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

Eliano P Navarese, Nicolaus Copernicus University
Kenneth Tandjung, Medical Spectrum Twente
Bimmer Claessen, University of Amsterdam
Felicita Andreotti, Catholic University
Mariusz Kowalewski, Nicolaus Copernicus University
David E Kandzari, Piedmont Heart Institute
Dean J Kereiakes, Christ Hospital Heart and Vascular Center
Ron Waksman, MedStar Washington Hospital Center
Laura Mauri, Harvard University
Ian T Meredith, Monash Medical Center

Only first 10 authors above; see publication for full author list.

Journal Title: BMJ
Volume: Volume 347, Number nov06 2
Publisher: BMJ Publishing Group: BMJ | 2013-11-06, Pages f6530-f6530
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1136/bmj.f6530
Permanent URL: https://pid.emory.edu/ark:/25593/vdvsf

Final published version: http://dx.doi.org/10.1136/bmj.f6530

Copyright information:
Copyright © Navarese et al 2013
This is an Open Access work distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License (https://creativecommons.org/licenses/by-nc/3.0/).

Accessed April 28, 2020 3:32 PM EDT
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

Eliano P Navarese assistant professor of medicine and director of research,1 Kenneth Tandjung resident,2 Bimmer Claessen resident,1 Felicita Andreotti aggregate professor of medicine,3 Mariusz Kowalewski research fellow,4 David E Kandzari professor of medicine,4 Dean J Kereiakes professor of medicine,4 Ron Waksman professor of medicine,7 Laura Mauri professor of medicine8, Ian T Meredith professor of medicine9, Alok V Finn assistant professor of medicine10, Hyo-Soo Kim professor of medicine11, Jacek Kubica professor of medicine1, Harry Suryapranata professor of medicine12, Toni Mustahsani Aprami professor of medicine13, Giuseppe Di Pasquale cardiologist14, Clemens von Birgelen professor of medicine15, Elvin Kedhi interventional cardiologist16

1Department of Cardiology and Internal Medicine, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; 2Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, Netherlands; 3Department of Cardiology, Academic Medical Centrum, Universiteit van Amsterdam, Netherlands; 4Department of Cardiology, Christ Hospital Heart and Vascular Center/Lindner Research Center, Cincinnati, OH, USA; 5Division of Cardiology, MedStar Washington Hospital Center, Washington DC, USA; 6Department of Cardiology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; 7Department of Cardiology, MonashHeart, Monash Medical Centre and Monash University, Melbourne, Australia; 8Department of Cardiology, Emory University School of Medicine, Atlanta, USA; 9Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; 10Department of Cardiology, UMC St Radboud, Nijmegen, Netherlands; 11Department of Cardiology, Padjadjaran University Hospital Hasan Sadikin, Bandung, Indonesia; 12Unità Ospedaliera di Cardiologia, Ospedale Maggiore, Bologna, Italy; 13Health Technology and Services Research, MIRA-Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, Netherlands; 14Department of Cardiology, Isala Klinieken, 8025 AB Zwolle, Netherlands

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...
Correspondence to: E Kidhi ekedhi@yahoo.com

Extra material supplied by the author (see http://www.bmj.com/content/347/bmj.f6530?tab=related#webextra)

Appendix: Supplementary tables (S1-6), summary of guideline recommendations, and supplementary figures (S1-2)

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, anti-proliferative 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. 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. 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”, “Endeavor zotarolimus-stent”, “Resolute zotarolimus-stent”, “Exe-
“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 τ<0.04 indicating low level and τ>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 91 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.11 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,8 9 10 93 trials with different stent metal platforms,9 94 post hoc analyses or substudies,97 100 the BMS arm or polymer free arm of six trials with three arms,14 17 39 104 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.11

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 2A), 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 byoneyear.Comparedwithpaclitaxel-ES, allDESeXceptbiodegradablepolymerbiolimus-ESsignificantly 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 3B). Compared with sirolimus-ES, the odds of myocardial infarction were not significantly reduced by

No commercial reuse: See rights and reprints http://www.bmj.com/permissions
Subscribe: http://www.bmj.com/subscribe
second generation DES, although everolimus-ES and Resolute zotarolimus-ES, unlike biodegradable polymer biolimus-ES, showed numerical reductions (fig 3ﬁ). 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 (t=0.007) or myocardial infarction (t=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 (t=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 5i). 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 6i). There was no evidence of high heterogeneity among trials for both target lesion revascularisation (t=0.13) and target vessel revascularisation (t=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 pacltaxel-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 paclttxel-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.\(^10\)\(^6\) Moreover, the safety and efficacy of durable polymer “limus”-ES compared with BMS has already been clarified.\(^4\) 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.\(^10\)\(^7\) 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.\(^7\)\(^9\) 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.\(^10\) Other factors such as stent malapposition and mechanical tissue injury caused by stent struts during implantation, however, also play a role in stent thrombosis.\(^10\)

