabilities of specific risk thresholds corresponding to minimal odds ratio compared with sirolimus-ES as reference treatment. For example, compared with sirolimus-ES, there is probability of 65% that Resolute zotarolimus-ES reduce odds of mortality by at least 20% corresponding to odds ratio of 0.80; conversely, this probability is estimated to be close to 0% with biodegradable polymer biolimus-ES (BP-BES), meaning no additional mortality benefit provided by biodegradable polymer biolimus-ES compared with sirolimus-ES; there is a probability of 56% and 49%, respectively, that Resolute zotarolimus-ES and everolimus-ES reduced odds of myocardial infarction by at least 10% corresponding to odds ratio of 0.90 but this probability is estimated close to 0% with biodegradable polymer biolimus-ES, meaning no additional myocardial infarction benefits provided by biodegradable polymer biolimus-ES compared with sirolimus-ES (reference treatment). PES=paclitaxel eluting stent; ZES-E=Endeavor zotarolimus-ES