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Outcomes of patients treated with durable polymer platinum-chromium everolimus-eluting stents: a meta-analysis of randomised trials

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KEYWORDS

- clinical research
- clinical trial
- drug-eluting stent

Abstract

Aims: The durable polymer platinum-chromium everolimus-eluting stent (PtCr-EES) is a new-generation drug-eluting stent (DES) with a platinum-enriched metallic platform developed to improve the percutaneous treatment of patients with coronary artery disease. We sought to investigate the performance of durable polymer PtCr-EES versus other new-generation DES.

Methods and results: We undertook a meta-analysis of trials in which patients receiving percutaneous coronary intervention (PCI) were randomly assigned to durable polymer PtCr-EES versus other new-generation DES (other DES). Primary efficacy and safety outcomes were target lesion revascularisation (TLR) and definite/probable stent thrombosis (ST), respectively. Secondary outcomes were myocardial infarction (MI), target vessel revascularisation (TVR), death, cardiac death and longitudinal stent deformation (LSD). A total of 11,036 patients in seven trials received a PCI with either durable polymer PtCr-EES (n=6,613) or other DES (n=4,423). This latter group comprised patients treated with biolimus- (n=325), cobalt-chromium everolimus- (n=1,940) or zotarolimus-eluting stents (n=2,158). After a median follow-up of 12 months (interquartile range 12-24), durable polymer PtCr-EES displayed a risk of TLR (odds ratio 0.98, 95% confidence interval [CI]: 0.75-1.29; p=0.90) and definite/probable ST (0.89 [0.55-1.45]; p=0.63) comparable to that of other DES. However, the durable polymer PtCr-EES was associated with a higher risk of LSD (12.05 [1.60-90.71], p=0.02) compared to other DES. There was no significant difference with regard to other secondary outcomes nor was there heterogeneity across trials.

Conclusions: At one-year follow-up, the durable polymer PtCr-EES displays a performance comparable to that of other new-generation DES platforms.

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Abbreviations

DES drug-eluting stent
EES everolimus-eluting stent
LSD longitudinal stent deformation
PCI percutaneous coronary intervention
PtCr platinum-chromium
ST stent thrombosis
TLR target lesion revascularisation

Introduction

Contemporary high-performance drug-eluting stent (DES) platforms are regarded as a first-line therapy for a large spectrum of coronary artery disease (CAD) patients, even for those individuals presenting with complex clinical and angiographic characteristics[1]. This achievement results from the continuous iterative process to which active drugs, polymer coatings and supportive metallic backbones have been subject in recent years[2].

Despite drugs and polymers having attracted considerable interest, the role of underlying scaffolds in DES-treated patients remains less studied[3,4]. On the one hand, the cobalt-chromium (CoCr) alloy, used in the majority of contemporary DES platforms, has enabled a reduction in stent strut thickness and improved device deliverability, though at the expense of greater recoil as compared with stainless steel alloy[5]. On the other hand, the introduction of platinum-enriched platforms and innovative backbone designs has permitted a further reduction of strut thickness while improving radiopacity and retaining radial strength at the cost of inferior longitudinal stent stability[5]. Preliminary investigations of stent platforms based on platinum-chromium (PtCr) alloy have demonstrated less thrombogenicity, favourable endothelial surface coverage[6] and better conformability to the vessel wall after implantation[7]. Whether these properties translate into measurable clinical benefits is still open to question.

The durable polymer, PtCr-based, everolimus-eluting stent (PtCr-EES) (PROMUS Element™; Boston Scientific, Marlborough, MA, USA) has been studied against other new-generation stainless steel or CoCr-DES platforms in a number of randomised clinical trials[8-14]. However, the overwhelming majority of these trials had a non-inferiority design and sufficient statistical power only for composite or surrogate outcomes.

Against this background, the present meta-analysis investigates the outcomes of patients treated with durable polymer PtCr-EES as compared with other new-generation DES.

Methods

SEARCH STRATEGY AND SELECTION CRITERIA

All details of the search strategy and selection criteria are provided in the **Online Appendix**.

DATA COLLECTION AND ASSESSMENT OF RISK OF BIAS

Two investigators (S. Cassese and G. Ndrepepa) independently assessed publications for eligibility at title and/or abstract level, with divergences resolved by a third investigator (M. Fusaro). Studies that met inclusion criteria were selected for further analysis. Freedom from bias was evaluated for each study by the same investigators, in accordance with the Cochrane Collaboration method[15]. No formal quality score adjudication was performed[16].

OUTCOME VARIABLES

For this report, the primary efficacy and safety outcomes were target lesion revascularisation (TLR) and definite/probable stent thrombosis (ST), respectively. Secondary outcomes of interest were myocardial infarction (MI), target vessel revascularisation (TVR), death, cardiac death and longitudinal stent deformation (LSD). All endpoints were evaluated at the longest available follow-up according to the definitions of the original protocols.

STATISTICAL ANALYSIS

The odds ratio (OR) and 95% confidence interval (95% CI) were used as summary statistics and were derived for comparison of durable polymer PtCr-EES versus other new-generation DES (other DES). The Mantel-Haenszel random effects model (DerSimonian and Laird) was used to calculate pooled ORs. Treatment effect was not assessed in the trials in which no events were reported within groups. The Breslow-Day chi^2 test and the I^2 statistic were used to test heterogeneity across the studies: I^2 values of <25%, 25-50% or >50% indicated low, moderate or high heterogeneity[15]. The restricted maximum likelihood method (Tau^2) took into account the occurrence of residual heterogeneity.

For the primary outcomes we performed: (i) a visual estimation of funnel plots, as well as statistical tests to evaluate the possibility of publication bias[17-19]; (ii) an influence analysis, in which meta-analysis estimates are computed omitting one study at a time; (iii) a trial sequential analysis, in which meta-analysis sample size calculations are combined with the threshold of statistical significance[20]. A sensitivity analysis evaluated the extent to which the comparator DES, the polymer serving as drug carrier (durable/bioresorbable) or the strut thickness (≥81 µm) in the control DES group, the all-comers design of the trials or the protocol-mandated control angiography might have influenced the risk calculations for the primary outcomes.

Statistical analysis was performed using Review Manager (RevMan), Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), Stata 11.4 (StataCorp, College Station, TX, USA) and trial sequential analysis (TSA), version 0.9 Beta software packages. This study was registered with PROSPERO, number CRD42016038594 and conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[21].

Results

ELIGIBLE STUDIES

Figure 1 shows the flow diagram for the trial selection process. Among studies selected for further analyses, four randomised trials were excluded[7,22-24]: the EVOLVE[22] and EVOLVE II[23] trials compared two PtCr-EES platforms; the PLATINUM China trial[24] compared the durable polymer PtCr-EES with

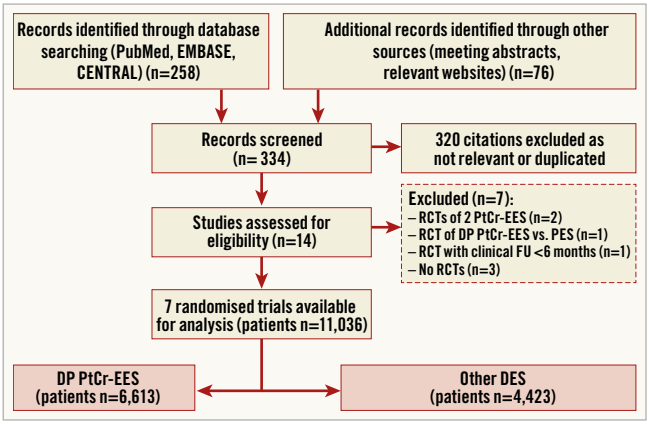

Figure 1. *PRISMA flow chart for the trial selection process. DES: drug-eluting stent; DP PtCr-EES: durable polymer platinum-chromium everolimus-eluting stent; FU: follow-up; PES: paclitaxel-eluting stent; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: randomised controlled trials*

early-generation DES; and the trial of Kim and co-workers[7] had a follow-up length <6 months. Finally, we selected seven trials (all with full-length manuscripts[8-14]) in which a total of 11,036 PCI patients were randomly assigned to durable polymer PtCr-EES (n=6,613) or other DES (n=4,423). Patients assigned to the control group received a biolimus-eluting stent (BES) (Nobori® [Terumo Corp., Tokyo, Japan], or BioMatrix Flex™ [Biosensors Inc., Newport Beach, CA, USA], n=325) in two trials[9,11], a cobalt-chromium EES (CoCr-EES) (PROMUS™ [Boston Scientific], or XIENCE V®/XIENCE Prime™ [Abbott Vascular, Santa Clara, CA, USA], n=1,940) in three trials[12-14], or a zotarolimus-eluting stent (ZES) (Resolute™/Resolute Integrity® [Medtronic, Santa Rosa, CA, USA], n=2,158) in two trials[8,10].

The main characteristics of the trials included are described in detail in **Online Table 1**. Briefly, patients with obstructive chronic/stable or unstable CAD were randomised to PCI with durable polymer PtCr-EES versus other DES. One trial[9] comprised a third treatment arm of patients randomised to an everolimus-eluting bioresorbable vascular scaffold (Absorb; Abbott Vascular); data belonging to this treatment arm were excluded as irrelevant to the study research question. All but two trials[9,12] had a multicentre design. Two studies[9,11] among those included required a protocol-mandated control angiography nine months after the index procedure; in these trials the percentage of patients with invasive surveillance data ranged from 64.3% to 90.8%. Loading doses of thienopyridines, as well as aspirin, were administered to all patients at the time of index PCI. In all cases, aspirin was recommended indefinitely, whilst the length and the type of thienopyridine prescription depended on clinical indication. All interventions were performed in accordance with standard of care including anticoagulation, stent deployment optimisation or use of intravascular imaging techniques, at the operators' discretion or according to protocols. In two trials[9,11], the primary endpoint consisted of angiographic measures of efficacy (namely, in-stent late lumen loss). For two trials[25,26], clinical endpoints after one-year follow-up were available: these data were used for the present report. The definitions of outcomes are reported in **Online Table 2** and the risk of bias among studies is reported in **Online Table 3**.

