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Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularisation: 5-year outcomes of the BIOSCIENCE randomised trial

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BOX: RESEARCH IN CONTEXT

Evidence before this study

Evidence from previous trials of biodegradable-polymer stents is conflicting. The BIOFLOW-II, BIOSCIENCE, and BIORESORT trials showed non-inferiority for biodegradable-polymer sirolimus-eluting stents compared with durable-polymer drug-eluting stents with regards to primary angiographic or composite clinical endpoints at 9 months or 1 year. By contrast, the BIOFLOW V trial found a lower incidence of target lesion failure at 1 year in patients treated with biodegradable-polymer sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents. We searched PubMed, the Cochrane Library Central Register of Controlled Trials, and Embase up to June 15, 2018, for randomised trials comparing ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents with durable-polymer everolimus-eluting stents. We searched without language restrictions and using the search algorithm (biodegradable* OR bioresorbable*) AND sirolimus* AND stent* AND random*. We identified four trials, in addition to BIOSCIENCE, that fulfilled the inclusion criteria. In a meta-analysis of these trials, we found that there was no

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difference between ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents and durable-polymer everolimus-eluting stents in the composite outcome of target lesion failure at the longest available follow-up. By contrast, ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents reduced risk of myocardial infarction by 23% (risk ratio 0·77, 95% CI 0·63–0·95) compared with durable-polymer everolimus-eluting stents.

Added value of this study

To our knowledge, this study is the first to assess long-term efficacy and safety outcomes of an ultrathin-strut, biodegradable-polymer, sirolimus-eluting stent, beyond the time of complete degradation of the polymer, in an adequately powered randomised trial with the best-in-class durable-polymer everolimus-eluting stent as a comparator. We found no difference between stents in the composite outcome of target lesion failure at 5 years (rate ratio 1·07, 95% CI 0·88–1·31). Additionally, we observed no difference in incidence of myocardial infarction between biodegradable-polymer sirolimus-eluting stents and durable-polymer everolimus-eluting stents at 5 years (0·85, 0·65–1·28). This study adds to existing clinical evidence on the newest generation of drug-eluting stents that combine biodegradable polymers with ultrathin-stent platforms.

Implication of all the available evidence

Ultrathin-strut, biodegradable-polymer, sirolimus-elutings stents have similar safety and efficacy to durable-polymer everolimus-eluting stents during long-term follow-up.

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SUMMARY

Background

Drug-eluting stents combining an ultrathin cobalt-chromium stent platform with a biodegradable polymer eluting sirolimus have been shown to be non-inferior or superior to thin-strut, durable-polymer, everolimus-eluting stents in terms of 1 year safety and efficacy outcomes.

Methods

In the randomised, single-blind, multicentre, non-inferiority BIOSCIENCE trial, we compared biodegradable-polymer sirolimus-eluting stents with durable-polymer everolimus-eluting stents in patients with chronic stable coronary artery disease or acute coronary syndromes. Here, we assess the final 5-year clinical outcomes of BIOSCIENCE with regards to the primary clinical outcome of target lesion failure, which was a composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation. The primary analysis was done by intention to treat. The BIOSCIENCE trial is registered with ClinicalTrials.gov, number NCT01443104.

Findings

2008 (95%) of 2119 patients recruited between March 1, 2012, and May 31, 2013, completed 5 years of followup. Target lesion failure occurred in 198 patients (cumulative incidence 20·2%) treated with biodegradable-polymer sirolimus-eluting stents and in 189 patients (18·8%) treated with durable-polymer everolimus-eluting stents (rate ratio [RR] 1·07, 95% CI 0·88–1·31; p=0·487). All-cause mortality was significantly higher in patients treated with biodegradable-polymer sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents (14·1% vs 10·3%; RR 1·36, 95% CI 1·06–1·75; p=0·017), driven by a difference in non-cardiovascular deaths. We observed no difference between groups in cumulative incidence of definite stent thrombosis at 5 years (1·6% in both groups; 1·02, 0·51–2·05; p=0·950).

Interpretation

5-year risk of target lesion failure among all-comer patients undergoing percutaneous coronary intervention is similar after implantation of ultrathin-strut, biodegradable-polymer, sirolimus-eluting

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stents or thin-strut, durable-polymer, everolimus-eluting stents. Higher incidences of all-cause and non-cardiovascular mortality in patients treated with biodegradable-polymer stents eluting sirolimus than in those treated with durable-polymer stents eluting everolimus warrant careful observation in ongoing clinical trials.

INTRODUCTION

Biodegradable-polymer stents are associated with improved vascular healing after implantation of drug-eluting stents and reduced risk of very late stent thrombosis compared with earlier generations of drug-eluting stents.[1,2] Newer-generation, biodegradable-polymer, drug-eluting stents differ from each other in polymer degradation times (ranging from 3 months to >1 year), drug-release kinetics, and strut thickness.[3–7]

Newer-generation drug-eluting stents combining ultrathin-strut cobalt-chromium platforms with biodegradable polymers eluting sirolimus have been associated with a reduced risk of definite stent thrombosis compared with thick-strut, stainless steel, biodegradable-polymer, drug-eluting stents,[8] and were non-inferior to thinstrut, durable-polymer, drug-eluting stents with regards to composites of clinical endpoints at 1 year in two randomised controlled trials.[5,9] More recently, the randomised controlled BIOFLOW V trial10 reported a lower incidence of target lesion failure at 1 year, driven by a lower incidence of myocardial infarction, in patients treated with biodegradable-polymer sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents.

The rationale for the use of biodegradable polymers is to mitigate a polymer-induced chronic inflammatory response, potentially translating into late clinical adverse events. The benefit of biodegradable polymers in newer-generation drug-eluting stents might therefore be expected to take effect beyond the degradation time of the polymer. Long-term clinical outcome data from randomised controlled trials investigating newer-generation, biodegradable-polymer, sirolimus-eluting stents have not yet been reported. Here, we report the 5-year outcomes of the BIOSCIENCE randomised controlled trial comparing efficacy and safety outcomes of an ultrathin-strut,

biodegradable-polymer, drug-eluting stent with those of a durable-polymer everolimus-eluting stent.

