

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

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## 28 **2 Tables and 4 Figures**

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

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

31 **Figure 1:** Trial profile

32 **Figure 2:** Time to event curves for the composite primary endpoint of target lesion failure and its  
33 individual components up to 5 years of follow-up

34 **Figure 3:** Stratified analyses of target lesion failure at 5 years across major subgroups

35 **Figure 4:** Time to event curve for definite stent thrombosis up to 5 years of follow-up

36

## 37 **BOX: RESEARCH IN CONTEXT**

### 38 **Evidence before this study**

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

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

56

#### 57 **Added value of this study**

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

67

#### 68 **Implication of all the available evidence**

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

71

72 **SUMMARY**

73 **Background**

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

77 **Methods**

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

85 **Findings**

86 2008 (95%) of 2119 patients recruited between March 1, 2012, and May 31, 2013, completed 5  
87 years of followup. Target lesion failure occurred in 198 patients (cumulative incidence 20·2%)  
88 treated with biodegradable-polymer sirolimus-eluting stents and in 189 patients (18·8%) treated  
89 with durable-polymer everolimus-eluting stents (rate ratio [RR] 1·07, 95% CI 0·88–1·31; p=0·487).  
90 All-cause mortality was significantly higher in patients treated with biodegradable-polymer  
91 sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents (14·1%  
92 vs 10·3%; RR 1·36, 95% CI 1·06–1·75; p=0·017), driven by a difference in non-cardiovascular deaths.  
93 We observed no difference between groups in cumulative incidence of definite stent thrombosis at 5  
94 years (1·6% in both groups; 1·02, 0·51–2·05; p=0·950).

95 **Interpretation**

96 5-year risk of target lesion failure among all-comer patients undergoing percutaneous coronary  
97 intervention is similar after implantation of ultrathin-strut, biodegradable-polymer, sirolimus-eluting

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

102

## 103 **INTRODUCTION**

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

109 Newer-generation drug-eluting stents combining ultrathin-strut cobalt-chromium platforms with  
110 biodegradable polymers eluting sirolimus have been associated with a reduced risk of definite stent  
111 thrombosis compared with thick-strut, stainless steel, biodegradable-polymer, drug-eluting stents,<sup>8</sup>  
112 and were non-inferior to thinstrut, durable-polymer, drug-eluting stents with regards to composites  
113 of clinical endpoints at 1 year in two randomised controlled trials.<sup>5,9</sup> More recently, the randomised  
114 controlled BIOFLOW V trial<sup>10</sup> reported a lower incidence of target lesion failure at 1 year, driven by  
115 a lower incidence of myocardial infarction, in patients treated with biodegradable-polymer  
116 sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents.

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

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

126

## 127 **METHODS**

### 128 **Study design and patients**

129 The BIOSCIENCE trial was an investigator-initiated, single-blind, multicentre, randomised, non-  
130 inferiority trial. Eligible patients had coronary artery disease and at least one lesion with more than  
131 50% diameter de-novo stenosis or restenosis in a native coronary artery or a bypass graft.  
132 Additionally, patients had to present with stable coronary artery disease or acute coronary  
133 syndromes.

134 The rationale of the trial, as well as details of randomisation, masking, and data management, have  
135 been described previously.<sup>11</sup> Briefly, patients were randomly assigned in a 1:1 ratio to  
136 biodegradable-polymer sirolimus-eluting stents or to durable-polymer everolimus-eluting stents in  
137 nine centres in Switzerland. The experimental stent (Orsiro; Biotronik AG, Bülach, Switzerland)  
138 consisted of an ultrathin (60 µm for stent diameters ≤3.0 mm, 80 µm for stent diameters >3.0 mm)  
139 cobalt-chromium L605 metallic carrier covered with an amorphous, hydrogen-rich, silicon-carbide  
140 layer (PROBIO) and an asymmetric biodegradable poly-L-lactic acid polymer that released sirolimus  
141 at a dose of 1.4 µg per mm<sup>2</sup> stent surface over a period of 12–14 weeks. The polymer matrix  
142 degraded in 12–24 months.<sup>12</sup> The control stent (Xience Prime/Xpedition stent; Abbott Vascular,  
143 Abbott Park, IL, USA) consisted of a thin (81 µm) L605 cobalt-chromium platform that released  
144 everolimus from a durable polymer (poly-n-butyl-methacrylate and co-polymer of vinylidene fluoride  
145 and hexafluoropropylene).