Baseline characteristics of the individuals enrolled are summarised in **Table 1**. Patients were mainly men, with a median age of 63.5 years (interquartile range, 63.3-65.0) and one quarter had diabetes. Nearly 45% of participants presented with ACS at the time of enrolment. Overall, the mean reference vessel diameter was 2.80 mm, the baseline diameter stenosis was 71.3%, the length of lesions treated was 19.2 mm, and roughly 60% of lesions had

Table 1. Main characteristics of patients enrolled among trials included in the study.

Trials	Patients, n	Age, years	Male, %	Diabetes, %	ACS at admission, %	Lesions, n	RVD, mm	Diameter stenosis, %	Length, mm	B2/C, %
DUTCH PEERS[8]	1,811	64.5	73	17.5	58.5	2,371	2.65	64.8	13.5	65.5
EVERBIO II[9]	160 (240)*	65	80	24	32	229 (325)*	2.46	79.2	N/R	32
HOST ASSURE[10]	3,755	63.3	67.7	32	65.5	5,087	3	73	19.5	50.7
LONG DES V[11]	500	63.3	70.2	33.5	42.6	500	3.02	72.2	30.7	N/R
PEXIP[12]	300	63.1	80	25.6	67.1	477	2.97	66.5	19.2	N/R
PLATINUM[13]	1,530	63.5	71.3	23.5	24.4	1,694	2.65	71.8	12.7	61.7
PLATINUM PLUS[14]	2,980	65.5	78	25.1	33.1	2,979	N/R	N/R	N/R	N/R

Overall mean values are reported. * without (with) patients/lesions included in the everolimus-eluting bioresorbable scaffold arm. ACS: acute coronary syndrome; N/R: not reported; RVD: reference vessel diameter. Trial acronyms: DUTCH PEERS: DUrable Polymer-based STent CHallenge of PROMUS Element Versus ReSolute Integrity; EVERBIO II: Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; HOST ASSURE: Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis - SAfety and EffectiveneSS of Drug-EIUting Stents and Anti-platelet Regimen; LONG DES V: Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-V: Everolimus-eluting (PROMUS-ELEMENT) vs. Biolimus A9-Eluting (NOBORI) Stents; PEXIP: An All Comers Randomized Trial Comparing Xience Prime and Promus Element stents; PLATINUM: A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System (PROMUS Element™) for the Treatment of up to Two De Novo Coronary Artery Lesions; PLATINUM PLUS: A Prospective, Randomized, Multicentre Trial to Assess the Everolimus-Eluting Coronary Stent System (PROMUS Element) for Coronary Revascularisation in a Population of Unrestricted Patients

a complex morphology. Among those randomised, 10,810 patients (98.0%) were available for outcome assessment. Median follow-up was 12 months (12-24; mean 17.6±9.5).

CLINICAL OUTCOMES

Figure 2 displays a summary of risk estimates for the primary and main secondary outcomes of this report. The details of risk estimates for each study endpoint are presented in the **Online Appendix**.

TLR (primary efficacy outcome) occurred in 261 patients (2.4%) **(Online Figure 1A)**. Patients treated with durable polymer PtCr-EES had a risk of TLR comparable to that observed with other DES (2.2% versus 2.6%; OR 0.98, 95% CI: 0.75-1.29, p=0.90; I^2=9%, p for heterogeneity - p_{het}=0.36). Of interest, in those trials with protocol-mandated control angiography[9,11], the degree of in-stent late lumen loss was comparable between durable polymer PtCr-EES and other DES (weighted mean difference 0.02, 95% CI: -0.05, 0.09, p=0.52; I^2=0%, p_{het}=0.50; data available for 475 patients).

Definite/probable ST (primary safety outcome) occurred in 71 patients (0.6%) **(Online Figure 1B)**. Patients treated with durable polymer PtCr-EES had a risk of definite/probable ST comparable to that observed with other DES (0.6% versus 0.7%; 0.89 [0.55-1.45], p=0.63; I^2=0%, p_{het}=0.56). The risk of early (0.2% versus 0.5%; 0.46 [0.19-1.11], p=0.08; I^2=0%, p_{het}=0.62) and late (0.1% versus 0.1%; 1.66 [0.23-12.05], p=0.61; I^2=23%, p_{het}=0.26) definite/probable ST was comparable between durable polymer PtCr-EES and other DES (data available for 5,851 participants).

Definite ST occurred in 44 patients (0.4%). Patients treated with durable polymer PtCr-EES had a risk of definite ST comparable to that observed with other DES (0.4% versus 0.5%; 0.96 [0.53-1.76], p=0.90; I^2=0%, p_{het}=0.88). The risk of early (0.2% versus 0.3%; 0.93 [0.34-2.49], p=0.88; I^2=0%, p_{het}=0.42) and late (0.2% versus 0.2%; 0.98 [0.43-34.55], p=0.98; I^2=25%, p_{het}=0.28) definite ST was comparable between durable polymer PtCr-EES and other DES (data available for 7,801 participants).

MI occurred in 244 patients (2.3%) **(Online Figure 2A)**. Patients treated with durable polymer PtCr-EES displayed a risk of MI comparable to that observed with other DES (2.2% versus 2.4%; 1.05 [0.81-1.38], p=0.70; I^2=0%, p_{het}=0.43). Of interest, MI related to the target vessel occurred in 130 patients (1.3%, data available for 10,010 participants). Patients treated with durable polymer PtCr-EES had a risk of MI related to the target vessel comparable to that observed with other DES (1.2% versus 1.7%; 0.97 [0.59-1.61], p=0.91; I^2=44%, p_{het}=0.15).

TVR occurred in 368 patients (3.5%, data available for 10,510 participants) **(Online Figure 2B)**. Patients treated with durable polymer PtCr-EES displayed a risk of TVR comparable to that observed with other DES (3.3% versus 3.8%; 1.04 [0.79-1.38], p=0.78; I^2=33%, p_{het}=0.19).

Death occurred in 259 patients (2.4%) **(Online Figure 3A)**. Patients treated with durable polymer PtCr-EES displayed a risk of death comparable to that observed with other DES (2.3% versus 2.5%; 1.00 [0.77-1.30], p=0.99; I^2=0%, p_{het}=0.44). Of interest, cardiac death occurred in 152 patients (1.4%) **(Online Figure 3B)**. Patients treated with durable polymer PtCr-EES displayed a risk of cardiac death comparable to that observed with other DES (1.3% versus 1.6%; 0.86 [0.61-1.19], p=0.36; I^2=0%, p_{het}=0.88).

LSD occurred in 16 patients (0.2%, data available for 7,372 participants) **(Online Figure 3C)**. Durable polymer PtCr-EES were

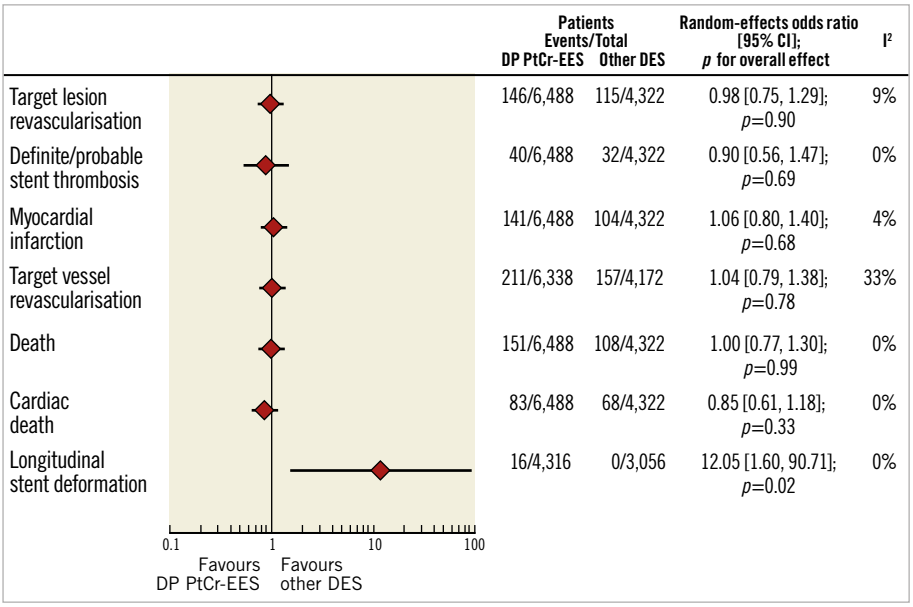

Figure 2. *Summary of risk estimates for primary and main secondary outcomes for DP PtCr-EES versus other DES. Plot of odds ratio associated with DP PtCr-EES versus other DES. The diamonds indicate the point estimate and the left and the right ends of the lines the 95% confidence interval (CI). DES: drug-eluting stent; DP PtCr-EES: durable polymer platinum-chromium everolimus-eluting stent*

associated with a higher risk of LSD as compared to other DES (0.4% versus 0%; 12.05 [1.60-90.71], p=0.02; I^2=0%, p_{het}=0.65). However, the higher risk of LSD with durable polymer PtCr-EES did not result in a higher risk of TLR (p for interaction - p_{int}=0.41) or definite/probable ST (p_{int}=0.72) as compared to other DES. A detailed description of clinical, angiographic and procedural features as well as of subsequent clinical outcomes of patients with LSD has been provided in **Online Table 4**.

SMALL STUDY EFFECTS, INFLUENCE AND SENSITIVITY ANALYSES

Funnel plot distribution of primary efficacy and safety outcomes was derived from the standard error of the natural logarithm OR plotted against the OR of TLR and definite/probable ST, respectively **(Online Figure 4A, Online Figure 4B)**. Of note, the absence of bias due to small study effects was confirmed both visually and mathematically. Additionally, influence analysis demonstrated that no single study significantly altered the summary OR for primary outcomes **(Online Table 5)**. The trial sequential analysis revealed that the accumulated sample size provided robust evidence for the primary efficacy outcome, but was still inadequate for the primary safety outcome **(Online Figure 5A, Online Figure 5B)**. Risk estimates for both TLR and definite/probable ST were independent from the comparator DES ($p_{int}\geq$0.29), the polymer releasing the antirestenotic drug ($p_{int}\geq$0.21) or the strut thickness ($p_{int}\geq$0.27) in the control DES group, the all-comers design of the trials ($p_{int}\geq$0.08) or the protocol-mandated control angiography ($p_{int}\geq$0.21) **(Online Figure 6A, Online Figure 6B)**.