METHODS

Study design and patients

The BIOSCIENCE trial was an investigator-initiated, single-blind, multicentre, randomised, non-inferiority trial. Eligible patients had coronary artery disease and at least one lesion with more than 50% diameter de-novo stenosis or restenosis in a native coronary artery or a bypass graft. Additionally, patients had to present with stable coronary artery disease or acute coronary syndromes.

The rationale of the trial, as well as details of randomisation, masking, and data management, have been described previously.[11] Briefly, patients were randomly assigned in a 1:1 ratio to biodegradable-polymer sirolimus-eluting stents or to durable-polymer everolimus-eluting stents in nine centres in Switzerland. The experimental stent (Orsiro; Biotronik AG, Bülach, Switzerland) consisted of an ultrathin (60 µm for stent diameters ≤3·0 mm, 80 µm for stent diameters >3·0 mm) cobalt-chromium L605 metallic carrier covered with an amorphous, hydrogen-rich, silicon-carbide layer (PROBIO) and an asymmetric biodegradable poly-L-lactic acid polymer that released sirolimus at a dose of 1·4 µg per mm^2 stent surface over a period of 12–14 weeks. The polymer matrix degraded in 12–24 months.[12] The control stent (Xience Prime/Xpedition stent; Abbott Vascular, Abbott Park, IL, USA) consisted of a thin (81 µm) L605 cobalt-chromium platform that released everolimus from a durable polymer (poly-n-butyl-methacrylate and co-polymer of vinylidine fluoride and hexafluoropropylene).

The study was approved by the institutional ethics committees of all participating sites and complied with the Declaration of Helsinki. All patients provided written, informed consent for participation. The trial is registered with ClinicalTrials.gov, number NCT01443104. The non-inferiority test was reported previously.[5]

Outcomes

Patients were followed up at 30 days, 1 year, 2 years, and 5 years in a standardised telephone interview or during a visit to the clinic. The primary endpoint, target lesion failure, was a composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation within 12 months. Cardiac death was defined as any death due to immediate cardiac cause, death related to the procedure, unwitnessed death, and death of unknown cause. Myocardial infarction was differentiated according to the electrocardiographic criteria of the Minnesota code manual into Q-wave and non-Q-wave myocardial infarction. [13] Spontaneous myocardial infarction was defined as a characteristic rise and fall of creatinine kinase-MB fraction or troponin in the presence of at least one of ischaemic symptoms, new pathological Q waves, ischaemic electrocardiographic changes, and pathological evidence of acute myocardial infarction.[14] Target lesion revascularisation was defined as any repeat percutaneous or surgical intervention due to a stenosis or occlusion within the stent or within the 5 mm borders proximal or distal to the stent. Target vessel revascularisation was defined as any revascularisation within the entire major coronary vessels proximal or distal to a target lesion including upstream and downstream side branches and the target lesion itself. Stent thrombosis was categorised according to the definitions provided by the Academic Research Consortium.[15] All definitions have been described previously. [11] Any death, reinfarction, revascularisation, stent thrombosis, cerebrovascular accident, or bleeding event was independently adjudicated by a clinical events committee masked to treatment assignment.

Statistical analysis

We compared patients' medications and anginal status at each follow-up visit using Fisher's exact test. The Mantel-Cox method was used to calculate rate ratios (RRs), with 95% CIs and p values calculated with the log-rank test. We used time to first event for each outcome, and report numbers of patients and Kaplan-Meier estimates of cumulative incidence. A landmark analysis was done by setting as a landmark at 1 year the p value of the interaction for effect modification by period. We

did stratified analyses of the primary endpoint for several prespecified subgroups: diabetes, acute coronary syndrome, ST-segment elevation myocardial infarction (STEMI), and off-label use. Off-label was defined as patients with STEMI, any lesion length greater than 30 mm, any restenotic lesion, any totally occluded lesion, or any lesion within a saphenous vein graft. We also did post-hoc subgroup analyses of small vessels (defined as stent diameter in any lesion ≤3 mm), in-stent restenosis, long lesions (defined as a total stent length in any lesion of ≥20 mm), multivessel percutaneous coronary intervention, sex, age, body-mass index, and renal failure (defined as creatinine-estimated glomerular filtration rate <60 mL/min using the Modification of Diet in Renal Disease[16] formula). To identify interactions between treatment group and each of these subgroups in the effect size, we did approximate Mantel-Haenszel χ^2 tests for effect modification. All patients who were randomly assigned and provided written, informed consent were included and analysed according to the intention-to-treat principle. Statistical analyses were done with Stata 14.2.

Role of the funding source

The funders had no role in study design, data collection, data monitoring, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The senior author (SW), the co-principal investigator (TP), and the trial statistician (DH) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between March 1, 2012, and May 31, 2013, 2119 patients with 3139 lesions were randomly assigned to receive biodegradable-polymer sirolimus-eluting stents (1063 patients, 1594 lesions) or durable-polymer everolimus-eluting stents (1056 patients, 1545 lesions; figure 1). At 5 years, follow-up data were available for 994 (94%) patients receiving biodegradable-polymer sirolimus-eluting stents and for 1014 (96%) patients receiving durable-polymer everolimus-eluting stents (p=0·009). Baseline clinical, angiographic, and procedural characteristics have been reported previously.[5]

The median age of patients was 66·7 years (IQR 33·5–90·2) in the biodegradable-polymer sirolimuse-luting stent group and 66·6 years (38·6–89·1) in the durable-polymer everolimus-eluting stent group. 257 (24%) of 1063 patients treated with biodegradable-polymer sirolimus-eluting stents had diabetes versus 229 (22%) of 1056 patients treated with durable-polymer everolimus-eluting stents. More than half of all patients presented with an acute coronary syndrome (577 [54%] patients in the biodegradable-polymer sirolimus-eluting stent group vs 554 [52%] patients in the durable-polymer everolimus-eluting stent group); 211 (20%) patients receiving biodegradable polymer sirolimus-eluting stents and 196 (19%) patients receiving durable polymer everolimus-eluting stents had STEMI.