146 The study was approved by the institutional ethics committees of all participating sites and complied  
147 with the Declaration of Helsinki. All patients provided written, informed consent for participation.

148 The trial is registered with ClinicalTrials.gov, number NCT01443104. The non-inferiority test was  
149 reported previously.<sup>5</sup>

150 **Outcomes**

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

169

170 **Statistical analysis**

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

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

188

#### 189 **Role of the funding source**

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

194

#### 195 **RESULTS**

196 Between March 1, 2012, and May 31, 2013, 2119 patients with 3139 lesions were randomly assigned  
197 to receive biodegradable-polymer sirolimus-eluting stents (1063 patients, 1594 lesions) or durable-  
198 polymer everolimus-eluting stents (1056 patients, 1545 lesions; figure 1). At 5 years, follow-up data  
199 were available for 994 (94%) patients receiving biodegradable-polymer sirolimus-eluting stents and  
200 for 1014 (96%) patients receiving durable-polymer everolimus-eluting stents ( $p=0.009$ ). Baseline  
201 clinical, angiographic, and procedural characteristics have been reported previously.<sup>5</sup>



202 The median age of patients was 66·7 years (IQR 33·5–90·2) in the biodegradable-polymer sirolimus-  
203 luting stent group and 66·6 years (38·6–89·1) in the durable-polymer everolimus-eluting stent group.  
204 257 (24%) of 1063 patients treated with biodegradable-polymer sirolimus-eluting stents had  
205 diabetes versus 229 (22%) of 1056 patients treated with durable-polymer everolimus-eluting stents.  
206 More than half of all patients presented with an acute coronary syndrome (577 [54%] patients in the  
207 biodegradable-polymer sirolimus-eluting stent group vs 554 [52%] patients in the durable-polymer  
208 everolimus-eluting stent group); 211 (20%) patients receiving biodegradable polymer sirolimus-  
209 eluting stents and 196 (19%) patients receiving durable polymer everolimus-eluting stents had  
210 STEMI.

211 Adherence to antiplatelet therapy was similar in the two treatment groups at 1 year, 2 years, and 5  
212 years (table 1). At 5 years, 68 (8%) of 849 patients with biodegradable-polymer sirolimus-eluting  
213 stents and 67 (7%) of 896 patients with durable-polymer everolimus-eluting stents were on dual  
214 antiplatelet therapy ( $p=0\cdot72$ ).

215 At 5 years, target lesion failure had occurred in 198 patients (cumulative incidence 20·2%) treated  
216 with biodegradable-polymer sirolimus-eluting stents and in 189 (18·8%) patients treated with  
217 durable-polymer everolimus-eluting stents (RR 1·07, 95% CI 0·88–1·31;  $p=0\cdot487$ ; table 2). Cumulative  
218 incidences of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion  
219 revascularisation were similar in the two treatment groups (figure 2). The findings for target lesion  
220 failure were consistent across various patient subsets in a stratified analysis (figure 3).

221 The cumulative incidence of definite thrombosis at 5 years was 1·6% in both groups (RR 1·02, 95% CI  
222 0·51–2·05;  $p=0\cdot950$ ; table 2). Within 1 year after implantation, definite stent thrombosis had  
223 occurred in nine patients (cumulative incidence 0·9%) in the biodegradable-polymer, sirolimus-  
224 eluting stent group and in four patients (0·4%) in the durable-polymer, everolimus-eluting stent  
225 group (RR 2·25, 95% CI 0·69–7·32). Between 1 year and 5 years after implantation, seven patients  
226 (0·8%) in the biodegradable-polymer, sirolimus-eluting stent group and 12 (1·3%) in the durable-  
227 polymer, everolimus-eluting stent group had definite stent thrombosis (0·61, 0·24–1·54; figure 4).