Discussion

We undertook this meta-analysis to investigate the outcomes of PCI patients treated with either durable polymer PtCr-EES or other new-generation DES. At one-year follow-up, the durable polymer PtCr-EES showed: (i) similar efficacy and safety though (ii) a higher susceptibility to longitudinal deformation as compared to other DES.

The use of platinum as an alloy compound was aimed at improving the mechanical properties of metallic stent backbones[5]. Although preclinical studies of PtCr-based platforms have demonstrated less thrombogenicity and favourable endothelialisation patterns[5,6], these qualities might be difficult to measure in patients, because differences between devices that are detectable at bench level might have no clinical counterpart *in vivo*[27].

The durable polymer PtCr-EES investigated in the present meta-analysis consists of a PtCr metallic scaffold (81 µm strut thickness) coated with a poly n-butyl methacrylate primer layer and a durable drug matrix layer composed of a copolymer of polyvinylidene fluoride and hexafluoropropylene blended with everolimus (100 µg/cm^2 stent surface). Apart from the metallic scaffold, the drug/polymer combination of this device has the same biological behaviour as the CoCr-EES platform, which represents a benchmark new-generation DES[28].

Randomised clinical trials[8-14] investigating the comparative efficacy of durable polymer PtCr-EES against other new-generation DES platforms lacked the statistical power to draw firm conclusions regarding clinical outcomes. With this in mind, and considering the number of ongoing, large-scale randomised trials aiming to address this issue (NCT02193971, NCT01979744, NCT01740479, NCT01347554), we conducted a meta-analysis to investigate the performance of durable polymer PtCr-EES in PCI patients. By aggregating the data from seven randomised trials with ≈11,000 PCI patients allocated to durable polymer PtCr-EES versus other DES, this is the most comprehensive meta-analysis dealing with this topic. Previous meta-analyses did not include all randomised trials comparing the durable polymer PtCr-EES versus new-generation DES[28], evaluated mixed PtCr-EES platforms with different polymer coatings[29], and based their conclusions predominantly on indirect comparisons of PtCr-EES with early- and new-generation DES platforms[30].

First, in this report patients treated with the durable polymer PtCr-EES showed a risk of target lesion and target vessel revascularisation comparable to that of patients treated with other DES at one-year follow-up. Neither stent- nor trial-related features influenced the risk estimation of repeat revascularisation. On the one hand, this result confirms the favourable antirestenotic efficacy of durable polymer PtCr-EES observed in large-scale registries of unselected patients[31,32], and corroborates the angiographic findings of those trials[9,11] with available invasive surveillance. On the other hand, we showed for the first time that the data accumulated in >10,000 PCI patients provides robust evidence to discard a clinically relevant benefit in terms of repeat revascularisation associated with durable polymer PtCr-EES.

Second, this meta-analysis found a comparable risk of ST for durable polymer PtCr-EES and other DES. The risk estimation for ST was independent from stent- and trial-related features. The present analysis confirms once more the excellent safety profile of current high-performance DES, with an overall rate of ST after 12 months of 0.6% among >10,000 patients. The overall risk of ST appeared low and comparable among DES platforms studied, even though a large proportion of participants were enrolled in trials with an "all-comers" design[8,9,12]. Notwithstanding this, the impact of durable polymer PtCr-EES on ST needs to be studied further, since the available sample size accounts for <20% of that required to address a measurable effect of this device with respect to this endpoint. Ongoing large-scale randomised trials remain instrumental to disclose whether the mechanical and biological properties of PtCr-based stent platforms may lead to a lower thrombotic risk in humans.

Finally, the durable polymer PtCr-EES studied in this report carried a 12-fold increase in the risk of longitudinal deformation as compared with other DES. The occurrence of LSD remained negligible in absolute terms and was not associated with a worse clinical prognosis. Although instances of distortion or shortening of a stent along the longitudinal axis following its successful deployment are described with all DES platforms[33], in recent

years the majority of cases of LSD have involved the durable polymer PtCr-EES studied in this report. If unrecognised or left untreated, LSD has occasionally been associated with acute MI, ST and worse prognosis[33]. The incidence of LSD observed in the current analysis is somewhat lower than that reported in other series[34,35]. The lack of systematic use of intracoronary imaging, the different definitions of LSD applied in the original trials (ranging from changes in radiopacity to longitudinal shortening), and the relatively favourable lesions treated, may possibly have led to underreporting. Notably, the durable polymer PtCr-EES investigated in this study has been subject to iterations in the frame design (more connectors between the proximal hoops), which reduce the risk of LSD[36]. In this regard, our findings should be restricted to PCI patients treated with the original durable polymer PtCr-EES configuration, and with clinical and angiographic features similar to those reported in the present analysis.

Study limitations

A number of limitations inherent to the present study should be discussed. First, this meta-analysis was based on aggregate data and shared the flaws of the original trials. Second, the median follow-up was limited to one year and a longer follow-up is certainly desirable in comparative studies, especially to disclose fully significant differences in terms of safety outcomes. Third, different stent platforms with various combinations of drugs, polymers and backbones were represented in the control group, a fact that weakens the weight of the final results. Despite this issue having been addressed by undertaking additional analyses based on comparison against each of the individual control stents, the complex interplay between main DES components and clinical outcomes cannot be fully disclosed in the context of this study.

Fourth, this report cannot exclude that the outcomes associated with durable polymer PtCr-EES versus other new-generation DES may differ in specific subgroups of lesions and patients. Fifth, the type and the length of dual antiplatelet therapy differed among the trials included, and the actual compliance to prescribed antithrombotic therapy was not routinely reported within the original trials. Finally, the protocol-mandated surveillance angiography in two trials[9,11] may have magnified differences in the absolute proportion of revascularisations across groups. However, relative differences are unlikely to have been affected.

Conclusions

At one-year follow-up, clinical outcomes of PCI patients treated with durable polymer PtCr-EES are comparable to those of patients treated with other new-generation DES. The risk of stent thrombosis with durable polymer PtCr-EES as compared to other new-generation DES requires further investigation. The higher susceptibility to longitudinal deformation associated with durable polymer PtCr-EES remains rare in absolute terms and does not lead to clinical sequelae.

Impact on daily practice

Innovative components and thinner strut designs are the mainstay of contemporary drug-eluting stent technology. Stents eluting everolimus from a thin platinum-chromium metallic platform are used widely in daily practice. This analysis found that durable polymer platinum-chromium everolimus-eluting stents are associated with similar clinical outcomes but inferior longitudinal stability as compared to other modern drug-eluting stents. Despite the fact that drug-eluting stents with thinner-strut design represent an attractive alternative for challenging coronary anatomies, the trade-off in terms of longitudinal stability associated with these devices should be considered when selecting the best platform to be implanted.

Conflict of interest statement

A. Kastrati reports patent applications related to drug-eluting stent technologies. R. Byrne reports receiving lecture fees from B. Braun Melsungen AG, Biotronik and Boston Scientific and scientific support from Boston Scientific and HeartFlow. R. Colleran reports support from the Irish Board for Training in Cardiovascular Medicine sponsored by MSD. D. Giacoppo is the recipient of a research fellowship grant funded by the European Association of Percutaneous Cardiovascular Interventions (EAPCI). The other authors have no conflicts of interest to declare.

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Supplementary data

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Online Figure 6. Sensitivity analysis for primary outcomes.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/123rd_issue/147

SUPPLEMENTARY DATA

Outcomes of patients treated with durable polymer platinum-chromium everolimus-eluting stents: a meta-analysis of randomised trials

Authors: Cassese S, Ndrepepa G, Byrne RA, et al.

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Online Appendix

Search strategy and selection criteria

We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific sessions abstracts and relevant websites (www.cardiosource.com, www.clinicaltrialresults.org, www.escardio.org, www.tctmd.com, www.theheart.org) without restricting language or publication status. The references listed in all eligible studies were checked to identify further citations. Two searches were performed, the first in May 2016, the last in December 2016. Search terms included the keywords and the corresponding Medical Subject Headings for: “drug-eluting stent(s)”, “platinum-chromium”, “everolimus-eluting stent”, “Promus Element”, “trial”, and “randomized trial”. Inclusion criteria were: (1) randomized design; (2) intention to treat analysis; (3) ≥6-month follow-up. Exclusion criteria were: (1) comparisons other than durable polymer PtCr-EES versus new-generation DES; (2) ongoing trials; (3) and duplicated data. Stent platforms other than the early-generation sirolimus-eluting stent (CYPHER; Cordis, Warren, NJ, USA), paclitaxel-eluting stent (TAXUS; Boston Scientific, Natick, MA, USA) and fast-release zotarolimus-eluting stent (ZES) (Endeavor; Medtronic Vascular, Santa Rosa, CA, USA) were considered new-generation DES.

Search strategy: PubMed

“("drug-eluting stents"[MeSH Terms] OR ("drug-eluting"[All Fields] AND "stents"[All Fields]) OR "drug-eluting stents"[All Fields] OR ("drug"[All Fields] AND "eluting"[All Fields] AND "stent"[All Fields]) OR "drug eluting stent"[All Fields]) AND platinum-chromium[All Fields] AND (everolimus-eluting[All Fields] AND ("stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields])) AND (Promus[All Fields] AND ("Element"[MeSH Terms] OR "Element"[All Fields] OR "element"[All Fields]) AND ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields]))

Online Table 1. Main characteristics of trials included in the study.