Adherence to antiplatelet therapy was similar in the two treatment groups at 1 year, 2 years, and 5 years (table 1). At 5 years, 68 (8%) of 849 patients with biodegradable-polymer sirolimus-eluting stents and 67 (7%) of 896 patients with durable-polymer everolimus-eluting stents were on dual antiplatelet therapy (p=0·72).

At 5 years, target lesion failure had occurred in 198 patients (cumulative incidence 20·2%) treated with biodegradable-polymer sirolimus-eluting stents and in 189 (18·8%) patients treated with durable-polymer everolimus-eluting stents (RR 1·07, 95% CI 0·88–1·31; p=0·487; table 2). Cumulative incidences of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation were similar in the two treatment groups (figure 2). The findings for target lesion failure were consistent across various patient subsets in a stratified analysis (figure 3).

The cumulative incidence of definite thrombosis at 5 years was 1·6% in both groups (RR 1·02, 95% CI 0·51–2·05; p=0·950; table 2). Within 1 year after implantation, definite stent thrombosis had occurred in nine patients (cumulative incidence 0·9%) in the biodegradable-polymer, sirolimus-eluting stent group and in four patients (0·4%) in the durable-polymer, everolimus-eluting stent group (RR 2·25, 95% CI 0·69–7·32). Between 1 year and 5 years after implantation, seven patients (0·8%) in the biodegradable-polymer, sirolimus-eluting stent group and 12 (1·3%) in the durable-polymer, everolimus-eluting stent group had definite stent thrombosis (0·61, 0·24–1·54; figure 4).

There was no difference between groups in the timing of events ($p_{interaction}$=0·080; figure 4). Landmark analyses of clinical outcomes, with the landmark set at 1 year, found no significant interaction between treatment effect and time (appendix).

At 5 years, a patient-oriented composite outcome consisting of all-cause mortality, any myocardial infarction, and any revascularisation had occurred in 325 patients (cumulative incidence 32·2%) treated with biodegradable-polymer sirolimus-eluting stents and in 308 patients (30·3%) treated with durable-polymer everolimus-eluting stents (RR 1·08, 95% CI 0·92–1·26; p=0·333; table 2; appendix). All-cause mortality was significantly higher in patients treated with biodegradable-polymer sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents (14·1% vs 10·3%; RR 1·36, 95% CI 1·06–1·75; p=0·017; table 2). This difference was driven by a higher incidence of non-cardiovascular death in the biodegradable-polymer sirolimus-eluting stent group than in the durable-polymer everolimus-eluting stent group, specifically by a two times increase in the incidence of death secondary to cancer (2·7% [26 patients] vs 1·3% [13 patients]; RR 2·03, 95% CI 1·04–3·95; p=0·037; appendix). The types of malignancy in patients who died from cancer are shown in the appendix; there was no evidence of a specific type of cancer driving the difference between groups.

DISCUSSION

In this large-scale, single blind, randomised trial, the cumulative incidence of target lesion failure over 5 years of follow-up did not differ between patients treated with biodegradable-polymer sirolimus-eluting stents and those treated with durable-polymer everolimus-eluting stents, and there was no significant interaction between treatment effect and time. All-cause mortality was significantly higher in patients treated with biodegradable-polymer sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents, which was driven by a difference in non-cardiovascular death.

Probably because of the all-comers design of the BIOSCIENCE trial, mortality was more than two times higher than in the FAME 2 trial,[17] and was within the upper range of mortality reported in other stent trials (appendix). Incidences of target vessel revascularisation and target lesion failure in our study were similar to those reported at 5 years in the LEADERS and RESOLUTE trials,[1,18] and were considerably higher than those reported in the COMPARE II trial,[19] the SORT OUT trials,[20–22] and the Twente trials.[23,24] Reported event rates across different trials are affected by a range of factors other than the stent and need to be interpreted in the context of patient and lesion complexity, medical treatment, functional testing for ischaemia, endpoint definitions, event reporting, extent of data monitoring, and event adjudication. We routinely relied on angiographic assessment to establish lesion severity and used fractional flow reserve only if we were in doubt about lesion severity. Therefore, the incidence of clinically indicated revascularisation in our study might have been overestimated.

This study extends the clinical evidence on the newest generation of drug-eluting stents combining biodegradable polymers with ultrathin-stent platforms. To our knowledge, this study is the first to assess the longer-term (beyond the degradation time of the polymer) clinical outcomes of an ultrathin-strut, biodegradable-polymer, sirolimus-eluting stent, in an adequately powered randomised trial, with the best-in-class durable-polymer everolimus-eluting stent as a comparator. Evidence from randomised controlled trials comparing Biodegradable polymer sirolimus-eluting stents with durable-polymer everolimus-eluting stents before full degradation of the polymer have been conflicting. Some trials (BIOFLOW-II,[25] BIOSCIENCE,[11] and BIORESORT[9]) found that biodegradable sirolimus-eluting stents were non-inferior to durable-polymer drug-eluting stents in terms of angiographic and composite clinical outcomes. The BIOFLOW-V trial,[10] by contrast, found that a lower proportion of patients treated with biodegradable-polymer sirolimus-eluting stents had target lesion failure within 1 year of implantation than did those treated with durable-polymer everolimus-eluting stents. This finding was driven by a difference between groups in the proportion of patients who had target vessel myocardial infarction, which was defined by both a protocol

definition[26] and an Academic Research Consortium definition[15] in the trial, whereas a less sensitive definition was used in BIOSCIENCE and BIOFLOW-II.[11,25] The less sensitive definition of myocardial infarction in our study could explain the lack of difference in incidence of myocardial infarction between the two treatment groups. Consistent with the 5 year clinical outcomes of BIOFLOW-II,[27] there were no differences in the occurrence of target lesion failure and its individual components of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revacularisation between the stent types in our study.

