Drug-Eluting or Bare-Metal Stents For Percutaneous Coronary Intervention: A Systematic Review and Individual Patient Data Meta-Analysis of Randomized Clinical Trials

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Summary

Background New-generation drug-eluting stents (DES) have been mostly investigated by means of head-to-head non-inferiority trials, which typically showed comparable efficacy and greater safety as compared with early-generation DES. Evidence related to new-generation DES versus bare-metal stents (BMS) is more limited, and there remain uncertainties on their comparative safety profile.

Methods We performed an individual patient data (IPD) meta-analysis of randomized trials comparing new-generation DES with BMS among patients undergoing percutaneous coronary intervention. The protocol of the study was registered in PROSPERO (CRD42017060520). The primary outcome was the composite of cardiac death or myocardial infarction. Data were pooled in a one-stage random effects meta-analysis and examined at maximum follow-up and with 1-year landmark. Risk estimates are reported as hazard ratio (HR) with 95% confidence intervals (95%CI).

Findings We obtained IPD data from 20 randomized trials including a total of 26,616 patients, with 3·2±1·8 years mean follow-up. The primary outcome occurred in fewer patients in the DES group than in the BMS group (HR 0·84, 95%CI 0·78 to 0·90, P<0·001) owing to lower risk of myocardial infarction (HR 0·79, 95%CI 0·71 to 0·88, P<0·001) and weaker evidence for a possible cardiac mortality benefit (HR 0·89, 95%CI 0·78 to 1·01, P=0·075). All-cause death was unaffected (HR with DES, 0·96, 95%CI 0·88 to 1·05, P=0·358), but DES reduced the risk of definite stent thrombosis (HR 0·63, 95%CI 0·50 to 0·80, P<0·001) and target-vessel revascularization (HR 0·55, 95%CI 0·50 to 0·60, P<0·001). There was evidence for a time-dependent treatment effect, with DES being associated with lower risks of the primary outcome during the first year followed by a null effect in the subsequent years.

Interpretation New-generation DES instead of BMS were associated with sustained reduction of cardiac death or myocardial infarction owing to lower event rates within the first year without offsetting effects thereafter.

Key words: Drug-eluting stent – Bare metal stents — Percutaneous coronary intervention — Meta-analysis

Introduction

Percutaneous coronary intervention (PCI) for the treatment of obstructive coronary artery disease is the most commonly performed cardiovascular procedure and one of the most frequent interventions in medicine. By using antiproliferative agents, drug-eluting stents (DES) reduce restenosis by inhibiting neointimal hyperplasia and have marked an important milestone in the field of myocardial revascularization, allowing PCI to be adopted in an increasing number of patient and lesion subsets.[1]

Early-generation DES, releasing sirolimus or paclitaxel were associated with similar risks of death and myocardial infarction (MI), but with an increased, albeit small, risk of stent thrombosis beyond 1 year after stent implantation as compared with bare-metal stents.[2,3] Since then, new platforms for DES that are aimed at improving safety and efficacy have been developed.

Contemporary DES reduce the risk of stent thrombosis as opposed to earlier iterations and retain greater efficacy than bare-metal stents (BMS) in limiting the risk of repeat revascularization.[4] In addition, randomized evidence mainly derived from network meta-analyses suggests that new-generation DES might also decrease the risk of stent thrombosis compared with BMS.[5,6] However, new-generation DES have been mostly investigated by means of head-to-head non-inferiority trials in comparison with early-generation DES and it remains unclear whether they improve other outcomes than stent thrombosis and repeat revascularization procedures as compared with BMS, which continue to be employed in a sizable proportion of patients worldwide.[7]

Methods

The protocol was developed according to the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) Development Group[8] and was registered online in the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017060520).

Search strategy and eligibility criteria

We performed an IPD meta-analysis of randomized trials that compared new-generation DES versus BMS among patients with coronary artery disease undergoing PCI. We used a broad definition for new-generation DES that were considered as any DES subsequent to the Cypher sirolimus-eluting stent (Cordis, Miami Lakes, Florida, USA) and the Taxus paclitaxel-eluting stent (Boston Scientific, Natick, Massachusetts, USA). In order to qualify, trials had to use new-generation DES in at least 90% of patients randomized to the

experimental arm. Two investigators (RP and AB) determined trial eligibility criteria and a third investigator (MV) was involved in case of disagreement. Randomized trials were identified by a systematic search in PubMed, EMBASE, and three websites (www.tctmd.com, www.escardio.org, www.cardiosource.com). Reference lists of retrieved articles were hand searched. There were no language restrictions. A search algorithm (last updated on December 19th, 2017) is provided in the web-appendix.

Data collection and quality assessment

We contacted the principal investigators of the eligible trials, requesting IPD to be provided in an anonymized electronic dataset (web appendix). Data for five randomized trials were already available from a previous study.[9] Data were checked for completeness and consistency, and were compared with the results of the original publications. The principal investigators of the included trials were contacted in case of missing data or when queries emerged during the integrity checks. Once queries had been resolved, the clean data were uploaded to the main study dataset. Two investigators (RP, AB) independently assessed the quality of included trials using the Cochrane Collaboration's tool for assessing risk of bias. Disagreements were resolved first by discussion and then by consulting a third author (MV) for arbitration. Each trial had been approved by its local medical ethics committee, and all patients had provided written informed consent.

Outcomes

The prespecified primary outcome in this meta-analysis was the composite of cardiac death or myocardial infarction. Secondary outcomes were all-cause death, cardiac death, MI, target-vessel revascularization (TVR), and definite stent thrombosis. Outcomes were analyzed at the longest available follow-up in the primary analysis, as well as at 5-year follow-up and with a 30-day and 1-year landmark.