Trial	Period of enrolment	Main inclusion criteria	Main exclusion criteria	Primary endpoints	Registration number
DUTCH PEERS[8]	2010-2012	Age ≥18 years; eligibility for PCI with DES ("all-comers" design)	Contraindications for or expected non-adherence to DAPT; life expectancy <1 year; planned major surgery ≤6 months, unless DAPT maintained; inability or refusal to comply with follow-up procedures; participation in other coronary device trial; inability to give informed consent	12-month TVF (composite of cardiac death-TV-MI and CD-TVR)	NCT01331707
EVERBIO II[9]	2012-2013	Age ≥18 years; eligibility for PCI with DES ("all-comers" design); reference vessel diameter ≤4.0 mm	Known or presumed hypersensitivity to heparin, antiplatelet drugs and hypersensitivity to contrast dye not controllable with standard premedication	9-month in-segment LLL	NCT01711931
HOST ASSURE[10]	2010-2011	Age ≥18 years; ≥1 coronary vessel disease with a diameter stenosis >50% (with proven ischaemia) or ≥1 coronary vessel disease with a diameter stenosis >70% (with or without proven ischaemia) eligible for DES implantation; reference vessel diameter ≥2.5 to ≤4.00 mm	LVEF ≤25% or cardiogenic shock; intolerance to antiplatelet or stent drugs; gastrointestinal or genitourinary bleeding ≤3 months; bleeding diathesis, known coagulopathy (including heparin-induced thrombocytopaenia), Hb <10 g/dl or platelet count <100,000/μL; planned surgery ≤2 months after index PCI; infusive therapy with everolimus or zotarolimus ≤12 months	12-month TLF (composite of cardiac death, TV-MI and TLR)	NCT01267734
LONG DES V[11]	2010-2012	Age ≥18 years; ischaemic heart disease (stable angina, unstable angina, NSTEMI, or inducible ischaemia); ≥1 *de novo* coronary lesion with a diameter stenosis ≥50%, a reference vessel diameter ≥2.5 mm, a lesion length ≥25 mm, and a	LVEF ≤30% or cardiogenic shock; STEMI; significant (>50%) left main disease; previous stenting of the target vessel; contraindications for or expected non-adherence to DAPT; life expectancy <1 year; planned surgery within 6 months after index PCI; serum creatinine concentration ≥2.0 mg/dl) or dependence on dialysis	9-month in-segment LLL	NCT01186120

		planned total stent length ≥28 mm			
PEXIP[12]	2009-2010	Age ≥18 years ("all-comers" design)	Cardiogenic shock; contraindications for or expected non-adherence to DAPT (chronic oral anticoagulation, planned surgery at short to medium term, and high risk of haemorrhage); life expectancy <2 years	12-month composite of death, MI and TLR	N/R
PLATINUM[13]	2009	Age ≥18 years; chronic ischaemic heart disease or acute coronary syndromes; ≤2 *de novo* coronary lesions with a diameter stenosis ≥50% and <100%, a reference vessel diameter ≥2.5 to ≤4.25 mm, a lesion length ≤24 mm and a TIMI flow grade 2-3	Acute or recent MI; LVEF ≤30% or cardiogenic shock; stroke or TIA within 6 months or any permanent neurologic defect; target vessel treatment with brachytherapy (anytime), atherectomy, laser, or cutting balloon before stent placement; lesion location in an ostial or left main location or in or through a bypass graft conduit; true bifurcation lesion (side branch ≥2.0 mm in diameter by visual estimate or with a significant ostial stenosis); excessive tortuosity, angulation, or calcification proximal to or within the lesion; or presence of thrombus in the target vessel; platelet count <100,000 or >700,000/µL; planned PCI or CABG after the index PCI; chemotherapy or immunosuppressive therapy planned after index PCI; planned surgery after index PCI; allergy or intolerance to antiplatelet or stent drugs; chronic oral anticoagulation; eGFR <50 ml/min or dependence on dialysis; active bleeding or bleeding diathesis; inability to give informed consent or to participate in protocol-required follow-up procedures; life expectancy <2 years	12-month TLF (composite of cardiac death related to the target vessel-TV-MI and CD-TLR)	NCT00823212
PLATINUM PLUS[14]	2009-2011	Age ≥18 years; symptomatic ischaemic heart disease (CCS	LVEF ≤20% or cardiogenic shock; medical illness (e.g., cancer, known malignancy,	12-month TVF (composite of	NCT01342822

		class 1-4, Braunwald Class IB-IC, and/or objective evidence of myocardial ischaemia); single or multiple coronary lesions with a reference vessel diameter ≥2.5 to ≤4.25 mm	congestive heart failure, organ transplant recipient or candidate) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause non-compliance with the protocol, confound the data interpretation or is associated with a limited life expectancy (i.e., life expectancy <1 year); known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, clopidogrel/ticlopidine, prasugrel, platinum-chromium alloy, everolimus, and/or contrast sensitivity that cannot be adequately pre-medicated	CD-TVR, TV-MI, cardiac death related to the target vessel)	

PCI: percutaneous coronary intervention; DES: drug-eluting stent; DAPT: dual antiplatelet therapy; TVF: target vessel failure; (TV)-MI: (target vessel)-myocardial infarction; TVR: target vessel revascularisation; TLR: target lesion revascularisation; ST: stent thrombosis; CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; LLL: late lumen loss; TIA: transient ischaemic attack; N/R: not reported

Trial acronyms: DUTCH PEERS: DUrable Polymer-based STent CHallenge of Promus Element Versus ReSolute Integrity; EVERBIO II: Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; HOST ASSURE: Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis, SAfety and EffectiveneSS of Drug-ElUting Stents and Anti-platelet Regimen; LONG DES V: Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-V:Everolimus-eluting (PROMUS-ELEMENT) vs. Biolimus A9-Eluting (NOBORI) Stents; PEXIP: An All Comers Randomized Trial Comparing Xience Prime and Promus Element stents; PLATINUM: A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System (PROMUS Element™) for the Treatment of up to Two De Novo Coronary Artery Lesions; PLATINUM PLUS: A Prospective, Randomized, Multi-center Trial to Assess the Everolimus-Eluting Coronary Stent System (PROMUS Element) for Coronary Revascularization in a Population of Unrestricted Patients

Online Table 2. Definitions of clinical outcomes according to protocols within trials included in the study.

Trial	TLR/TVR	Definite/probable ST	Death/cardiac death	MI	LSD
DUTCH PEERS[8]	Any clinically indicated repeat target lesion (vessel) revascularisation by means of coronary artery bypass graft or PCI	ARC definitions	Any death caused by proximate cardiac cause (e.g., MI, low-output failure, or fatal arrhythmia), unwitnessed death, death of unknown cause, and all procedure-related deaths, including those related to concomitant therapy. All deaths are considered cardiac, unless an unequivocal non-cardiac cause can be established	ARC definitions	Any distortion or shortening of an implanted stent in the longitudinal axis after initially successful deployment. On angiography, any localised change in radiopacity pattern of a stent that occurred between initial deployment and the end of the procedure, after manipulations with the guiding catheter, or after the use of further catheter-based devices (e.g., an attempt to recross a deployed stent with a balloon catheter, imaging catheter, or another stent).
EVERBIO II[9]	TLR: any repeat revascularisation within the stent or the 5 mm borders proximal and distal to the stent; TVR: any revascularisation in the stented vessel	ARC definitions	Death was considered of cardiac origin when due to proximate cardiac cause, unwitnessed death, or death of unknown cause	New pathological Q-waves ≥0.04 s in duration in ≥2 contiguous leads or an elevation of CK levels to >2 times ULN with	N/A

				positive CK-MB or troponin I levels	
HOST ASSURE[10]	Any repeat PCI of the target lesion (vessel) or CABG of the target vessel performed for restenosis or other complication of the target lesion, with the target lesion defined as the treated segment including 5 mm proximal and distal to the stent (clinically driven)	ARC definitions	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established	Clinical signs of MI combined with a CK-MB fraction or troponin-T or -I increase >ULN	Any inconsistency in the radio-density pattern along the length of the stent, or other gross irregularities or deformities
LONG DES V[11]	Any revascularisation of the target lesion (vessel) considered to be ischaemia-driven if the treated lesion (vessel) had ≥50% diameter stenosis, with ischaemic signs or symptoms; or the target lesion (or vessel) had ≥70% diameter stenosis, with or without documented ischaemia	ARC definitions	All deaths were considered to be from cardiac causes unless a non-cardiac cause could be identified	New Q-waves in ≥2 contiguous leads on an ECG or an elevation in the CK-MB iso-enzyme fraction or troponin-I concentration >3 times ULN in ≥2 blood samples. Periprocedural MI: elevation of CK-MB >3 times ULN in ≥2 blood samples with a normal range in the baseline value within 48 hours of the PCI. If the pre-PCI CK-MB values were >ULN, as in the case of patients initially presenting	N/A

				with acute MI, a CK-MB re-elevation ≥50% greater than the most recent pre-PCI concentration, with documentation that the values were stable or falling before PCI	
PEXIP[12]	TLR: a revascularisation upon a restenotic lesion, including the stent and the 5 mm of vessel adjacent to the stent; TVR: a new revascularisation procedure, conducted at any level of the coronary tree	ARC definitions	Any death where a cardiac cause can be determined, and those deaths where no aetiology can be determined	Increase and gradual fall (troponin), or a faster increase and fall (CK-MB) of biochemical markers for myocardial necrosis with at least one of the following: ischaemic symptoms; development of pathological Q-waves, pathological ECG changes indicating ischaemia (ST-segment elevation or depression), or pathological results of acute MI	Any longitudinal deformation or shortening of an implanted stent
PLATINUM[13]	Any (clinically driven) revascularisation of the target lesion (vessel) with a stenosis ≥50% if associated with clinical or functional ischaemia (ischaemic symptoms, electrocardiographic	ARC definitions	Any death other than those confirmed to have a non-cardiac cause were considered cardiac	New Q-waves in ≥2 leads lasting >0.04 s with CK-MB or troponin levels elevated above ULN; in the absence of new Q-waves, elevation of total CK levels >3	Difference in the QCA measured:nominal stent length ratio

	changes, or positive functional study), or stenosis ≥70% without documented ischaemia			times ULN (peri-PCI) or >2 times ULN (spontaneous) with elevated CK-MB, or troponin >3 times ULN (peri-PCI) or >2 times ULN (spontaneous) plus ≥1 of the following: ECG changes indicative of new ischaemia (new ST-T changes or LBBB); or imaging evidence of new loss of viable myocardium; or new regional wall motion abnormality. The diagnosis of MI after CABG surgery required CK-MB or troponin threshold of >5 times ULN	
PLATINUM PLUS[14]	Any clinically indicated repeat target lesion (vessel) revascularisation by means of coronary artery bypass graft or PCI	ARC definitions	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established	Q-wave and non-Q-wave	N/A

PCI: percutaneous coronary intervention; TLR/TVR: target lesion/vessel revascularisation; ST: stent thrombosis; MI: myocardial infarction; LSD: longitudinal stent deformation; CK-(MB): creatine kinase (myocardial band); ULN: upper level of normal; RVD: reference vessel diameter; QCA: quantitative coronary angiography; ARC: Academic Research Consortium; CABG: coronary artery bypass graft; N/A: not applicable.
Trial acronyms are reported in Online Table 1.