228 There was no difference between groups in the timing of events ( $p_{\text{interaction}}=0.080$ ; figure 4).  
229 Landmark analyses of clinical outcomes, with the landmark set at 1 year, found no significant  
230 interaction between treatment effect and time (appendix).  
231 At 5 years, a patient-oriented composite outcome consisting of all-cause mortality, any myocardial  
232 infarction, and any revascularisation had occurred in 325 patients (cumulative incidence 32.2%)  
233 treated with biodegradable-polymer sirolimus-eluting stents and in 308 patients (30.3%) treated  
234 with durable-polymer everolimus-eluting stents (RR 1.08, 95% CI 0.92–1.26;  $p=0.333$ ; table 2;  
235 appendix). All-cause mortality was significantly higher in patients treated with biodegradable-  
236 polymer sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting  
237 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  
238 higher incidence of non-cardiovascular death in the biodegradable-polymer sirolimus-eluting stent  
239 group than in the durable-polymer everolimus-eluting stent group, specifically by a two times  
240 increase in the incidence of death secondary to cancer (2.7% [26 patients] vs 1.3% [13 patients]; RR  
241 2.03, 95% CI 1.04–3.95;  $p=0.037$ ; appendix). The types of malignancy in patients who died from  
242 cancer are shown in the appendix; there was no evidence of a specific type of cancer driving the  
243 difference between groups.

244

## 245 **DISCUSSION**

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

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

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

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

286 A meta-analysis<sup>28</sup> of ten trials comparing three different types of ultrathin-strut drug-eluting stents  
287 with thicker-strut, second-generation, drug-eluting stents found that ultrathin-strut stents reduced  
288 target lesion failure by 16% compared with thicker-strut stents (RR 0·84, 95% CI 0·72–0·99). This  
289 difference was driven by a lower incidence of myocardial infarction in patients treated with  
290 ultrathin-strut stents than in those treated with thicker-strut stents (0·72, 0·51–1·01). These findings  
291 (which occurred before complete resolution of the polymer) suggest an effect related to strut  
292 thickness; in particular, ultrathin struts might mitigate the compromise of flow in side branches. In  
293 the biodegradable-polymer sirolimus-eluting stent group of our trial, patients with small vessels of  
294 3·0 mm or less were treated with stents of 60 µm strut thickness, whereas those with larger vessels  
295 were treated with stents of 80 µm strut thickness. We therefore did a subgroup analysis by vessel  
296 size using this cutoff, and found no variation in treatment effect.

297 By contrast with the invariable effect of the ultrathin metallic stent platform, the potential benefit of  
298 the polymer is expected to come into effect after its complete bioresorption, which occurs between  
299 12 months and 24 months after stent implantation. Durable polymers have been shown to sustain a  
300 chronic inflammatory response in histopathologic analyses,<sup>29</sup> providing a substrate for incomplete  
301 vascular healing<sup>2</sup> and leading to an increased risk of very late stent thrombosis.<sup>30</sup> Early generations  
302 of biodegradable-polymer stents based on thick-strut stainless steel platforms were associated with  
303 a decreased risk of very late stent thrombosis compared with durable-polymer drug-eluting  
304 stents.<sup>1,30</sup> The 5 year outcomes of the BIOFLOW-II trial did not show a significantly lower incidence of

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

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

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

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

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

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

354 **CONTRIBUTORS**

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

360

361 **DECLARATION OF INTERESTS**

362 TP has received research grants to his institution from Biotronik, Boston Scientific, and Edwards  
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371 Edwards Lifesciences, Medtronic, Medicines Company, and St Jude. All other authors declare no  
372 competing interests.

373

374 **DATA SHARING**

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

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

383

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386

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390



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- 521

## 522 TABLES

523 **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)
<b>Discharge</b>		
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%)
<b>1 year follow-up</b>		
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%)
<b>2 year follow-up</b>		
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)		
(Continued from previous column)		
<b>5 year follow-up</b>		
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.		

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.