Data analysis

Continuous variables were summarized by their means and standard deviation across all included patients. The two treatment groups were compared with ANOVA statistic stratified by trial. Categorical variables were summarized by the corresponding counts and percentages, and were compared with the Cochran-Mantel-Haenszel statistic stratified by trial.

All outcomes were analyzed using time-to-event analysis. We first summarized the data using unadjusted Kaplan-Meier estimates at the longest available follow-up. We then performed a series of IPD random-effects meta-analyses. All analyses were performed according to the intention-to-treat principle and utilized

IPD. For all analyses, the pooled risk estimates were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). For the primary analysis, we used a one-stage IPD meta-analysis model.[10] In this approach, we synthesized IPD from all trials simultaneously while preserving the randomization of the original trials. In sensitivity analyses we used a two-stage approach and analyzed the data from each study independently, using a Cox-regression model and then combined the study-specific logarithms of the HR and the corresponding standard errors at the second stage, using the DerSimonian-Laird random effects model with Hartung-Knapp variance estimator.[11] In a further analysis, we performed a one-stage fixed-effect analysis by using Cox-regression model stratified by trial. For the one-stage IPD meta-analysis we assessed the extend of heterogeneity by assessing the estimated value of τ, i.e. the standard deviation of random effects; for the two-stage IPD meta-analysis we also calculated visually inspected the forest plots and calculated the I^2 statistic.[12] To account for τ in the uncertainty around the pooled risk estimates, we also calculated 95% prediction intervals for hazard ratios.[13] The number needed to treat for benefit (NNTB) was derived from the inverse of the absolute risk reduction. We performed a landmark analysis by setting as a landmark at 1 year and derived the p value of the interaction for effect modification by period (**web-appendix**).[14]

Possible sources of heterogeneity in treatment effect were explored by assessing the effect of prespecified variables on the primary outcome using a one-stage IPD meta-analysis model with treatment-covariate interactions.[15] The model is described in the **web-appendix**. We fitted a separate model for each covariate. The prespecified variables were: age (analyzed as a continuous variable), gender, diabetes, clinical presentation at the time of PCI, overlapping stent, multivessel disease, number of implanted stents, PCI on the left anterior descending artery, mean stent diameter, use of glycoprotein IIb/IIIa receptor inhibitors, use of newer $P2Y_{12}$ receptor inhibitors. In a sensitivity analysis we also fitted an IPD model that separated the within- and across-trial treatment-covariate interactions, so as to avoid ecological bias.[15]

All P values we calculated were based on 2-sided tests. A P-value less than 0·05 was considered significant for all analyses. We used Stata Statistical Software, release 14 (StataCorp LP, College Station, Texas) and R version 3.2.1 for all statistical analyses.

Additional analyses

We conducted sensitivity analyses excluding patients who underwent PCI with implantation of early-generation DES (115 patients had received the Cypher DES and 90 patients had received Taxus DES) and patients who received thick-struts BMS (defined as a strut thickness >100 μm). A landmark analysis with two timepoints (30 days and 365 days) was also performed in order to further appraise the differential

contribution of very early stent failure events, mainly thrombotic in nature, as opposed to those occurring in between 30 days and 1 year, mostly related to an abnormal healing process leading to neointimal hyperplasia (**web-appendix**).

Role of the funding source

There was no industry involvement in the design, analysis or funding of this study. This study was funded by institutional support of the Department of Cardiology at Bern University Hospital, Bern, Switzerland, which had no role in the data analysis, interpretation, or writing of the report. The corresponding and first and third authors (MV, RP, and OE) had full access to the data and had final responsibility for the decision to submit for publication.

Results

We screened 19,454 unique citations. Of these, 601 were judged potentially eligible during screening of titles and abstracts, and 20 deemed eligible after full text review (**Figure 1**). IPD were sought and obtained for all 20 studies, which, therefore, contributed to the IPD meta-analysis. The **web-appendix** describes trial characteristics, patient populations, and the definitions used for outcomes (**Tables S1-S3**). Overall, we obtained data for 26,616 participants; 14,070 (53%) randomized to DES and 12,546 (47%) randomized to BMS. Baseline clinical characteristics were largely balanced between the two study groups (**Table 1**). Slightly more males were allocated to DES and patients randomized to BMS tended to receive stents with larger diameters and shorter lengths. Supplementary **Table S4** provides details on the risk of bias assessment. Overall, trials were judged at low risk of bias, although blinding of patients and performing physicians was done only in four trials.

Most patients received thin-strut stents, which, however, were less frequently implanted among those assigned to DES than BMS (79·7% vs. 85·3%, p<0·001). In the DES group, the following devices were implanted in more than 90% of patients: everolimus-eluting stents (Xience in 4,064 or 28·9%, Promus in 2,866 or 20·4%, and Synergy in 596 or 4·2%), zotarolimus-eluting stents (Endeavor in 1,932 or 13·7%, and Resolute in 475 or 3·4%), biolimus-eluting stents (Biofreedom in 1,221 or 8·7%, Nobori in 765 or 5·68%, and BioMatrix in 655 or 4·86%), and sirolimus-eluting stents (Ultimaster in 375 or 2·78%) (**Table S5**). Early-generation DES were implanted in a small proportion of patients (1·4%). In the BMS group, the following devices were implanted in about 80% of patients: Driver in 3,076 or 24·5%, Vision in 2,742 or 21·9%, Gazelle in 1,793 or 14·3%, Integrity in 914 or 7·3%, Libertè in 778 or 6·2%, Pro-kinetic in 768 or 6·1%, Omega/Rebel in 604 or 4·8%. Duration of dual antiplatelet therapy was on average 50 days longer after DES than BMS (302±179 vs. 253±176 days, p<0·001).