Online Table 3. Assessment of risk of bias.

Trial	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Description of incomplete outcome data	Selective outcome reporting	Sample size calculation	Funding source
DUTCH PEERS[8]	Yes (computer-generated, block)	Yes (numbered, opaque, sealed envelopes)	Yes	Yes (independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority design)	Yes (industry research grant)
EVERBIO II[9]	Yes (computer-generated)	Yes (numbered, opaque, sealed envelopes)	No	Yes (independent CEC)	Yes (flow diagram)	No	Yes (superiority design)*	Yes (industry and institutional research grant)
HOST ASSURE[10]	Yes (web-based)	No	Yes	Yes (independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority design)	Yes (industry and institutional research grant)
LONG DES V[11]	Yes (IWRS-based, block)	No	Yes	Yes (independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority design)	Yes (industry and institutional research grant)
PEXIP[12]	Yes (computer-generated)	N/R	No	N/R	No	No	No	Yes (investigator-initiated)
PLATINUM[13]	Yes (computer-generated, block)	No	Yes	Yes (independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority design)	Yes (industry research grant)
PLATINUM PLUS[14]	Yes (computer-generated)	N/R	No	Yes (independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority design)	Yes (industry research grant)

*For the angiographic comparison of everolimus/biolimus-eluting stents versus everolimus-eluting bioresorbable vascular scaffold.
IWRS: interactive web.response system; N/R: not reported; CEC: clinical events committee.
Trial acronyms are reported in Online Table 1.

Online Table 4. Main characteristics and clinical outcomes of patients with LSD as reported in the original trials.

Case	Age, years	Gender	Stent type/size, mm	Vessel/segment	Complex lesion	Cause for LSD	Procedural consequences	Clinical consequences
1_DUP	62	Male	DP PtCr-EES/3.0 x 38	LAD/mid	Yes, bifurcation	Deformation following attempts to recross implanted stent	Additional proximal stent	None
2_DUP	77	Female	DP PtCr-EES/2.5 x 32	RCA/mid	Yes, severe calcification	Deformation following attempts to recross implanted stent	Additional proximal stent	None
3_DUP	48	Male	DP PtCr-EES/3.5 x 24	LAD/proximal	Yes, bifurcation	Deformation following attempts to recross implanted stent	Additional proximal stent	None
4_DUP	63	Female	DP PtCr-EES/2.25 x 16	LAD/proximal	Yes, bifurcation	Deformation following attempts to recross implanted stent	Additional proximal stent	None
5_DUP	74	Male	DP PtCr-EES/2.25 x 22	LAD/proximal	Yes, severe calcification	Deformation following very oversized stent post-dilation	Additional proximal stent	None
6_DUP	36	Male	DP PtCr-EES/3.5 x 16	LMCA	Yes, bifurcation	Deformation following very oversized stent post-dilation	No additional stent	None
7_DUP	41	Male	DP PtCr-EES/2.5 x 32	RCA/distal	Yes, bifurcation	Deformation following contact of stent with guiding catheter or balloon catheter	Additional proximal stent	None
8_DUP	53	Male	DP PtCr-EES/3.0 x 12	LAD/proximal	Yes, moderate calcification	Deformation following contact of stent with guiding catheter or balloon catheter	Additional proximal stent	None

9_DUP	73	Male	DP PtCr-EES/3.0 x 24	RCA/mid	Yes, severe calcification	Deformation following contact of stent with guiding catheter or balloon catheter	No additional stent	None
10_HOA	61	Male	DP PtCr-EES/3.0 x 24	LMCA	Yes, bifurcation	Deformation following contact of stent with guiding catheter or balloon catheter	No additional stent	None
11_HOA	59	Male	DP PtCr-EES/3.0 x 28	LMCA	No	Deformation following contact of stent with guiding catheter or balloon catheter	No additional stent	None
12_HOA	50	Female	DP PtCr-EES/4.0 x 28	LAD/mid	No	Deformation following contact of stent with guiding catheter or balloon catheter	No additional stent	None
13_HOA	72	Male	DP PtCr-EES/3.0 x 28	RCA/proximal	No	Deformation following contact of stent with guiding catheter or balloon catheter	No additional stent	None
14_HOA	39	Male	DP PtCr-EES/4.0 x 28	LAD/proximal	Yes, bifurcation	Deformation following contact of stent with guiding catheter or balloon catheter	No additional stent	None
15_HOA	81	Female	DP PtCr-EES/3.0 x 20	LAD/mid	Yes, bifurcation	Deformation following contact of stent with guiding catheter or balloon catheter	Additional proximal stent	None
16_HOA	68	Male	DP PtCr-EES/3.0 x 28	LAD/mid	No	Deformation following contact of stent with guiding catheter or balloon catheter	No additional stent	None

LSD: longitudinal stent deformation; DP PtCr-EES: durable-polymer platinum-chromium everolimus-eluting stent; LAD: left anterior descending (artery); RCA; right coronary artery; LMCA: left main coronary artery; DUP: DUTCH PEERS; HOA: HOST ASSURE.
Trial acronyms are reported in Online Table 1.

Online Table 5. Influence analysis of primary outcomes.

Study omitted	TLR Overall OR [95% CI]	*p*	I^2	Definite/probable ST Overall OR [95% CI]	*p*	I^2
DUTCH PEERS[8]	1.02 [0.71-1.46]	0.93	24%	0.84 [0.47-1.51]	0.57	0%
EVERBIO II[9]	0.92 [0.71-1.20]	0.54	0%	0.89 [0.55-1.45]	0.63	0%
HOST ASSURE[10]	0.99 [0.70-1.39]	0.94	24%	1.05 [0.59-1.84]	0.88	0%
LONG DES V[11]	1.02 [0.76-1.36]	0.91	14%	0.94 [0.57-1.54]	0.79	0%
PEXIP[12]	0.98 [0.72-1.33]	0.89	22%	0.91 [0.55-1.50]	0.71	0%
PLATINUM[13]	1.08 [0.81-1.45]	0.59	0%	0.85 [0.50-1.43]	0.54	0%
PLATINUM PLUS[14]	0.94 [0.68-1.29]	0.70	15%	0.76 [0.44-1.33]	0.34	0%

TLR: target lesion revascularisation; ST: stent thrombosis; OR: odds ratio; CI: confidence interval. Trial acronyms are reported in Online Table 1.

Online Figure legends

Online Figure 1. Risk estimates of primary outcomes.

Plot of odds ratio for A) target lesion revascularisation and B) definite/probable stent thrombosis associated with DP PtCr-EES versus other DES. The diamonds indicate the point estimate and the left and the right ends of the lines the 95% confidence interval (CI).

DP PtCr-EES: durable polymer platinum-chromium everolimus-eluting stent; DES: drug-eluting stent.

Trial acronyms are reported in Online Table 1.

Online Figure 2. Risk estimates of secondary outcomes (MI, TVR).

Plot of odds ratio for A) myocardial infarction and B) target vessel revascularisation associated with DP PtCr-EES versus other DES. The diamonds indicate the point estimate and the left and the right ends of the lines the 95% confidence interval (CI). Abbreviations as in Online Figure 1.

Online Figure 3. Risk estimates of secondary outcomes (death, cardiac death, LSD).

Plot of odds ratio for A) death, B) cardiac death, and C) longitudinal stent deformation associated with DP PtCr-EES versus other DES. The diamonds indicate the point estimate and the left and the right ends of the lines the 95% confidence interval (CI). Abbreviations as in Online Figure 1.

Online Figure 4. Funnel plot distribution of trials according to primary outcomes.

The standard error (SE) of the logarithm of odds ratio – log(OR) – is plotted against the OR of A) target lesion revascularisation and B) definite/probable stent thrombosis. Abbreviations as in Online Figure 1.

Online Figure 5. Trial sequential analysis for primary outcomes.

A) Trial sequential analysis for target lesion revascularisation. Heterogeneity-adjusted estimated sample size (ESS) of 16,521 participants calculated on the basis of odds ratio of TLR of 2.6% in the other DES group, relative risk (RR) reduction=25%, alpha=5%, beta=20%, I^2=0%. Dashed blue cumulative Z-curve crossed neither the light green dashed traditional boundary nor the dashed red information size boundary; however, the dashed blue cumulative Z-curve crossed the dashed red futility boundary, thereby suggesting robust evidence in the DP PtCr-EES group compared with the other DES group for this outcome. Horizontal dashed light green lines illustrate the traditional level of statistical significance (p=0.05).

B) Trial sequential analysis for definite/probable stent thrombosis. Heterogeneity-adjusted ESS of 66,400 participants calculated on the basis of odds ratio of definite/probable stent thrombosis of 0.7% in the other DES group, RR reduction=25%, alpha=5%, beta=20%, I^2=0%. The dashed blue cumulative Z-curve neither crossed the light green dashed traditional boundary nor the dashed red information size boundary, thereby suggesting a lack of firm evidence in the DP PtCr-EES group compared with the other DES group for this outcome. Horizontal dashed green blue lines illustrate the traditional level of statistical significance (p=0.05). Abbreviations as in Online Figure 1.