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.\(^10\)\(^8\) Conversely, second generation durable polymer DES have replaced first generation polymers with more biocompatible and thinner polymers.\(^10\)\(^9\)\(^10\)\(^11\)\(^12\) 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 paclttxel-ES and sirolimus-ES in both early and late and very late phases of follow-up.\(^4\)\(^7\)\(^9\) 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”\(^9\) and more biocompatible than BMS,\(^4\)\(^11\) in turn generating a shift from the contention of an increased risk of stent thrombosis with \(^1\)“ES 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.\(^7\)\(^9\)\(^8\) Therefore, the five year follow-up of LEADERS\(^5\)—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

No commercial reuse: See rights and reprints http://www.bmj.com/permissions

Subscribe: http://www.bmj.com/subscribe
line with the results of the NEXT and COMPARE II trials, 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 peri-procedural myocardial infarction resulting from side branch jailing, which in turn for mechanistic reasons might be more frequent with thick strut devices. Higher degrees of re-endothelialisation achievable with these stents compared with the thick strut devices have been shown in preclinical and optical coherence tomography studies 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. 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. 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. 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. 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 cellular healing process, with prolonged fibrin deposition and inflammation, as shown in preclinical and postmortem studies. 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 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.

Contributors: EK and EPN designed the analysis. EPN, KT, BC, and MK and EK analysed and interpreted the data and critically revised the manuscript for important intellectual content. The contents of this study are solely the responsibility of the authors and do not necessarily represent the official view of their institutions or any other party. EPN and EK are guarantors.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request through http://www.bmj.com/permissions No commercial reuse: See rights and reprints http://www.bmj.com/subscribe
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.


120 Nakazawa G, Finn AV, John MC, Kologeris FO, Verrani R. The significance of preclinical evaluation of sirolimus-, paclitaxel-, and zotarolimus-eluting stents. Am J Cardiol 2007;100:36-44M.