A meta-analysis[28] of ten trials comparing three different types of ultrathin-strut drug-eluting stents with thicker-strut, second-generation, drug-eluting stents found that ultrathin-strut stents reduced target lesion failure by 16% compared with thicker-strut stents (RR 0·84, 95% CI 0·72–0·99). This difference was driven by a lower incidence of myocardial infarction in patients treated with ultrathin-strut stents than in those treated with thicker-strut stents (0·72, 0·51–1·01). These findings (which occurred before complete resolution of the polymer) suggest an effect related to strut thickness; in particular, ultrathin struts might mitigate the compromise of flow in side branches. In the biodegradable-polymer sirolimus-eluting stent group of our trial, patients with small vessels of 3·0 mm or less were treated with stents of 60 μm strut thickness, whereas those with larger vessels were treated with stents of 80 μm strut thickness. We therefore did a subgroup analysis by vessel size using this cutoff, and found no variation in treatment effect.

By contrast with the invariable effect of the ultrathin metallic stent platform, the potential benefit of the polymer is expected to come into effect after its complete bioresorption, which occurs between 12 months and 24 months after stent implantation. Durable polymers have been shown to sustain a chronic inflammatory response in histopathologic analyses,[29] providing a substrate for incomplete vascular healing[2] and leading to an increased risk of very late stent thrombosis.[30] Early generations of biodegradable-polymer stents based on thick-strut stainless steel platforms were associated with a decreased risk of very late stent thrombosis compared with durable-polymer drug-eluting stents.[1,30] The 5 year outcomes of the BIOFLOW-II trial did not show a significantly lower incidence of

stent thrombosis in patients treated with biodegradable-polymer sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents (0·7% vs 2·8%; hazard ratio 0·25, 95% CI 0·05–1·39; p=0·088).[27] Similarly, long-term data of the BIOSCIENCE trial did not show a difference in timing of definite stent thrombosis in patients treated with biodegradable-polymer sirolimus-eluting stents between the first year of stent implantation and 1–5 years after stent implantation ($p_{interaction}$=0·080). Of note, adherence to antiplatelet treatment was high in both treatment groups, and most patients had discontinued treatment with P2Y12 inhibitors beyond 1 year.

A significant difference in all-cause mortality was driven by higher rates of non-cardiovascular death in patients treated with biodegradable polymer sirolimus-eluting stents than in those treated with durable polymer everolimus-eluting stents. In particular, patients in the biodegradable polymer sirolimus-eluting stent group more commonly died from cancer. The difference in all-cause mortality emerged within 2 years of stent implantation and was not corroborated in the long-term follow-up of the angiographically powered BIOFLOW-II trial.[27,31] Other studies comparing biodegradable-polymer sirolimus-eluting stents with durable-polymer everolimus-eluting stents with follow-up limited to 1 year did not show a mortality difference between the two types of stents.[10,32] Although the observed difference in this trial might be a chance finding, it warrants further observation during long-term follow-up of ongoing studies.

Analyses of prespecified subgroups showed a consistent effect of the two stent types across subsets of patients with diabetes, acute coronary syndromes, and renal failure. A lower incidence of target lesion failure in patients with STEMI treated with biodegradable sirolimus-eluting stents at 1 year[33,34] was not substantiated in the 5-year outcome data. The safety and efficacy of biodegradable polymer sirolimus-eluting stents compared with durable polymer everolimus-eluting stents in the setting of STEMI is currently under investigation in the BIOSTEMI trial (NCT02579031).[35]

Our study has several limitations. First, it was powered to detect non-inferiority with regards to a primary composite endpoint at 1 year. Potential differences between the two treatment groups with regards to individual clinical endpoints are hypothesis generating. Event rates for the primary

endpoint were similar to the original hypothesis,[11] and high event rates throughout 5 years underscore the complexity of the population enrolled in the trial. The medical regimen adhered to current recommendations and included a substantial proportion of patients treated with novel P2Y12 inhibitors. Second, follow-up information was missing for 71 patients because of loss to follow-up, and for 40 patients because of refusal of follow-up. Completeness of follow-up at 5 years was similar to that in other stent trials that used conventional means of follow-up,[36–38] but was lower than in trials that used ascertainment of outcomes based on health-care registries.[20–22] There was a small but significant difference in completeness of follow-up at 5 years between the two groups. We are unable to explain this difference and understand its effect on the estimated treatment effects, but consider it likely to be a chance finding. Third, a significant difference in non-cardiovascular death was largely driven by an increased incidence of death secondary to cancer in patients in the biodegradable polymer sirolimus-eluting stent group. A history of cancer was not prospectively recorded at baseline; hence, we cannot differentiate between death secondary to pre-existing, recurring, and newly developed cancer in our study population. Fourth, tests for interaction have low power.[39] Finally, although, to our knowledge, our analysis provides the longest available experience of ultrathin strut biodegradable polymer sirolimus-eluting stents, a difference in very late stent thrombosis might become apparent only during extended follow-up beyond 5 years.

In conclusion, the final 5 year outcomes of the BIOSCIENCE trial show similar outcomes for ultrathin strut biodegradable sirolimus-eluting stents and thin strut durable polymer everolimus-eluting stents with regards to a composite of target lesion failure among patients undergoing percutaneous coronary intervention for stable coronary artery disease or acute coronary syndromes. Higher incidences of all-cause and non-cardiovascular mortality in patients treated with biodegradable polymer sirolimus-eluting stents warrant careful observation in ongoing studies.

CONTRIBUTORS

TP, DH, PJ, and SW conceived the study and were responsible for designing the study. TP, RP, DH, MR, DT, OM, IM, GCMS, SC, DW, CK, FC, LH, FRE, and SW were responsible for data collection. DH did the analysis and interpreted the results in collaboration with all other authors. TP, GCMS, RP, DH, and SW wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version.