Online Figure 6. Sensitivity analysis for primary outcomes.

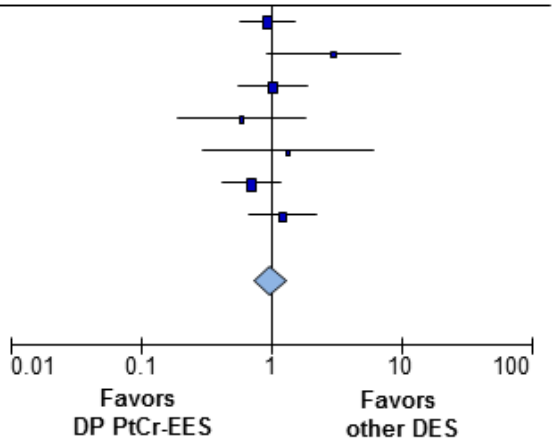
Plot of odds ratio (OR) for A) target lesion revascularisation and B) definite/probable stent thrombosis associated with DP PtCr-EES versus other DES among subgroups of interest. The square indicates the point estimate and the left and the right ends of the line the 95% confidence interval (CI) for the subgroup of interest; p_{int}: p-values for interaction between treatment effect and subgroups are derived with the Cochran's Q test.

BES: biolimus-eluting stents; CoCr-EES: cobalt-chromium everolimus-eluting stents; ZES: zotarolimus-eluting stents. Other abbreviations as in Online Figure 1.

A. Target lesion revascularization

Trial	DP PtCr-EES Events	DP PtCr-EES Total	Other DES Events	Other DES Total	Weight	Random-effects odds ratio [95% CI]
DUTCH PEERS	32	905	34	905	25.9%	0.94 [0.57, 1.54]
EVERBIO II	11	80	4	80	5.2%	3.03 [0.92, 9.96]
HOST ASSURE	31	2503	15	1252	17.4%	1.03 [0.56, 1.92]
LONG DES V	5	255	8	245	5.7%	0.59 [0.19, 1.84]
PEXIP	4	150	3	150	3.2%	1.34 [0.30, 6.10]
PLATINUM	26	733	35	703	23.7%	0.70 [0.42, 1.18]
PLATINUM Plus	37	1862	16	987	18.9%	1.23 [0.68, 2.22]
Total	**146**	**6488**	**115**	**4322**	**100.0%**	**0.98 [0.75, 1.29]**

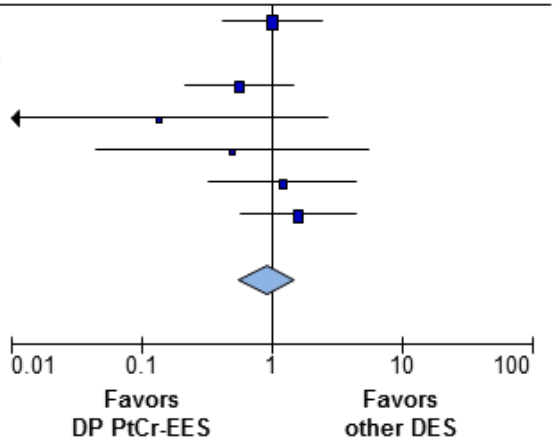
Heterogeneity: Tau² = 0.01; Chi² = 6.60, df = 6 (P = 0.36); I² = 9%
Test for overall effect: Z = 0.13 (P = 0.90)



B. Definite/probable stent thrombosis

Trial	DP PtCr-EES Events	DP PtCr-EES Total	Other DES Events	Other DES Total	Weight	Random-effects odds ratio [95% CI]
DUTCH PEERS	10	905	10	905	30.5%	1.00 [0.41, 2.41]
EVERBIO II	0	80	0	80		Not estimable
HOST ASSURE	9	2503	8	1252	26.0%	0.56 [0.22, 1.46]
LONG DES V	0	255	3	245	2.7%	0.14 [0.01, 2.64]
PEXIP	1	150	2	150	4.1%	0.50 [0.04, 5.54]
PLATINUM	5	733	4	703	13.6%	1.20 [0.32, 4.49]
PLATINUM Plus	15	1862	5	987	23.0%	1.60 [0.58, 4.40]
Total	**40**	**6488**	**32**	**4322**	**100.0%**	**0.90 [0.56, 1.47]**

Heterogeneity: Tau² = 0.00; Chi² = 4.20, df = 5 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

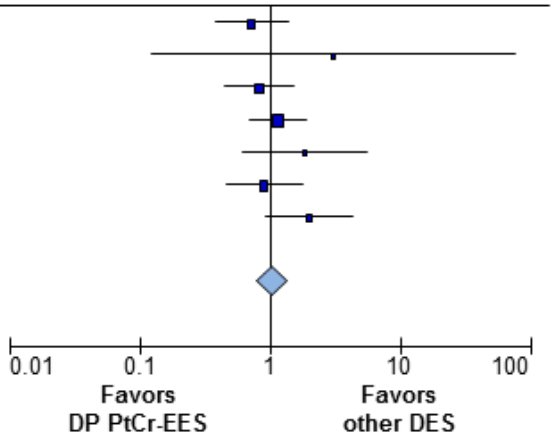


S-Figure 1.

A. Myocardial infarction

Trial	DP PtCr-EES Events	DP PtCr-EES Total	Other DES Events	Other DES Total	Weight	Random-effects odds ratio [95% CI]
DUTCH PEERS	16	905	22	905	17.1%	0.72 [0.38, 1.38]
EVERBIO II	1	80	0	80	0.7%	3.04 [0.12, 75.69]
HOST ASSURE	28	2503	17	1252	19.5%	0.82 [0.45, 1.51]
LONG DES V	40	255	34	245	28.5%	1.15 [0.70, 1.89]
PEXIP	9	150	5	150	6.0%	1.85 [0.61, 5.66]
PLATINUM	17	733	18	703	16.1%	0.90 [0.46, 1.77]
PLATINUM Plus	30	1862	8	987	12.0%	2.00 [0.92, 4.39]
Total	**141**	**6488**	**104**	**4322**	**100.0%**	**1.06 [0.80, 1.40]**

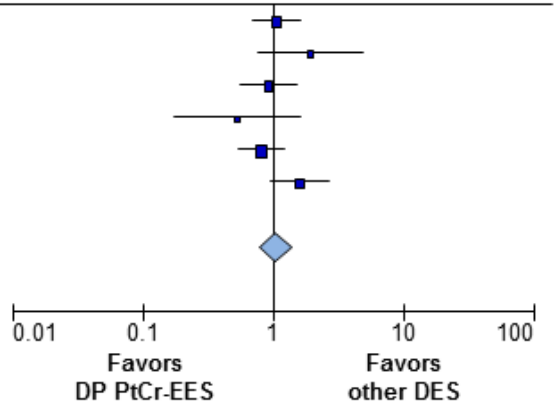
Heterogeneity: Tau² = 0.01; Chi² = 6.26, df = 6 (P = 0.39); I² = 4%
Test for overall effect: Z = 0.42 (P = 0.68)



B. Target vessel revascularization

Trial	DP PtCr-EES Events	DP PtCr-EES Total	Other DES Events	Other DES Total	Weight	Random-effects odds ratio [95% CI]
DUTCH PEERS	44	905	42	905	23.3%	1.05 [0.68, 1.62]
EVERBIO II	14	80	8	80	7.7%	1.91 [0.75, 4.84]
HOST ASSURE	42	2503	23	1252	19.0%	0.91 [0.55, 1.52]
LONG DES V	5	255	9	245	5.7%	0.52 [0.17, 1.59]
PLATINUM	47	733	55	703	25.2%	0.81 [0.54, 1.21]
PLATINUM Plus	59	1862	20	987	19.0%	1.58 [0.95, 2.64]
Total	**211**	**6338**	**157**	**4172**	**100.0%**	**1.04 [0.79, 1.38]**

Heterogeneity: Tau² = 0.04; Chi² = 7.43, df = 5 (P = 0.19); I² = 33%
Test for overall effect: Z = 0.28 (P = 0.78)

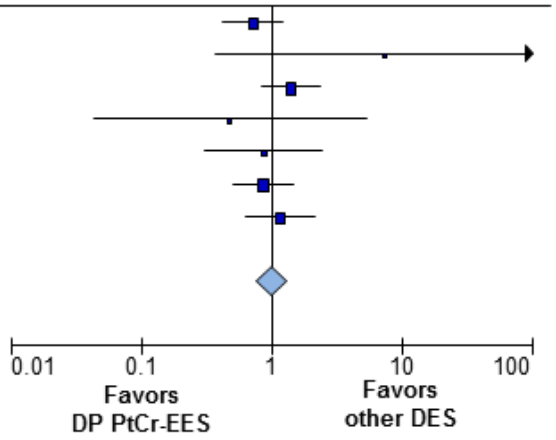


S-Figure 2.