Cite this as: BMJ 2013;347:f6530

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See http://creativecommons.org/licenses/by-nc/3.0/.
# 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total sample size</th>
<th>Stent comparators</th>
<th>Trial design</th>
<th>Maximum follow-up (months)</th>
<th>Clinical setting (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET, 2005(^a)</td>
<td>525 (826)</td>
<td>SES v PES (v BMS)</td>
<td>Superiority (cost effectiveness)/single centre</td>
<td>6</td>
<td>Stable coronary artery disease/ACS (42/58)</td>
</tr>
<tr>
<td>BASKET-PROVE, 2010(^b)</td>
<td>1549 (2314)</td>
<td>EES v SES (v BMS)</td>
<td>Superiority (cost effectiveness)/multicentre</td>
<td>24</td>
<td>Stable coronary artery disease/ACS (35/65)</td>
</tr>
<tr>
<td>CATOS, 2012(^c)</td>
<td>160</td>
<td>ZES-E v SES</td>
<td>Parallel/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease</td>
</tr>
<tr>
<td>CIBELES, 2013(^d)</td>
<td>207</td>
<td>EES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease</td>
</tr>
<tr>
<td>COMPARE, 2010(^e)</td>
<td>1800</td>
<td>EES v PES</td>
<td>Superiority/single centre</td>
<td>24</td>
<td>Stable coronary artery disease/ACS (40/60)</td>
</tr>
<tr>
<td>COMPARE II, 2013(^e)</td>
<td>2707</td>
<td>BP-BES v EES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (42/58)</td>
</tr>
<tr>
<td>CORPAL, 2005(^e)</td>
<td>515</td>
<td>SES v PES</td>
<td>Parallel/multicentre</td>
<td>6</td>
<td>Stable coronary artery disease</td>
</tr>
<tr>
<td>CREST MI, 2011(^f)</td>
<td>875</td>
<td>ZES-E v SES</td>
<td>Parallel/multicentre</td>
<td>6</td>
<td>STEMI</td>
</tr>
<tr>
<td>DES-diabetes, 2008(^g)</td>
<td>400</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>48</td>
<td>Stable coronary artery disease/ACS (42/58)</td>
</tr>
<tr>
<td>DiabeDES, 2009(^h)</td>
<td>153</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>8</td>
<td>Stable coronary artery disease/ACS (67/33)</td>
</tr>
<tr>
<td>ENDEAVOR III, 2006(^i)</td>
<td>436</td>
<td>ZES-E v SES</td>
<td>Non-inferiority/multicentre</td>
<td>60</td>
<td>Stable coronary artery disease</td>
</tr>
<tr>
<td>ENDEAVOR IV, 2010(^j)</td>
<td>1548</td>
<td>ZES-E v PES</td>
<td>Non-inferiority/multicentre</td>
<td>60</td>
<td>Stable coronary artery disease/ACS (53/47)</td>
</tr>
<tr>
<td>ESSENCE-Diabetes, 2011(^k)</td>
<td>300</td>
<td>EES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (58/42)</td>
</tr>
<tr>
<td>EXCELLENT, 2010(^l)</td>
<td>1443</td>
<td>EES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (48/52)</td>
</tr>
<tr>
<td>Hong et al, 2010(^m)</td>
<td>169</td>
<td>SES v PES</td>
<td>Parallel/multicentre</td>
<td>36</td>
<td>Stable coronary artery disease/ACS (39/61)</td>
</tr>
<tr>
<td>ISAR-DIABETES, 2005(^n)</td>
<td>250</td>
<td>SES v PES</td>
<td>Non-inferiority/multicentre</td>
<td>9</td>
<td>Stable coronary artery disease/ACS (60/40)</td>
</tr>
<tr>
<td>ISAR-Left-Main, 2009(^n)</td>
<td>607</td>
<td>SES v PES</td>
<td>Non-inferiority/multicentre</td>
<td>24</td>
<td>Stable coronary artery disease</td>
</tr>
<tr>
<td>ISAR-Left-Main 2, 2012(^n)</td>
<td>650</td>
<td>ZES-R v EES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (64/36)</td>
</tr>
<tr>
<td>ISAR-SMART 3, 2006(^n)</td>
<td>360</td>
<td>SES v PES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (69/31)</td>
</tr>
<tr>
<td>ISAR-TEST 2, 2009(^o)</td>
<td>674 (1007)</td>
<td>ZES-E v SES (v polymer Superiority/multicentre free dual DES)</td>
<td>Non-inferiority/multicentre</td>
<td>24</td>
<td>Stable coronary artery disease/ACS (58/42)</td>
</tr>
<tr>
<td>Juwana et al, 2009(^p)</td>
<td>397</td>
<td>SES v PES</td>
<td>Superiority/single centre</td>
<td>12</td>
<td>STEMI</td>
</tr>
<tr>
<td>Kamoi et al, 2011(^q)</td>
<td>100</td>
<td>SES v PES</td>
<td>Parallel/single centre</td>
<td>12</td>
<td>Stable coronary artery disease</td>
</tr>
<tr>
<td>Kim et al, 2008(^r)</td>
<td>169</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>6</td>
<td>Stable coronary artery disease/ACS (39/61)</td>
</tr>
<tr>
<td>KOMER, 2011(^s)</td>
<td>611</td>
<td>ZES-E v SES v SES</td>
<td>Parallel/multicentre</td>
<td>18</td>
<td>STEMI</td>
</tr>
<tr>
<td>LEADERS, 2008(^t)</td>
<td>1707</td>
<td>BP-BES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>60</td>
<td>Stable coronary artery disease/ACS (45/55)</td>
</tr>
<tr>
<td>Long DES II, 2006(^u)</td>
<td>500</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>9</td>
<td>Stable coronary artery disease/ACS (45/55)</td>
</tr>
<tr>
<td>LONG-DES III, 2011(^u)</td>
<td>450</td>
<td>EES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (58/42)</td>
</tr>
<tr>
<td>LONG-DES V, 2012(^u)</td>
<td>500</td>
<td>ZES-R v SES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (64/36)</td>
</tr>
</tbody>
</table>
Naples diabetes, 2010<sup>44</sup> 226  ZES-E v SES v PES  Superiority single-centre  36  Stable coronary artery disease/ACS (86/14)

(continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total sample size</th>
<th>Stent comparators</th>
<th>Trial design</th>
<th>Maximum follow-up (months)</th>
<th>Clinical setting (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEXT, 2013&lt;sup&gt;35&lt;/sup&gt;</td>
<td>3235</td>
<td>BP-BES v EES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (84/16)</td>
</tr>
<tr>
<td>NOBORI 1-Phase 1, 2007&lt;sup&gt;27&lt;/sup&gt;</td>
<td>120</td>
<td>BP-BES v PES</td>
<td>Non-inferiority/multicentre</td>
<td>9</td>
<td>Stable coronary artery disease/ACS (80/20)</td>
</tr>
<tr>
<td>NOBORI 1-Phase 2, 2009&lt;sup&gt;27&lt;/sup&gt;</td>
<td>243</td>
<td>BP-BES v PES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (72/28)</td>
</tr>
<tr>
<td>NOBORI Japan, 2012&lt;sup&gt;31&lt;/sup&gt;</td>
<td>335</td>
<td>BP-BES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>36</td>
<td>Stable coronary artery disease/ACS (86/14)</td>
</tr>
<tr>
<td>Pan et al, 2007&lt;sup&gt;41&lt;/sup&gt;</td>
<td>205</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>24</td>
<td>Stable coronary artery disease/ACS (40/60)</td>
</tr>
<tr>
<td>PASEO, 2009&lt;sup&gt;25&lt;/sup&gt;</td>
<td>180 (270)</td>
<td>SES v PES (v BMS)</td>
<td>Superiority/single centre</td>
<td>48</td>
<td>STEMI</td>
</tr>
<tr>
<td>Petronio et al, 2007&lt;sup&gt;32&lt;/sup&gt;</td>
<td>100</td>
<td>SES v PES</td>
<td>Superiority/single centre</td>
<td>9</td>
<td>Stable coronary artery disease/ACS (52/48)</td>
</tr>
<tr>
<td>PRISON III, 2013&lt;sup&gt;24&lt;/sup&gt;</td>
<td>304</td>
<td>SES v ZES-E + SES v ZES-R</td>
<td>Superiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease</td>
</tr>
<tr>
<td>PROSIT, 2008-11&lt;sup&gt;16&lt;/sup&gt;</td>
<td>308</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>36</td>
<td>STEMI</td>
</tr>
<tr>
<td>PROTECT, 2012&lt;sup&gt;24&lt;/sup&gt;</td>
<td>8709</td>
<td>ZES-E v SES</td>
<td>Superiority/multicentre</td>
<td>36</td>
<td>Stable coronary artery disease/ACS (55/45)</td>
</tr>
<tr>
<td>R-CHINA RCT, 2013&lt;sup&gt;34&lt;/sup&gt;</td>
<td>400</td>
<td>ZES-R v PES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (9/91)</td>
</tr>
<tr>
<td>REALITY, 2006&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1386</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (70/30)</td>
</tr>
<tr>
<td>RESET, 2011&lt;sup&gt;25&lt;/sup&gt;</td>
<td>3197</td>
<td>EES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (82/18)</td>
</tr>
<tr>
<td>Separham et al, 2011&lt;sup&gt;44&lt;/sup&gt;</td>
<td>200</td>
<td>BP-BES v EES</td>
<td>Parallel/single centre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (29/71)</td>
</tr>
<tr>
<td>SIRTAIT, 2005-11&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1012</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>60</td>
<td>Stable coronary artery disease/ACS (49/51)</td>
</tr>
<tr>
<td>SORT OUT II, 2008&lt;sup&gt;44&lt;/sup&gt;</td>
<td>2098</td>
<td>SES v PES</td>
<td>Superiority/multicentre</td>
<td>18</td>
<td>Stable coronary artery disease/ACS (45/55)</td>
</tr>
<tr>
<td>SORT OUT III, 2010-12&lt;sup&gt;16&lt;/sup&gt;</td>
<td>2332</td>
<td>ZES-E v SES</td>
<td>Superiority/multicentre</td>
<td>36</td>
<td>Stable coronary artery disease/ACS (55/45)</td>
</tr>
<tr>
<td>SORT OUT IV, 2012&lt;sup&gt;16&lt;/sup&gt;</td>
<td>2774</td>
<td>EES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>24</td>
<td>Stable coronary artery disease/ACS (58/42)</td>
</tr>
<tr>
<td>SORT OUT V, 2013&lt;sup&gt;9&lt;/sup&gt;</td>
<td>2468</td>
<td>BP-BES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>9</td>
<td>Stable coronary artery disease/ACS (51/49)</td>
</tr>