The maximum length of follow-up ranged from 1 to 6 years with a duration of follow-up of 2 years or more in 14 trials and up to, or more than, 5 years in 6 trials. The mean (±standard deviation) follow-up time was 3·2±1·8 years (median, 2·1; interquartile range, 1·9 to 4·9). Ten trials reported sponsorship to be independent from industry (**Table S1**).

At longest available follow-up, the risk of the primary outcome of cardiac death or MI was significantly lower among patients randomized to DES than BMS (14·49% vs. 16·65%, respectively; HR 0·84, 95%CI 0·78 to 0·90, P<0·001), yielding a number needed to treat for benefit (NNTB) in the range of 46 (**Table 2, Figure 2**). We found evidence that DES were associated with a reduced risk of MI as compared with BMS (HR 0·79, 95%CI 0·71 to 0·88, P<0·001), whereas the effect of DES vs. BMS on cardiac fatality

rates was weaker and did not reach conventional levels of statistical significance (HR 0·89, 95%CI 0·78 to 1·01, p=0·075). We found no difference between DES and BMS in terms of all-cause death (HR 0·96, 95%CI 0·88 to 1·05, P=0·358). As compared with BMS, patients assigned to DES had a reduced risk of definite stent thrombosis (HR 0·63, 95%CI 0·50 to 0·80, P<0·001) and TVR (HR 0·55, 95%CI 0·50 to 0·60, P<0·001). Risk estimates for primary and secondary outcomes at 5-year follow-up were consistent with those observed at time of longest follow-up (**Table 2**).

Results of the landmark analysis are reported in **Figure 3** and Kaplan-Meier curves during different time intervals are shown in the **web-appendix** (**Figure S1**). For the primary outcome, there was significant heterogeneity in the treatment effect of DES vs. BMS before and after 1 year (P-int<0·001). DES compared with BMS reduced the risk of cardiac death or MI during the first year after implantation (HR 0·74, 95%CI 0·67 to 0·81), but not beyond 365 days (HR 1·04, 95%CI 0·92 to 1·18). During the first year after PCI, DES use was also associated with a reduced risk of cardiac death (HR 0·82, 95%CI 0·70 to 0·96) and MI (HR 0·69, 95%CI 0·62 to 0·78) when separately appraised, with no detectable treatment effect beyond 1-year (HR 1·03, 95%CI 0·84 to 1·26; P-int=0·079 and HR 1·06, 95%CI 0·93 to 1·22; P-int <0·001, respectively). A similar pattern was found for other secondary outcomes, such as stent thrombosis and TVR. In a further analysis with two landmark points, DES remained associated to consistently lower risks of the primary outcome, MI, ST, and TVR between 0 and 30 days as well as between 31 and 365 days (**Table S6**).

The effect of DES versus BMS on the rate of the primary outcome at longest available follow-up was consistent across subgroups, including age, gender, clinical presentation, number and size of implanted stents, with the only exception for the target-vessel location (P-int=0·010) (**Figure 4)**. There was strong evidence that DES lowers the risk of cardiac death or MI among patients undergoing stent implantation in the left anterior descending artery (HR 0·76, 95%CI 0·68 to 0·85, P<0·001). There was weak evidence of an effect in patients undergoing treatment in other coronary vessels (HR 0·92, 95%CI 0·82 to 1·02, P=0·112).

We did not find clinically important heterogeneity in all meta-analyses, although there was a moderate heterogeneity for MI at longest follow-up, resulting in non-significant prediction intervals (**Figure S2**).

Sensitivity analyses

The main results of the IPD meta-analysis remained entirely consistent at the two-stage random effects approach (**Table S7, Figure S2-S4**) and one-stage fixed effect approach (**Table S8**). Results for primary and secondary outcomes remained unchanged after excluding patients who were randomized to BMS and

received thick-strut stents and after excluding patients who randomized to DES and received early-generation devices (**Tables S9-S10**). In a sensitivity analysis, we fitted a model including both within- and across-studies interactions between treatment and target-vessel location. Results were similar (P-int =0·018) to the ones obtained by the model including only a within-studies interaction.

Discussion

Using the totality of available data from randomized trials comparing new-generation DES with BMS among 26,616 participants undergoing PCI, our collaborative IPD meta-analysis provides strong evidence that DES reduce the risk of cardiac death or MI compared with BMS at a mean follow-up time of 3·2 years or up to 5 years. This benefit was mainly due to a decreased risk of MI with DES and a non-significant reduction of cardiac death as compared with BMS. The use of DES was also associated with a significantly lower risk of stent thrombosis and TVR at longest available follow-up or at 5 years.

Introduced in 2002, DES represented a paradigm shift in the treatment of patients undergoing PCI owing to a convincing reduction in the need for repeat revascularization compared with BMS. However, after initial use and evaluation in clinical trials, safety concerns were raised due to excess of very late (>1 year) thrombotic events with early-generation devices.

The transition from early- to new-generation DES, which are vastly represented in this study (>98% of participants), entailed a broad range of refinements, including the use of lower antiproliferative drug loads, the omission of paclitaxel as antiproliferative agent, thinner metallic stent struts, and more biocompatible durable or biodegradable polymers as well as polymer-free stents. Nevertheless, a lingering controversy exists as to whether the introduction of new-generation DES impacts on more prognostically relevant endpoints, such as death or MI.