A. Death

Trial	DP PtCr-EES Events	DP PtCr-EES Total	Other DES Events	Other DES Total	Weight	Random-effects odds ratio [95% CI]
DUTCH PEERS	24	905	33	905	23.9%	0.72 [0.42, 1.23]
EVERBIO II	3	80	0	80	0.8%	7.27 [0.37, 143.09]
HOST ASSURE	56	2503	20	1252	25.7%	1.41 [0.84, 2.36]
LONG DES V	1	255	2	245	1.2%	0.48 [0.04, 5.31]
PEXIP	7	150	8	150	6.3%	0.87 [0.31, 2.46]
PLATINUM	27	733	30	703	24.2%	0.86 [0.50, 1.46]
PLATINUM Plus	33	1862	15	987	18.0%	1.17 [0.63, 2.16]
Total	**151**	**6488**	**108**	**4322**	**100.0%**	**1.00 [0.77, 1.30]**

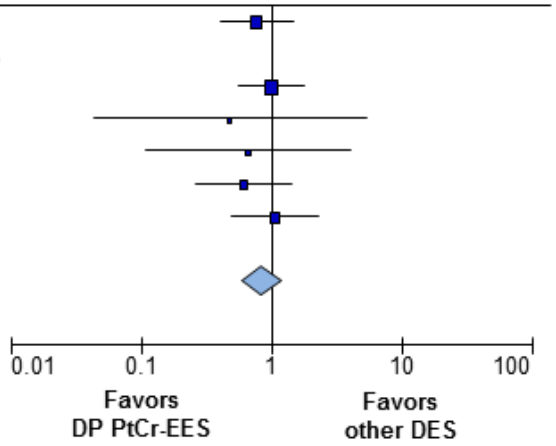
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.88$, df = 6 (P = 0.44); $I^2 = 0\%$
Test for overall effect: Z = 0.01 (P = 0.99)



B. Cardiac death

Trial	DP PtCr-EES Events	DP PtCr-EES Total	Other DES Events	Other DES Total	Weight	Random-effects odds ratio [95% CI]
DUTCH PEERS	17	905	22	905	27.3%	0.77 [0.41, 1.46]
EVERBIO II	0	80	0	80		Not estimable
HOST ASSURE	34	2503	17	1252	32.5%	1.00 [0.56, 1.80]
LONG DES V	1	255	2	245	1.9%	0.48 [0.04, 5.31]
PEXIP	2	150	3	150	3.4%	0.66 [0.11, 4.02]
PLATINUM	9	733	14	703	15.7%	0.61 [0.26, 1.42]
PLATINUM Plus	20	1862	10	987	19.2%	1.06 [0.49, 2.28]
Total	**83**	**6488**	**68**	**4322**	**100.0%**	**0.85 [0.61, 1.18]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.59$, df = 5 (P = 0.90); $I^2 = 0\%$
Test for overall effect: Z = 0.97 (P = 0.33)

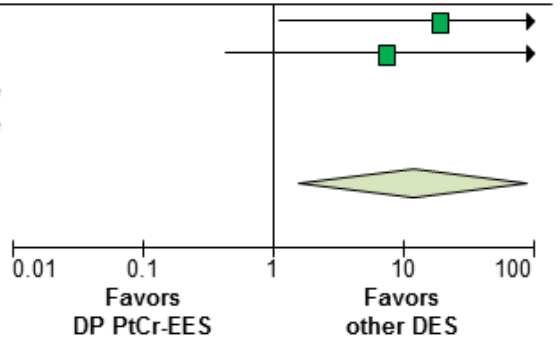


S-Figure 3.

C. Longitudinal stent deformation

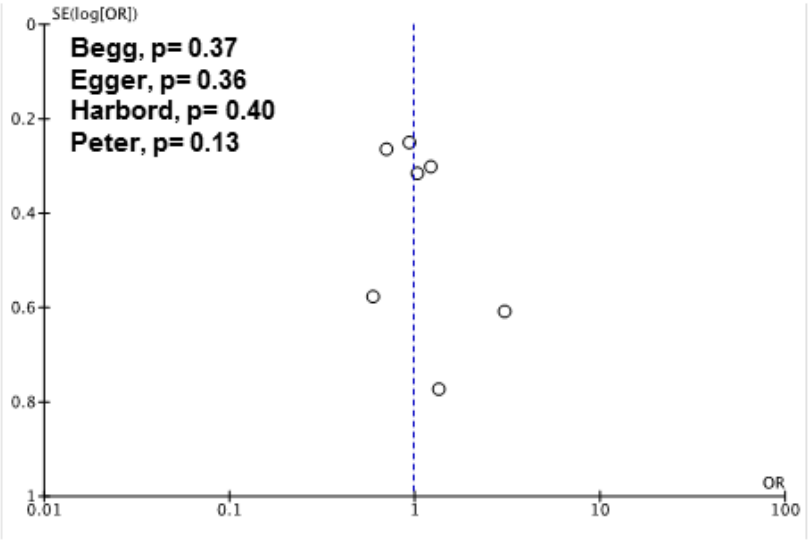
Trial	DP PtCr-EES Events	DP PtCr-EES Total	Other DES Events	Other DES Total	Weight	Random-effects odds ratio [95% CI]
DUTCH PEERS	9	905	0	905	50.3%	19.19 [1.12, 330.21]
HOST ASSURE	7	2503	0	1252	49.7%	7.53 [0.43, 131.87]
PEXIP	0	150	0	150		Not estimable
PLATINUM	0	758	0	749		Not estimable
Total	**16**	**4316**	**0**	**3056**	**100.0%**	**12.05 [1.60, 90.71]**

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

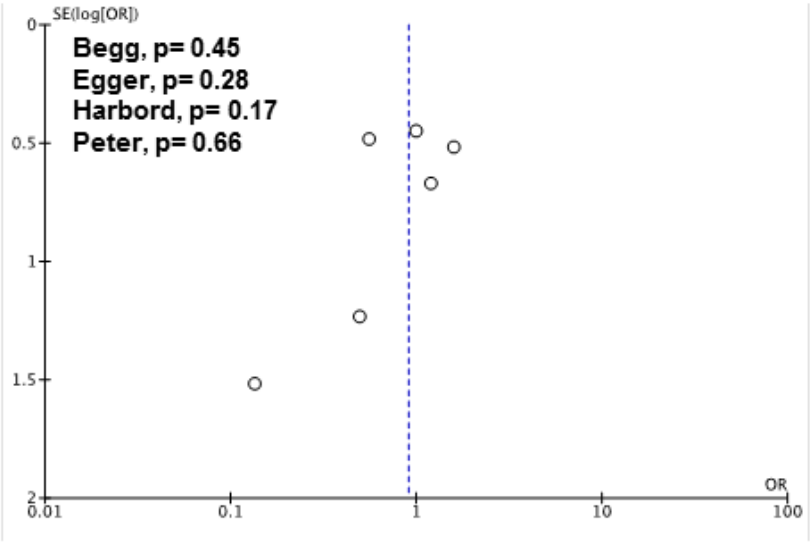


S-Figure 3.