<tr>
<td>SPIRIT II, 2006-12&lt;sup&gt;16&lt;/sup&gt;</td>
<td>300</td>
<td>EES v PES</td>
<td>Non-inferiority/multicentre</td>
<td>60</td>
<td>Stable coronary artery disease/ACS (62/38)</td>
</tr>
<tr>
<td>SPIRIT III, 2008-11&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1001</td>
<td>EES v PES</td>
<td>Non-inferiority/multicentre</td>
<td>36</td>
<td>Stable coronary artery disease/ACS (80/20)</td>
</tr>
<tr>
<td>SPIRIT IV, 2010-11&lt;sup&gt;16&lt;/sup&gt;</td>
<td>3717</td>
<td>EES v PES</td>
<td>Superiority/multicentre</td>
<td>24</td>
<td>Stable coronary artery disease/ACS (72/28)</td>
</tr>
<tr>
<td>SPIRIT V, 2012&lt;sup&gt;16&lt;/sup&gt;</td>
<td>324</td>
<td>EES v PES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (64/36)</td>
</tr>
<tr>
<td>TAXI-LATE, 2005-07&lt;sup&gt;16&lt;/sup&gt;</td>
<td>202</td>
<td>SES v PES</td>
<td>Superiority/single centre</td>
<td>36</td>
<td>Stable coronary artery disease/ACS (84/16)</td>
</tr>
<tr>
<td>TWENTE, 2012-13&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1391</td>
<td>ZES-R v EES</td>
<td>Non-inferiority/single centre</td>
<td>24</td>
<td>Stable coronary artery disease/ACS (49/51)</td>
</tr>
<tr>
<td>XAMI, 2012&lt;sup&gt;16&lt;/sup&gt;</td>
<td>625</td>
<td>EES v SES</td>
<td>Non-inferiority/multicentre</td>
<td>12</td>
<td>STEMI</td>
</tr>
<tr>
<td>Trial</td>
<td>Total sample size</td>
<td>Stent comparators</td>
<td>Trial design</td>
<td>Maximum follow-up (months)</td>
<td>Clinical setting (%)</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------------------------</td>
<td>---------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>ZEST, 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2645</td>
<td>ZES-E v SES v PES</td>
<td>Superiority (ZES-E v SES)/non-inferiority (ZES-E v SES)/multicentre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (45/55)</td>
</tr>
<tr>
<td>ZEST-AMI, 2009&lt;sup&gt;6&lt;/sup&gt;</td>
<td>328</td>
<td>ZES-E v SES v PES</td>
<td>Superiority/multicentre</td>
<td>12</td>
<td>STEMI</td>
</tr>
<tr>
<td>Zhang et al, 2006&lt;sup&gt;7&lt;/sup&gt;</td>
<td>673</td>
<td>SES v PES</td>
<td>Superiority/single centre</td>
<td>12</td>
<td>Stable coronary artery disease/ACS (45/55)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>SES</th>
<th>PES</th>
<th>EES</th>
<th>ZES-E</th>
<th>BP-BES</th>
<th>ZES-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.45 (1.86 to 3.14)</td>
<td>2.68 (1.88 to 3.75)</td>
<td>2.27 (1.59 to 3.17)</td>
<td>3.05 (1.96 to 4.62)</td>
<td>2.48 (1.64 to 3.67)</td>
<td>1.80 (1.04 to 3.00)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.58 (1.98 to 3.30)</td>
<td>3.44 (2.53 to 4.61)</td>
<td>2.32 (1.68 to 3.16)</td>
<td>2.47 (1.67 to 3.58)</td>
<td>3.00 (2.07 to 4.27)</td>
<td>2.28 (1.52 to 3.39)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.42 (0.98 to 1.96)</td>
<td>2.38 (1.27 to 4.30)</td>
<td>0.89 (0.44 to 1.66)</td>
<td>2.74 (1.01 to 6.91)</td>
<td>1.38 (0.57 to 3.03)</td>
<td>1.11 (0.33 to 3.01)</td>
</tr>
<tr>
<td>Target revascularisation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion</td>
<td>3.25 (2.57 to 4.04)</td>
<td>5.92 (4.30 to 8.05)</td>
<td>3.03 (2.06 to 4.40)</td>
<td>7.52 (4.97 to 11.29)</td>
<td>3.18 (1.95 to 4.97)</td>
<td>3.25 (1.77 to 5.71)</td>
</tr>
<tr>
<td>Vessel</td>
<td>4.91 (4.07 to 5.86)</td>
<td>7.05 (5.21 to 9.41)</td>
<td>4.30 (3.11 to 5.87)</td>
<td>7.93 (5.11 to 12.29)</td>
<td>4.93 (3.27 to 7.43)</td>
<td>4.59 (2.45 to 8.36)</td>
</tr>
</tbody>
</table>

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 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, 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