DECLARATION OF INTERESTS

TP has received research grants to his institution from Biotronik, Boston Scientific, and Edwards Lifesciences, and speaker fees from Biotronik and Boston Scientific. MR reports institutional research grants from Terumo, Boston Scientific, Medtronic, Abbott Vascular, and Biotronik, outside the submitted work. FRE reports grants from Biotronik, Abbott Vascular, Biosensors, Medtronic, and Boston Scientific, outside the submitted work. PJ is a tier 1 Canada research chair in clinical epidemiology of chronic diseases; this research was completed, in part, with funding from the Canada Research Chairs Programme. PJ also serves as an unpaid member of the steering group for trials funded by AstraZeneca, Biotronik, Biosensors, St Jude Medical, and The Medicines Company. SW received research grants to his institution from Abbott, Amgen, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, Medicines Company, and St Jude. All other authors declare no competing interests.

DATA SHARING

The BioScience trial is an investigator-initiated trial. Multiple sub-studies were predefined. Internal investigators (ie, those who actively participated in the study) who provide a methodologically sound study proposal will be granted priority access to the study data for a period of 24 months. The study protocol will immediately be available on The Lancet's website. After 24 months, data that underlie the results reported in this Article, plus relevant documentation, will be made available to external

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investigators (ie, those not affiliated with the trial), whose proposed use of the data has been approved by an independent review committee identified by the steering committee for this purpose. Data will be deposited at https://boris.unibe.ch, where study proposals can also be filed.

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TABLES

Table 1: Medications at discharge and 1 year, 2 years, and 5 years of follow-up

	Biodegradable-polymer sirolimus-eluting stent (n=1063)	Durable-polymer everolimus-eluting stent (n=1056)
Discharge		
Aspirin	1050/1061 (99%)	1045/1054 (99%)
Clopidogrel	473/1061 (45%)	474/1054 (45%)
Prasugrel	296/1061 (28%)	284/1054 (27%)
Ticagrelor	283/1061 (27%)	292/1054 (28%)
Any dual antiplatelet treatment	1039/1061 (98%)	1040/1054 (99%)
Oral anticoagulants	68/1061 (6%)	69/1054 (7%)
Novel oral anticoagulants	6/1061 (1%)	6/1054 (1%)
Any antithrombotic treatment	74/1061 (7%)	75/1054 (7%)
Statin	1003/1061 (95%)	992/1054 (94%)
ACE inhibitor	600/1061 (57%)	607/1054 (58%)
β blocker	819/1061 (77%)	809/1054 (77%)
1 year follow-up		
Aspirin	959/997 (96%)	961/1006 (96%)
Clopidogrel	404/997 (41%)	418/1006 (42%)
Prasugrel	253/997 (25%)	228/1006 (23%)
Ticagrelor	212/997 (21%)	223/1006 (22%)
Any dual antiplatelet treatment	833/997 (84%)	828/1006 (82%)
Oral anticoagulants	67/995 (7%)	74/1006 (7%)
Novel oral anticoagulants	12/995 (1%)	11/1006 (1%)
Any antithrombotic treatment	79/995 (8%)	85/1006 (8%)
Statin	889/992 (90%)	925/1006 (92%)
ACE inhibitor	464/992 (47%)	453/1004 (45%)
β blocker	705/993 (71%)	727/1006 (72%)
2 year follow-up		
Aspirin	903/955 (95%)	927/982 (94%)
Clopidogrel	102/955 (11%)	118/982 (12%)
Prasugrel	20/955 (2%)	29/982 (3%)
Ticagrelor	43/955 (5%)	23/982 (2%)
Any dual antiplatelet treatment	145/955 (15%)	142/982 (14%)
Oral anticoagulants	64/955 (7%)	68/982 (7%)
Novel oral anticoagulants	19/955 (2%)	22/982 (2%)
Any antithrombotic treatment	83/955 (9%)	90/982 (9%)
Statin	822/955 (86%)	885/982 (90%)
ACE inhibitor	412/955 (43%)	403/982 (41%)
β blocker	636/955 (67%)	660/982 (67%)

(Table 1 continues in next column)

	Biodegradable-polymer sirolimus-eluting stent (n=1063)	Durable-polymer everolimus-eluting stent (n=1056)
(Continued from previous column)		
5 year follow-up		
Aspirin	751/849 (88%)	787/896 (88%)
Clopidogrel	69/849 (8%)	73/896 (8%)
Prasugrel	13/849 (2%)	14/896 (2%)
Ticagrelor	18/849 (2%)	16/896 (2%)
Any dual antiplatelet treatment	68/849 (8%)	67/896 (7%)
Oral anticoagulants	55/849 (6%)	52/896 (6%)
Novel oral anticoagulants	62/849 (7%)	58/896 (6%)
Any antithrombotic treatment	117/849 (14%)	110/896 (12%)
Statin	689/849 (81%)	743/896 (83%)
ACE inhibitor	343/849 (40%)	350/896 (39%)
β blocker	537/849 (63%)	572/896 (64%)

Denominators are lower than total numbers of patients in each group because patients who had died or been lost to follow-up could not provide information about medications (and one patient in the biodegradable-polymer sirolimus-eluting stent group refused to provide information about medication).
ACE=angiotensin-converting enzyme.

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525 **Table 2:** Clinical outcomes at 5 years of follow-up.

526 Number of first events (cumulative incidence) are reported. All events were censored after 1825

527 days. MI=myocardial infarction. TLR=target lesion revascularisation. TVR=target vessel

528 revascularisation. BARC=Bleeding Academic Research Consortium. *Primary endpoint, defined as the

529 composite of cardiac death, target vessel Q-wave or non-Q-wave MI, and clinically indicated TLR.