A. Target lesion revascularization

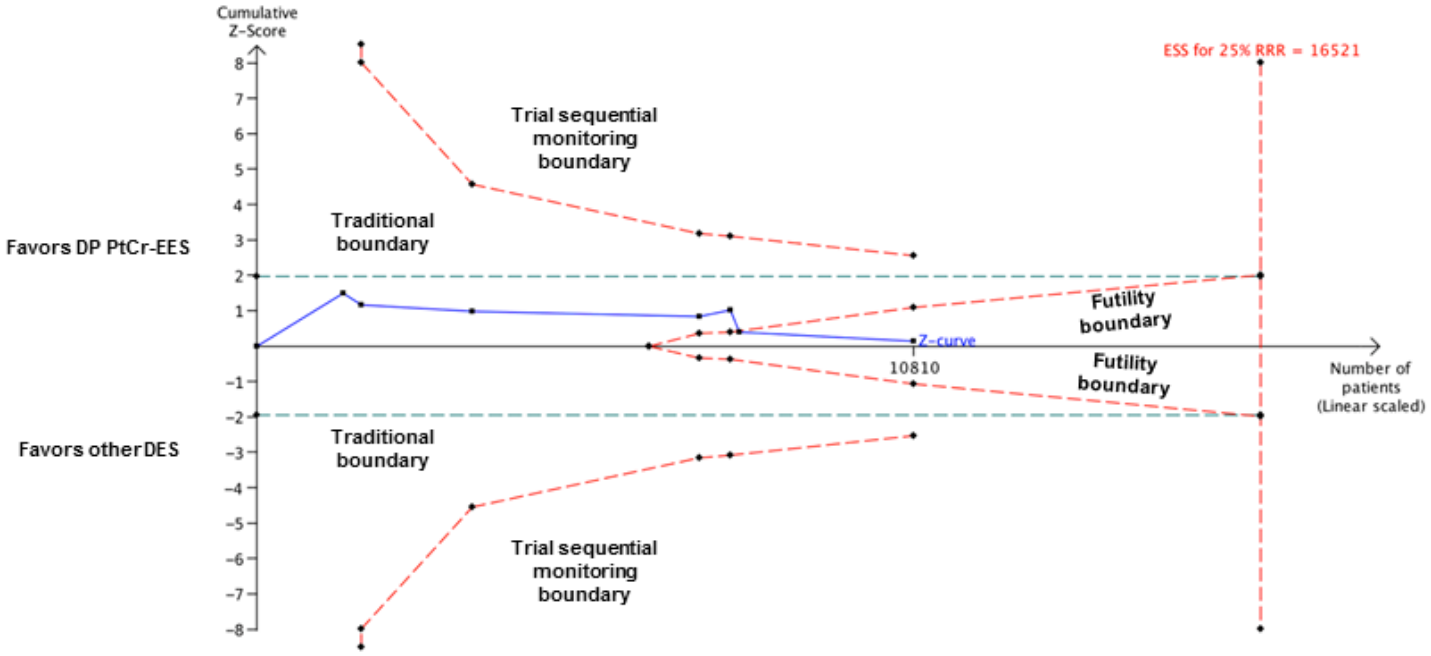


B. Definite/probable stent thrombosis



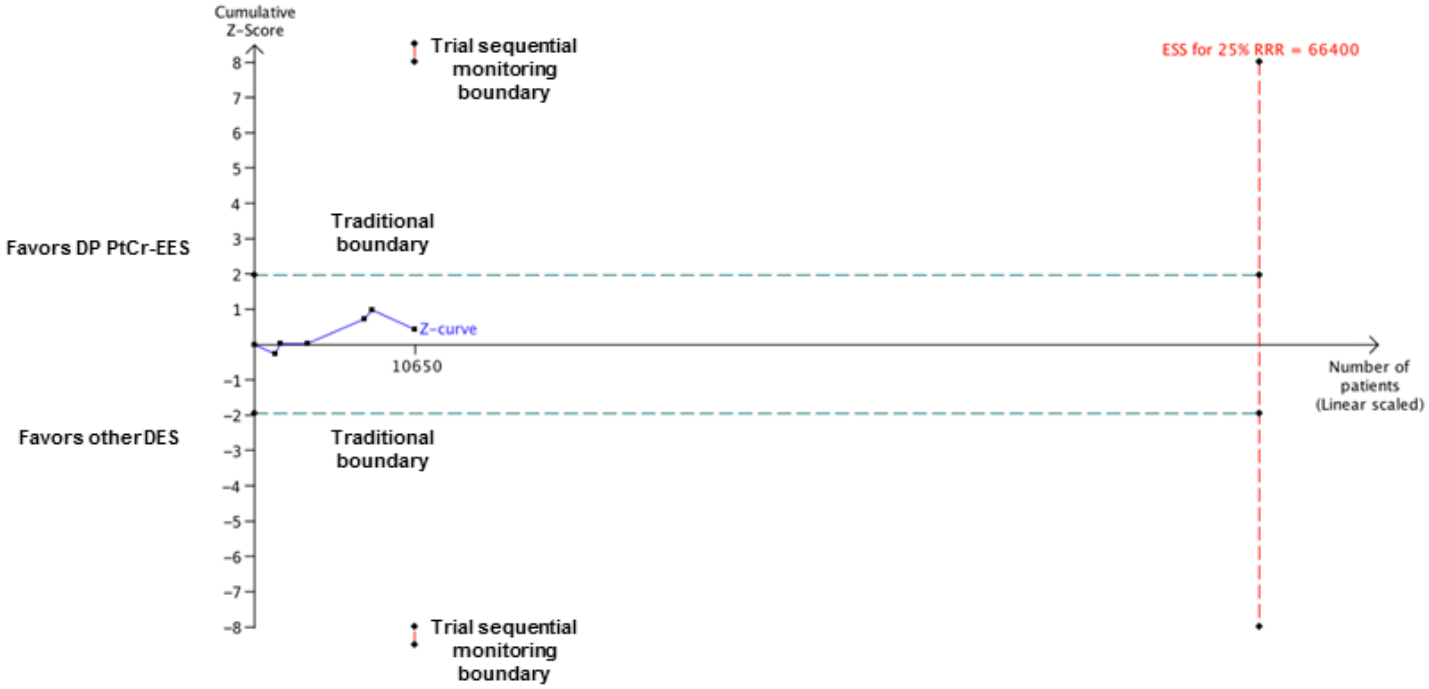
S-Figure 4.

A. Target lesion revascularization



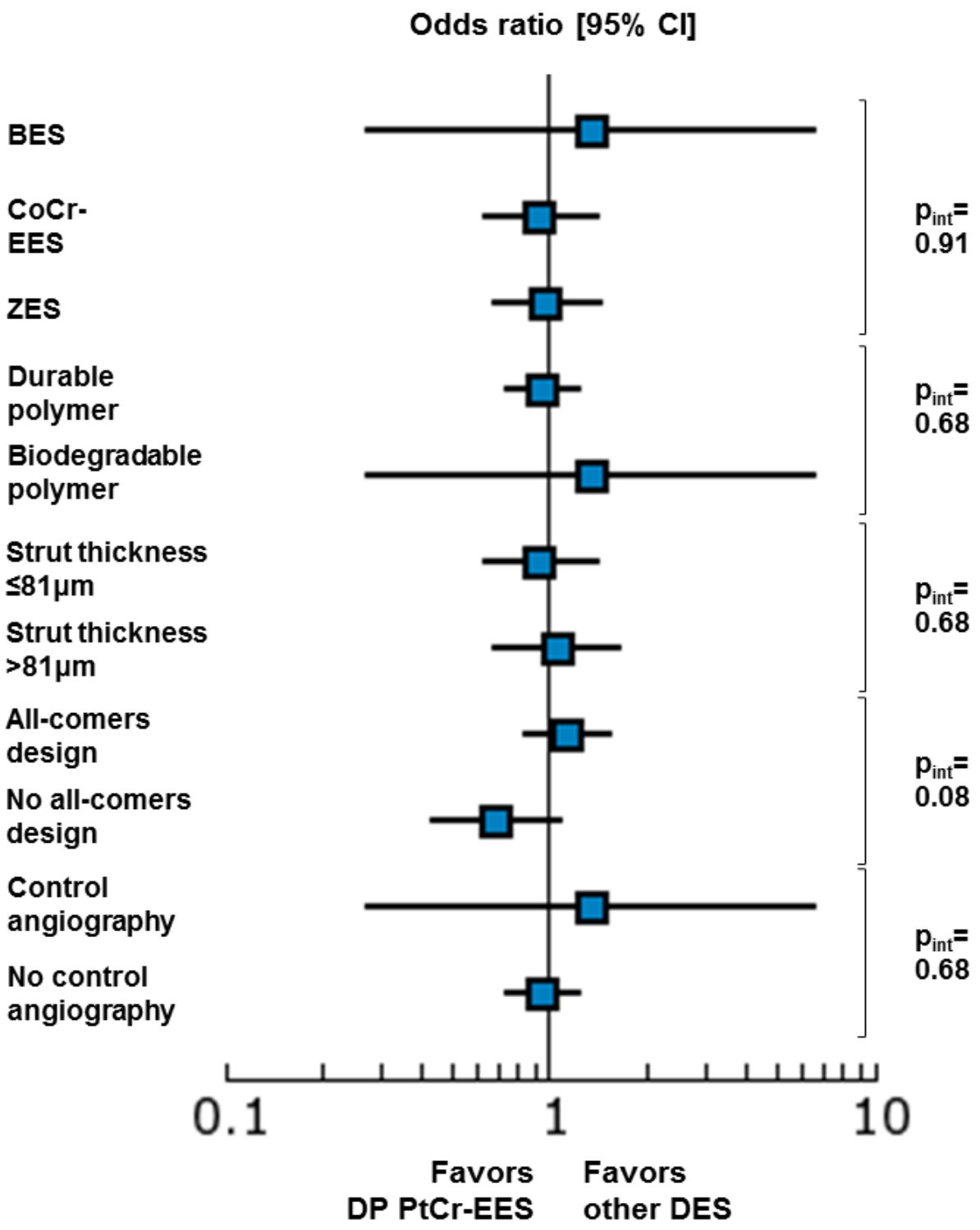
S-Figure 5.

B. Definite/probable stent thrombosis



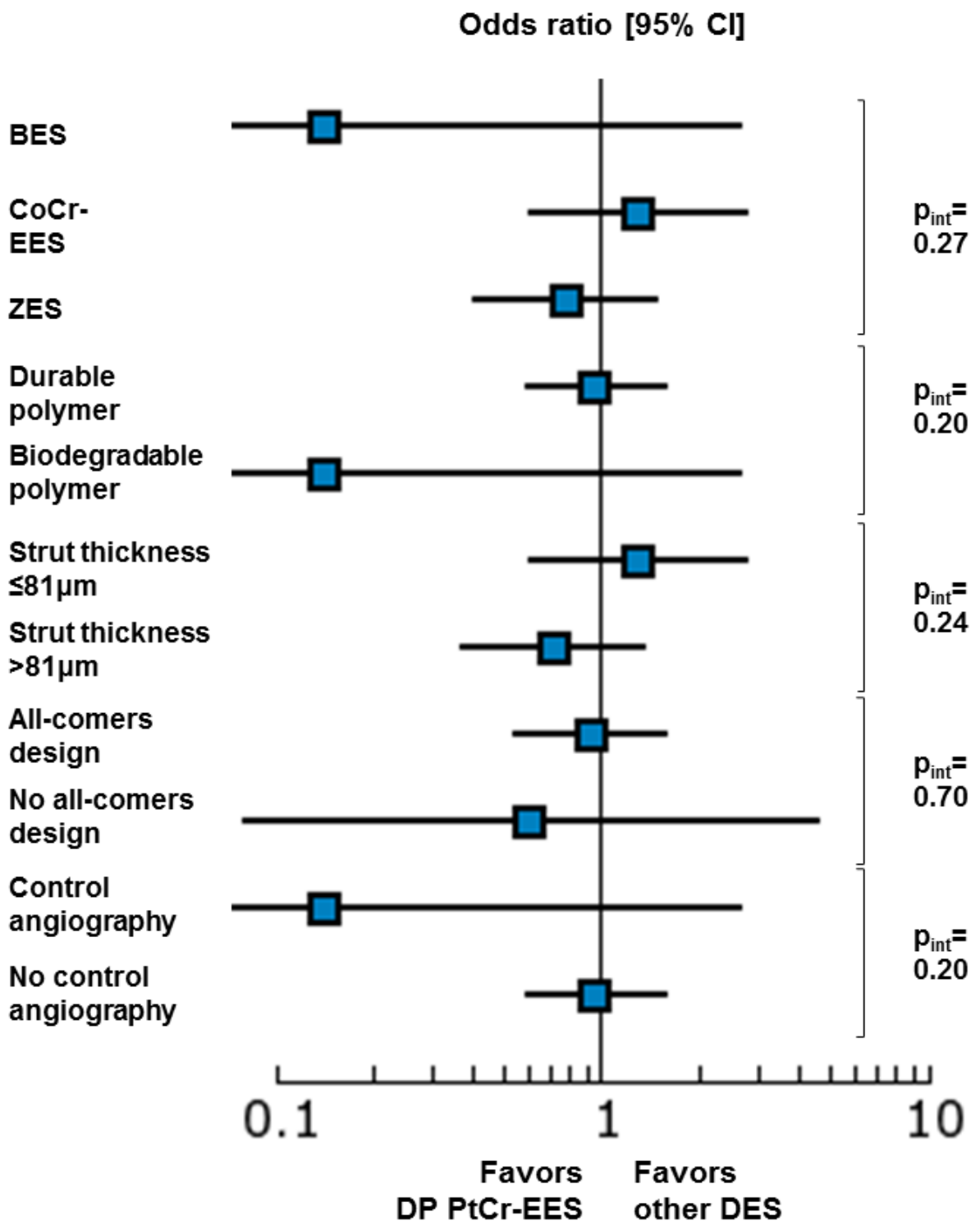
S-Figure 5.

A. Target lesion revascularization



S-Figure 6.

B. Definite/probable stent thrombosis



S-Figure 6.