In the EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) trial, which included 1,498 patients with acute myocardial infarction, there was a significant reduction in the risk of all-cause death with DES compared with BMS at 5-year follow-up.[16] Although this observation was mainly related to a decrease in non-cardiac fatalities, it has been speculated that the prevention of stent thrombosis and repeat revascularization among patients randomized to DES might have led to less rehospitalization and other complications including infections and sepsis, which were the second major cause of non-cardiac death in the trial.[16] Conversely, the larger Norwegian Coronary Stent Trial (NORSTENT), which included 9,013 patients, did not find evidence of a benefit of DES in terms of all-cause as well as cardiac death or MI rates.[17] Yet, there was a significant 36% risk reduction for definite stent thrombosis with DES as compared to BMS. Fueled by greater safety perceptions and lower costs, BMS continue to be implanted in 20% of contemporary PCI procedures involving patients aged 65 years or older.[7] While the use of BMS is no longer recommended across several guidelines of the European Society of Cardiology,[18] no such position is endorsed by ACC/AHA guidelines, which, however, were published in 2011.[19]

Our IPD meta-analysis provides robust evidence that the use of DES reduced by 21% the hazard of MI compared with BMS. This finding is relevant as only two out of 20 trials have individually reported a difference in MI between DES and BMS.[20,21] Interestingly, both of these studies recruited mainly[20] or exclusively[21] patients deemed at high bleeding risk and mandated 1-month duration of dual antiplatelet therapy irrespective of stent types. Hence, the argument that DES implantation lowers MI rates because of concomitant longer duration of dual antiplatelet therapy seems invalid. The decreased hazard of MI with DES is biologically plausible given the concurrent reductions in stent thrombosis and TVR. The clinical correlate of stent thrombosis is death or MI in more than 90% of cases[22] and roughly one third of patients with in-stent restenosis requiring repeat revascularization in a target-vessel is admitted with acute coronary syndrome.[23] Furthermore, restenosis after coronary stenting has been associated with a higher risk of mortality in cohorts undergoing angiographic surveillance.[24] Even elective and uncomplicated revascularization in the target-vessel is associated with an increased risk of mortality, partly related to a higher risk of myocardial infarction following repeat revascularization procedures.[25]

Yet, we did not find evidence that the use of DES affects all-cause mortality whereas cardiac fatalities were only marginally and not significantly lower with DES at longest available follow-up.

In our IPD analysis, 2,027 fatal events were observed of which less than 50% (997 or 49·2%) were from cardiac causes. Consequently, the predominant mode of death in patients undergoing PCI, particularly during the long-term follow-up, was non-cardiac, which is unlikely to be prevented by the type of coronary stent. These findings align well with other registry data showing a pronounced temporal switch from predominantly cardiac to predominantly non-cardiac causes of death after PCI in the past two decades.[26]

There was evidence for time-dependent treatment effects, with DES being associated with lower risks of cardiac death during the first year followed by a null effect in the subsequent years. While interaction testing provided only borderline significance, the time-dependent distribution of the treatment benefit observed for cardiac mortality was highly consistent with those observed for other safety endpoints, including MI or stent thrombosis and even TVR, which was numerically but not significantly reduced from the second year onwards with DES. Hence, it remains plausible that an early cardiac mortality benefit, likely arisen by MI, ST and even TVR risk mitigation by DES within the first year, diminishes over time due to non-stent related fatalities.

The observation that beneficial effects of DES on safety endpoints, including MI and ST, accrued exclusively within the first year after treatment and consistently within 30 days or in between 30 days and 1 year with no signal of further incremental benefit or loss thereafter is remarkable and deserves attention. First, it suggests

that contemporary DES technology is less prone to thrombotic events early (i.e. within 30 days) after stent implantation and confirms the lower risk of non-fatal ischemic events associated to lower intimal hyperplasia. Second, it provides reassuring evidence that the long-term (beyond 1 year) safety issues, in terms of increased MI and ST rates observed with early generation DES as compared to BMS, has been resolved. Third, it shows that contemporary DES technology outperforms the safety and efficacy profile of BMS within the first year after implantation, without further comparative improvements being visible in the subsequent years. Hence, while BMS should no longer be considered the gold standard for safety, the observation that the risks of death or MI beyond 1 year after implantation do not differ between current generation DES as compared to BMS carries relevant clinical and pathophysiological implications and suggests that the focus of future technology should target clinical outcome improvements not only within but also beyond 1-year after stent implantation.

A further strength of this IPD meta-analysis was the opportunity to explore the treatment effect of DES vs. BMS across several subgroups. We did not find any evidence of interaction between the primary outcome (cardiac death or MI) and any patient or lesion characteristic, except for target-vessel location. The reduction of the primary outcome with DES over BMS was more evident among patients who underwent PCI of the left anterior descending artery as opposed to other locations. As the myocardial territory supplied by the left anterior descending artery is larger than other vessels (45-55% of the left ventricle), it is likely that this patient population derived a greater benefit from the prevention of restenosis and stent thrombosis with DES compared with BMS.

The results of this study should be interpreted in view of several limitations. First, the study has limitations inherent in patient-level, pooled analyses reflecting the shortcomings of the original studies. Second, although 90% of patients received a limited number of DES with everolimus-eluting stents being implanted in more than 50% of cases, a mixture of DES was used in the experimental arm. Third, a minority of patients received early-generation DES that are associated with lower safety and efficacy than new-generation DES and are no longer used in clinical practice. However, after the exclusion of these patients, results remained unchanged. Fourth, although there was no signal of difference between DES and BMS beyond 1 year, the mean follow-up in our IPD analysis was about 3 years and therefore longer duration follow-up is needed to confirm the durability of the benefit observed here at a medium-term time point. Fifth, the effect of stent selection on the MI type could not be assessed, as many of the included studies failed to collect this

information. Finally, we did not adjust or account for post-randomization covariates, such as actual duration of dual antiplatelet therapy, to avoid violating the principle of randomization. However, several trials are under way to address the efficacy and safety of abbreviated antiplatelet regimens after contemporary PCI.[27]

In conclusion, our collaborative meta-analysis based on the totality of available randomized data showed that the use of new generation DES rather than BMS, is associated with a sustained reduction in the risk of cardiac death or myocardial infarction, with time-dependent treatment effects characterized by a lower risk of the composite endpoint accrued during the first year without an off-setting effect during the subsequent years.