530 †Includes ischaemic stroke, intracerebral haemorrhagic stroke, and cerebrovascular events with

531 unclear cause. ‡Defined as the composite of cardiac death, any Q-wave or non-Q-wave MI, and any

532 TVR. §Defined as all-cause death, any MI, and any repeat revascularisation.

	Biodegradable-polymer sirolimus-eluting stent (n=1063)	Durable-polymer everolimus-eluting stent (n=1056)	Rate ratio (95% CI)	p value
Target lesion failure*	198 (20·2%)	189 (18·8%)	1·07 (0·88–1·31)	0·487
Cardiac death	81 (8·6%)	76 (7·5%)	1·10 (0·80–1·50)	0·569
Target vessel MI	62 (6·3%)	69 (7·1%)	0·91 (0·65–1·28)	0·595
Clinically indicated TLR	103 (10·8%)	97 (10·0%)	1·10 (0·83–1·45)	0·504
All-cause mortality	139 (14·1%)	105 (10·3%)	1·36 (1·06–1·75)	0·017
Any MI	99 (10·4%)	118 (12·3%)	0·85 (0·65–1·11)	0·225
Q-wave	32 (3·7%)	24 (2·8%)	1·37 (0·81–2·33)	0·240
Non-Q-wave	72 (7·4%)	97 (9·9%)	0·75 (0·55–1·02)	0·062
Cardiac death or MI	168 (17·2%)	179 (18·0%)	0·95 (0·77–1·17)	0·636
Repeat revascularisation	188 (19·3%)	195 (19·9%)	1·00 (0·82–1·22)	0·995
Any TLR	110 (11·5%)	106 (10·9%)	1·07 (0·82–1·40)	0·609
Any TVR	130 (13·5%)	132 (13·5%)	1·02 (0·80–1·29)	0·897
Clinically indicated TVR	125 (13·0%)	123 (12·6%)	1·05 (0·82–1·35)	0·692
Cerebrovascular event	37 (3·9%)	38 (3·9%)	0·99 (0·63–1·56)	0·981
Stroke†	27 (2·8%)	34 (3·5%)	0·81 (0·49–1·34)	0·413
Target vessel failure‡	220 (22·4%)	219 (21·7%)	1·03 (0·85–1·24)	0·782
Patient-oriented composite outcome§	325 (32·2%)	308 (30·3%)	1·08 (0·92–1·26)	0·333
Definite stent thrombosis	16 (1·6%)	16 (1·6%)	1·02 (0·51–2·05)	0·950
Definite or probable stent thrombosis	62 (6·3%)	76 (7·7%)	0·83 (0·59–1·16)	0·264
BARC bleeding events type 3–5	56 (5·7%)	51 (5·1%)	1·12 (0·76–1·63)	0·571

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FIGURES

Figure 1: Trial profile

BP SES=biodegradable-polymer sirolimus-eluting stent. DP EES=durable-polymer everolimus-eluting stent. BMS=bare metal stent. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft.