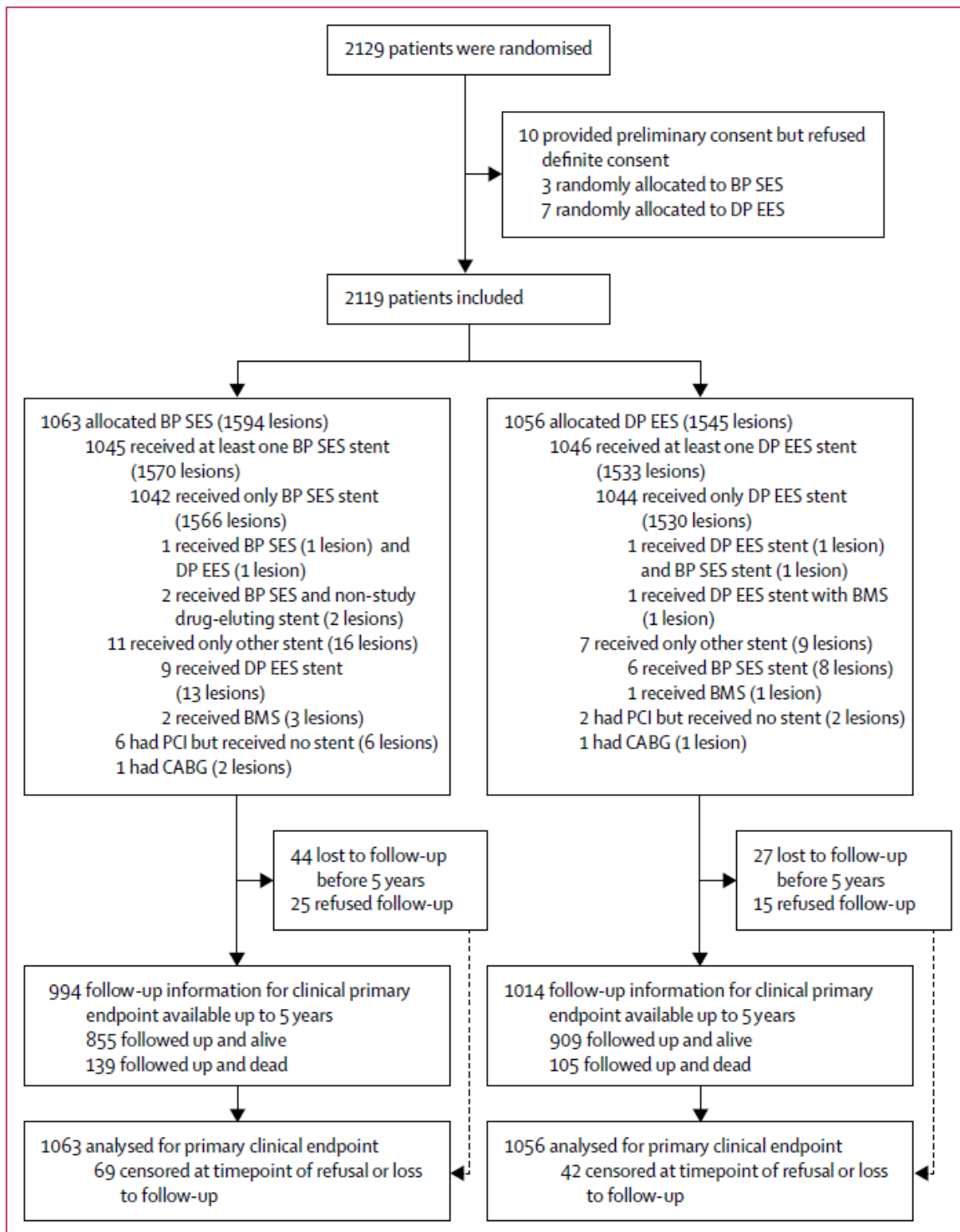
	Biodegradable-polymer sirolimus-eluting stent (n=1063)	Durable-polymer everolimus-eluting stent (n=1056)	Rate ratio (95% CI)	p value
Target lesion failure*	198 (20.2%)	189 (18.8%)	1.07 (0.88-1.31)	0.487
Cardiac death	81 (8.6%)	76 (7.5%)	1.10 (0.80-1.50)	0.569