Research in context

Evidence before this study

We searched PubMed, EMBASE, and three websites (www.tctmd.com, www.escardio.org, www.cardiosource.com) up to December 19th, 2017, to identify randomized trials comparing new-generation drug-eluting stents (DES) with bare-metal stents (BMS) in patients undergoing percutaneous coronary intervention (PCI). We used search terms “stents”, “drug-eluting stents”, “percutaneous coronary intervention” and “random*”. Trials were included if patients underwent PCI with the use of new-generation DES in at least 90% of the population allocated to the experimental arm. Evidence to support the use of new-generation DES for PCI is mainly based on trials showing the superiority of newer DES in comparison to earlier generation DES or the non-inferiority between different types of new-generation DES. In contrast, evidence related to head-to-head comparisons between new-generation DES and BMS is more fragmented and, so far, it remains unclear whether new-generation DES improve clinical outcomes, such as myocardial infarction or cardiac death, as opposed to BMS. Only two separate studies have observed a reduction in the risk of myocardial infarction in favor of new-generation DES compared with BMS. Yet, almost all trials included repeat revascularization procedures in their primary endpoint and therefore provided imprecise estimates for less common but more prognostically relevant adverse events, such as myocardial infarction or cardiac death. After electronic search, we found 20 trials eligible for the study for which we requested and obtained IPD.

Added value of this study

In this IPD meta-analysis of randomized trials, we found that new-generation DES reduced the risk of cardiac death or myocardial infarction as compared with BMS. There was also strong evidence for a reduction of myocardial infarction, stent thrombosis and target-vessel revascularization, whereas cardiac death was numerically lower with DES without reaching formal statistical significance after a mean follow-up of 3·2±1·8 years. By further investigating the treatment effects across different time-periods, we found that new-generation DES reduced adverse events including cardiac death within 1-year with no signal of further incremental benefit or loss thereafter. At pre-defined subgroup analysis, we identified a stronger reduction in cardiac death or myocardial infarction with DES instead of BMS for patients who received stents in the left anterior descending artery, with positive interaction testing.

Implications of all the available evidence

Our study provides evidence that the use of new-generation DES instead of BMS is associated to improved outcomes as compared with BMS with reductions in both efficacy and safety parameters. The benefit of DES

accrues early (i.e. within 1 year) after PCI and is maintained over longer term follow-up. The meta-analysis provides strong evidence that BMS should no longer be considered the gold standard for safety and questions their use in current clinical practice.

Contributors

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Manel Sabaté, Interpreted data, revised and approved the final version of the manuscript.

Robert A. Byrne, Interpreted data, revised and approved the final version of the manuscript.

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FIGURES LEGEND

Figure 1. PRISMA Flow Diagram for the Systematic Review.

Figure 2. Kaplan-Meier curves at longest follow-up for cardiac death or myocardial infarction (**Panel A**), all-cause death (**Panel B**), cardiac death (**Panel C**), myocardial infarction (**Panel D**), target-vessel revascularization (**Panel D**), and definite stent thrombosis (**Panel E**). Red lines represent bare-metal stents and blue lines represent drug-eluting stents.

Figure 3. Landmark analysis. P values for interaction are between hazard ratios (HR) with 95% confidence intervals (95%CI) calculated from 0 to 365 days and after 365 days.

Figure 4. Subgroup analysis and meta-regressions for the primary outcome. BMS: bare-metal stents. CAD: coronary artery disease. ACS: acute coronary syndrome. BMS: bare-metal stents. CAD: coronary artery disease. DES: drug-eluting stents. LAD: left anterior descending artery. 7: PCI percutaneous coronary intervention.

Table 1. Baseline and procedural characteristics.