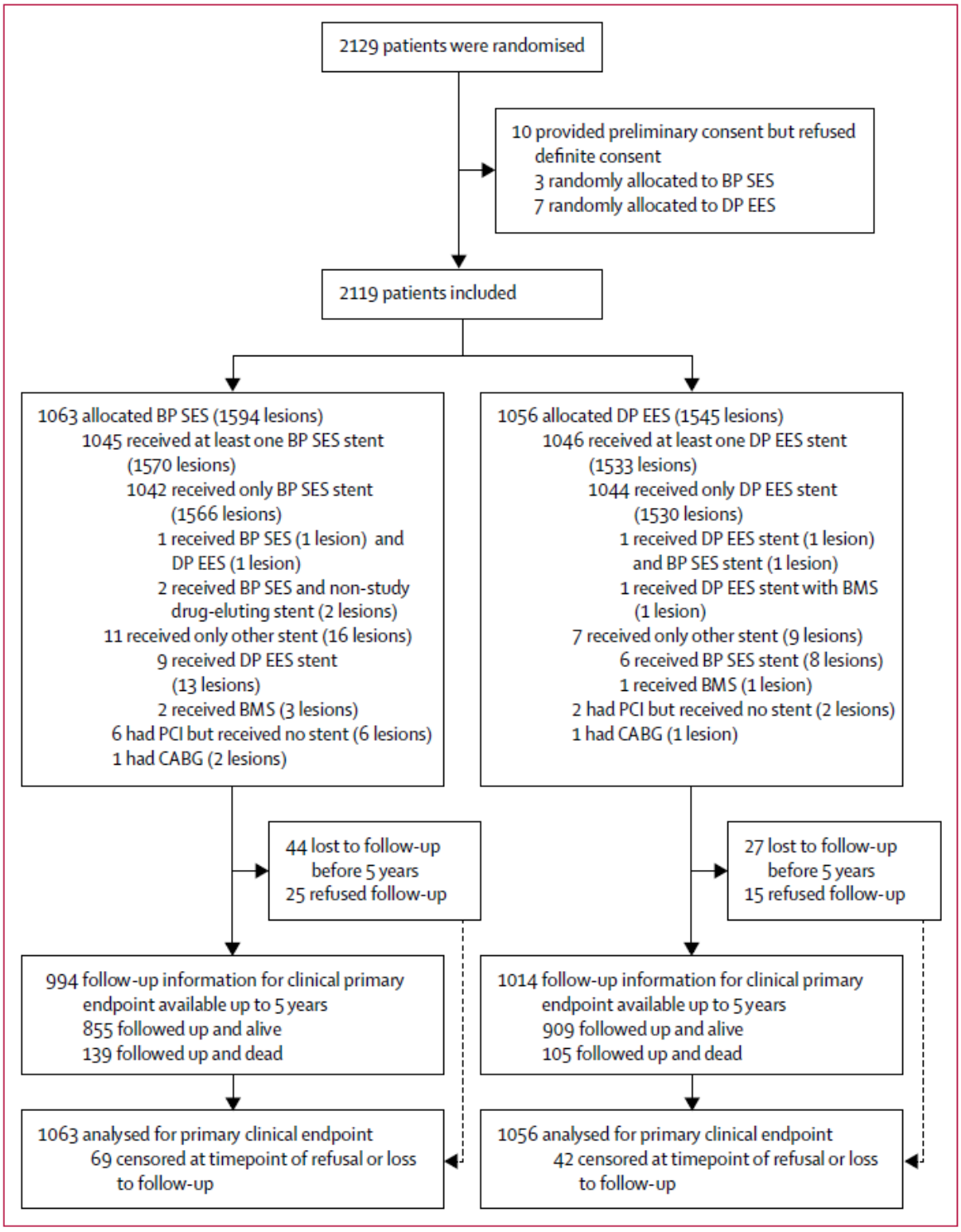

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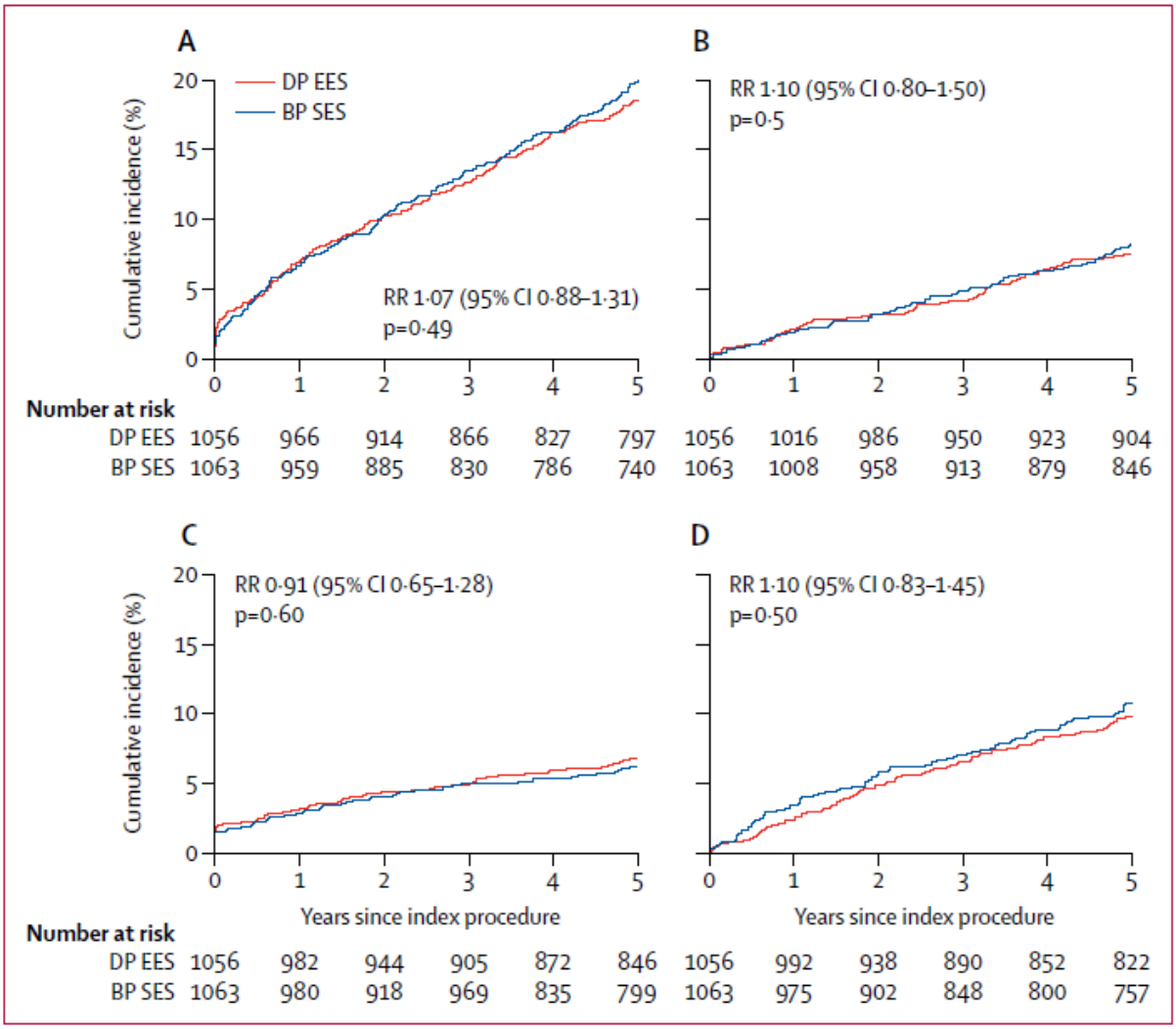
Figure 2: Time to event curves for the composite primary endpoint of target lesion failure and its individual components up to 5 years of follow-up. RR=rate ratio. DP EES=durable-polymer everolimus-eluting stent. BP SES=biodegradable-polymer sirolimus-eluting stent. (A) Target lesion failure. (B) Cardiac death. (C) Target vessel myocardial infarction. (D) Clinically indicated target lesion revascularisation.