	Drug-eluting stents (N=14,070)	Bare-metal stents (N=12,546)	P-value
Age, years	n = 14067, 65·7±12·3	n = 12541, 66·3±12·4	0·458
Male	n = 14069, 10542 (74·9%)	n = 12543, 9269 (73·9%)	0·067
Smokers	n = 13654, 4277 (31·3%)	n = 12149, 3809 (31·4%)	0·092
Hypertension	n = 14029, 8259 (58·9%)	n = 12500, 7324 (58·6%)	0·156
Hyperlipidemia	n = 13731, 7904 (57·6%)	n = 12208, 6974 (57·1%)	0·208
Diabetes	n = 14046, 2740 (19·5%)	n = 12525, 2344 (18·7%)	0·069
Insulin-treated	n = 2677, 446 (16·7%)	n = 2323, 378 (16·3%)	0·426
Previous MI	n = 14025, 2143 (15·3%)	n = 12505, 2007 (16·0%)	0·548
Previous PCI	n = 9950, 1901 (19·1%)	n = 8507, 1806 (21·2%)	0·074
Previous CABG	n = 14060, 905 (6·4%)	n = 12541, 1004 (8·0%)	0·605
Indication to PCI			
Stable CAD	n = 13927, 4047 (29·1%)	n = 12408, 3644 (29·4%)	0·907
Unstable angina	n = 14012, 1959 (14·0%)	n = 12478, 1871 (15·0%)	0·956
Non-ST-elevation MI	n = 13975, 3479 (24·9%)	n = 12462, 3164 (25·4%)	0·636
ST-elevation MI	n = 13922, 4105 (29·5%)	n = 12406, 3427 (27·6%)	0·522
Gp IIb/IIIa receptor inhibitors	n = 12344, 2781 (22·5%)	n = 11020, 2378 (21·6%)	0·420
Multivessel disease	n = 13517, 5837 (43·2%)	n = 11993, 4968 (41·4%)	0·239
Number of implanted stents	n = 14039, 1·6±1·0	n = 12507, 1·6±1·0	0·391
Total stent length, mm	n = 13956, 28·4±19·5	n = 12424, 26·9±18·2	<0·001
Mean stent diameter, mm	n = 13956, 3·3±0·5	n = 12421, 3·3±0·6	<0·001
Overlapping stent	n = 13403, 2395 (17·9%)	n = 11877, 2152 (18·1%)	0·201
Number of stented segments	n = 14052,	n = 12524,	0·088
0	5 (0·0%)	5 (0·0%)	
1	10297 (73·3%)	9231 (73·7%)	
2	2758 (19·6%)	2480 (19·8%)	
3	751 (5·3%)	608 (4·9%)	
4	188 (1·3%)	141 (1·1%)	
5	40 (0·3%)	52 (0·4%)	
6	10 (0·1%)	6 (0·0%)	
7	3 (0·0%)	1 (0·0%)	
Target-vessel location			
Left main artery	n = 13968, 1022 (7·3%)	n = 12463, 591 (4·7%)	0·499
Left anterior descending artery	n = 13968, 6476 (46·4%)	n = 12463, 5805 (46·6%)	0·859
Left circumflex artery	n = 13968, 4047 (29·0%)	n = 12463, 3433 (27·5%)	0·51
Right coronary artery	n = 13968, 5260 (37·7%)	n = 12462, 4674 (37·5%)	0·279
Thin-strut stent (<100 μm)	n = 14046, 11198 (79·7%)	n = 12526, 10681 (85·3%)	<0·001
Type of $P2Y_{12}$ receptor inhibitor	n = 12123,	n = 10814,	0·919
None	1 (0·0%)	3 (0·0%)	

Clopidogrel	10726 (84·8%)	10217 (90·0%)	
Ticagrelor	89 (0·7%)	63 (0·6%)	
Prasugrel	1837 (14·5%)	1069 (9·4%)	
Duration of DAPT, days	n = 12200, 291·7±180·4	n = 10805, 244·2±175·9	<0·001

All data are shown at patient-level. CABG: coronary artery bypass grafting; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; Gp: glycoprotein·; MI: myocardial infarction.

Table 2· Results of one-stage meta-analysis.

	Drug-eluting stents (N=14,070)	Bare-metal stents (N=12,546)	HR (95%CI)	P-value	τ
At longest available follow-up					
Cardiac death or MI	1371 (14·49)	1472 (16·65)	0·84 (0·78 to 0·90)	<0·001	0·003
All-cause death	1031 (10·97)	996 (11·98)	0·96 (0·88 to 1·05)	0·358	0·004
Cardiac death	494 (4·76)	503 (5·75)	0·89 (0·78 to 1·01)	0·075	0·003
Myocardial infarction	1020 (11·65)	1124 (13·58)	0·79 (0·71 to 0·88)	<0·001	0·070
Target-vessel revascularization	920 (9·56)	1448 (14·95)	0·55 (0·50 to 0·60)	<0·001	0·003
Definite stent thrombosis	125 (1·20)	173 (1·70)	0·63 (0·50 to 0·80)	<0·001	0·008
At 5-year follow-up					
Cardiac death or MI	1345 (12·48)	1446 (14·16)	0·83 (0·78 to 0·90)	<0·001	0·003
All-cause death	1013 (9·82)	974 (10·44)	0·95 (0·88 to 1·05)	0·400	0·004
Cardiac death	490 (4·55)	492 (4·84)	0·90 (0·79 to 1·03)	0·116	0·003
Myocardial infarction	994 (9·56)	1099 (11·04)	0·78 (0·72 to 0·88)	<0·001	0·056
Target-vessel revascularization	904 (8·38)	1436 (13·40)	0·54 (0·50 to 0·59)	<0·001	0·003
Definite stent thrombosis	123 (1·09)	171 (1·58)	0·63 (0·50 to 0·80)	<0·001	0·008
At 1-year follow-up					
Cardiac death or MI	829 (5·95)	989 (7·96)	0·74 (0·67 to 0·81)	<0·001	0·003
All-cause death	499 (3·58)	495 (3·98)	0·94 (0·81 to 1·04)	0·197	0·003
Cardiac death	301 (2·20)	331 (2·72)	0·82 (0·70 to 0·96)	0·016	0·003
Myocardial infarction	591 (4·25)	746 (6·03)	0·69 (0·62 to 0·78)	<0·001	0·070
Target-vessel revascularization	547 (3·98)	1073 (8·77)	0·43 (0·39 to 0·48)	<0·001	0·015
Definite stent thrombosis	83 (0·60)	137 (1·11)	0·52 (0·40 to 0·69)	<0·001	0·008

BMS: bare-metal stents. DES: drug-eluting stents. MI: myocardial infarction.

Figure 1. PRISMA Flow Diagram for the Systematic Review.