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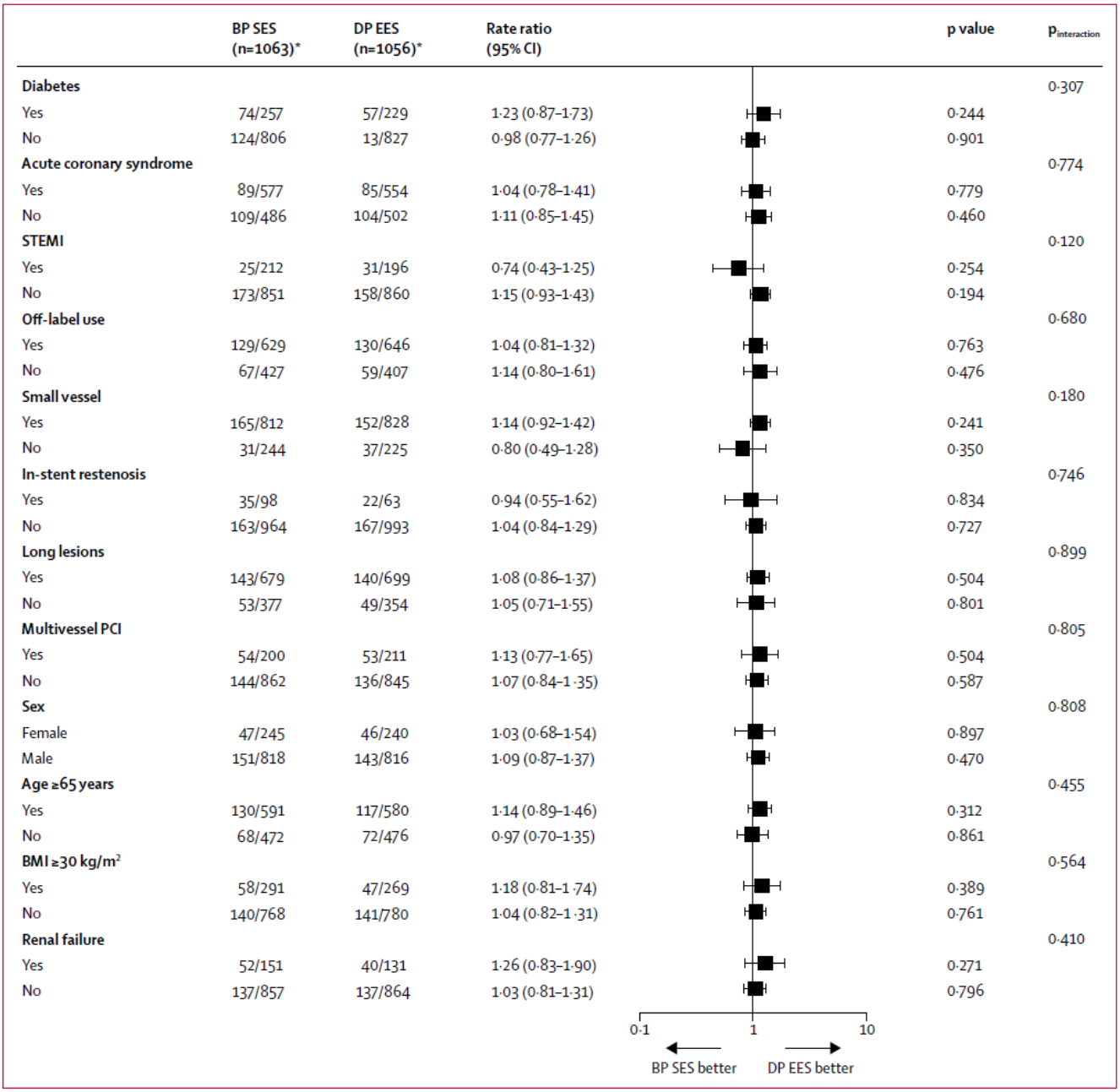
547 **Figure 3:** Stratified analyses of target lesion failure at 5 years across major subgroups. BP
548 SES=biodegradable-polymer sirolimus-eluting stent. DP EES=durable-polymer everolimus-eluting
549 stent. STEMI=ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention.
550 BMI=body-mass index. *Data in these columns are events/number of patients.



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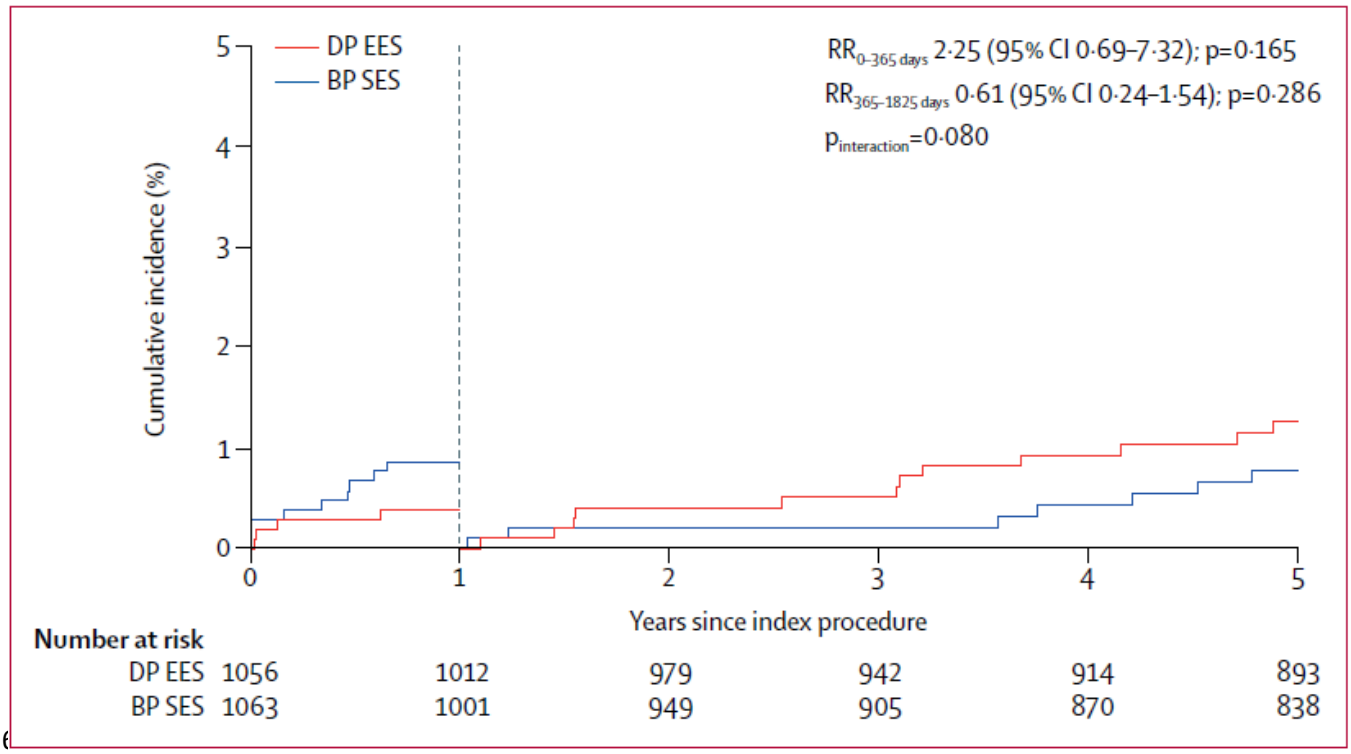
553 **Figure 4:** Time to event curve for definite stent thrombosis up to 5 years of follow-up. A landmark
554 was set at 1 year. RR=rate ratio. DP EES=durable-polymer everolimus-eluting stent. BP
555 SES=biodegradable-polymer sirolimus-eluting stent.



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