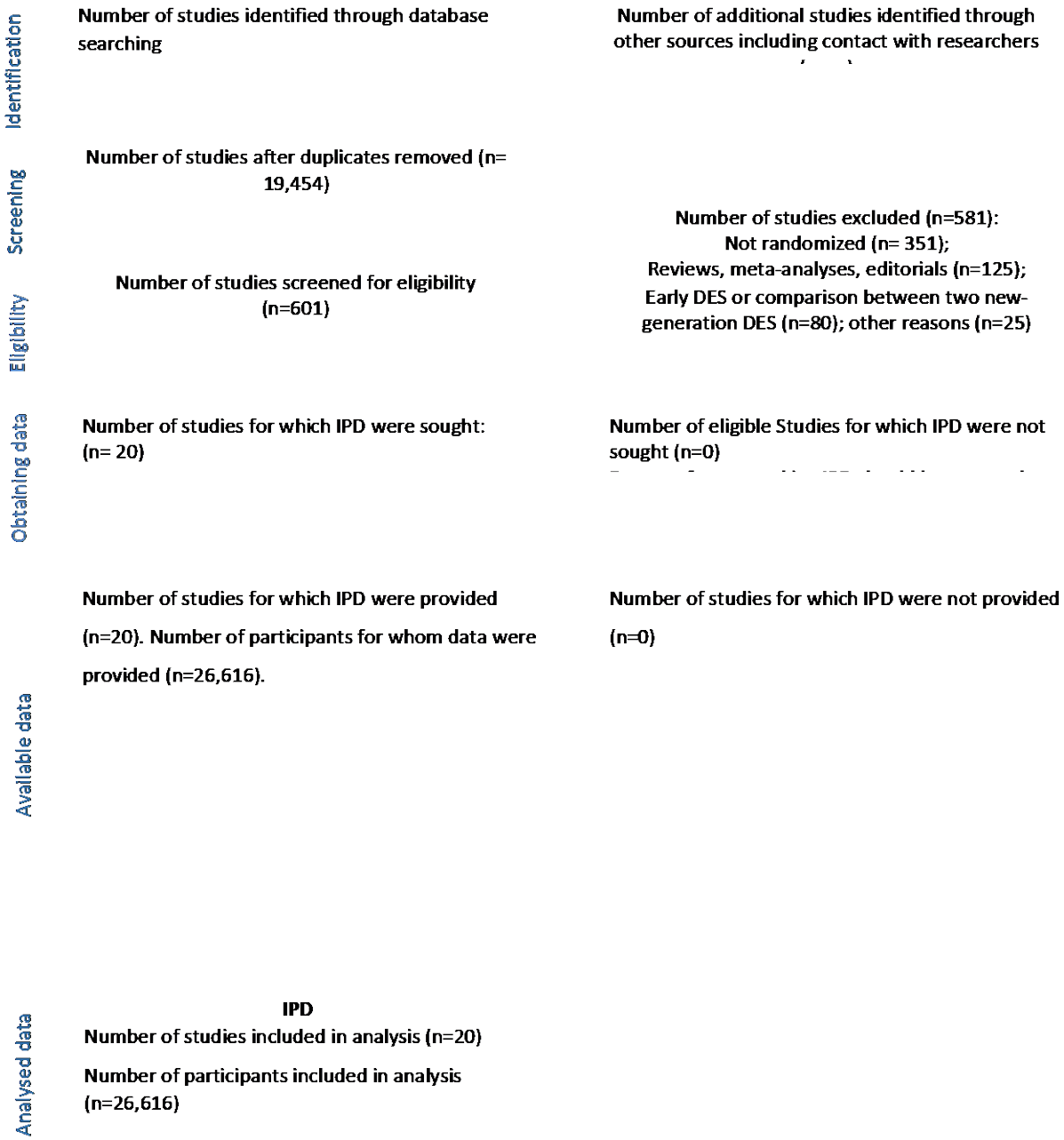

Figure 2. Kaplan-Meier curves at longest follow-up.

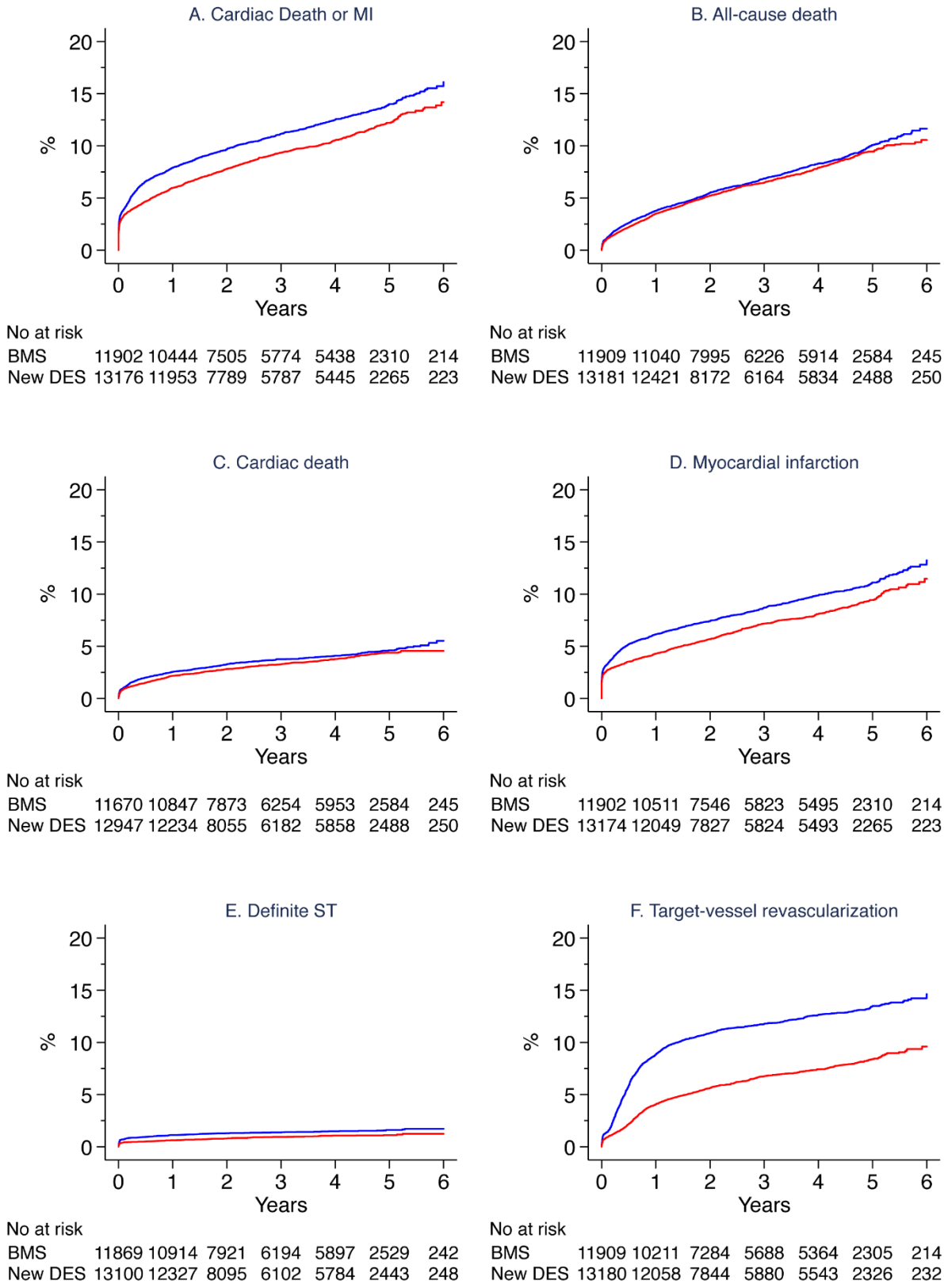

Figure 3. Landmark analysis.

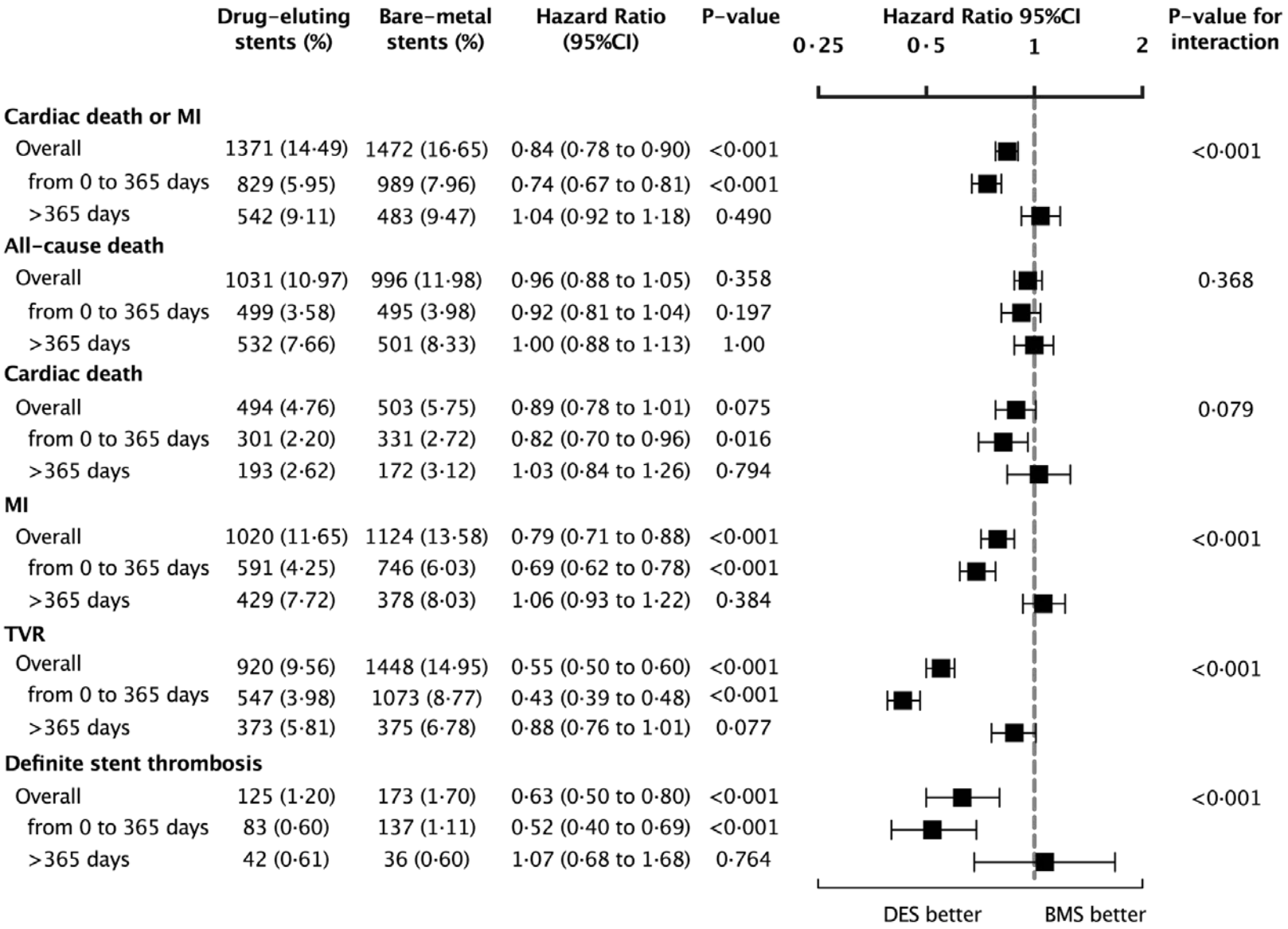

Figure 4. Subgroup analysis and meta-regressions for the primary outcome.