Target vessel MI	62 (6.3%)	69 (7.1%)	0.91 (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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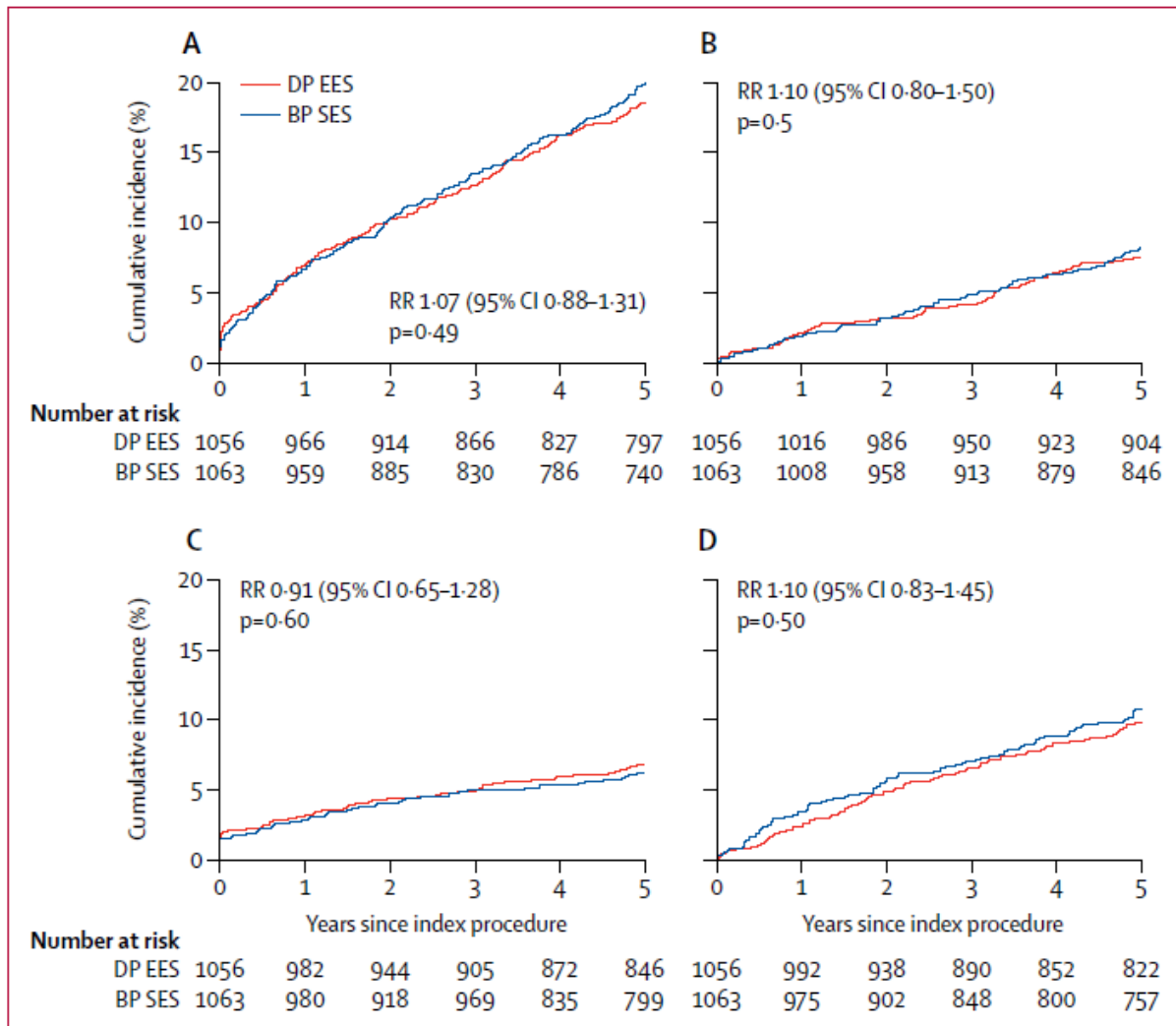
534 **FIGURES**

535 **Figure 1: Trial profile**

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



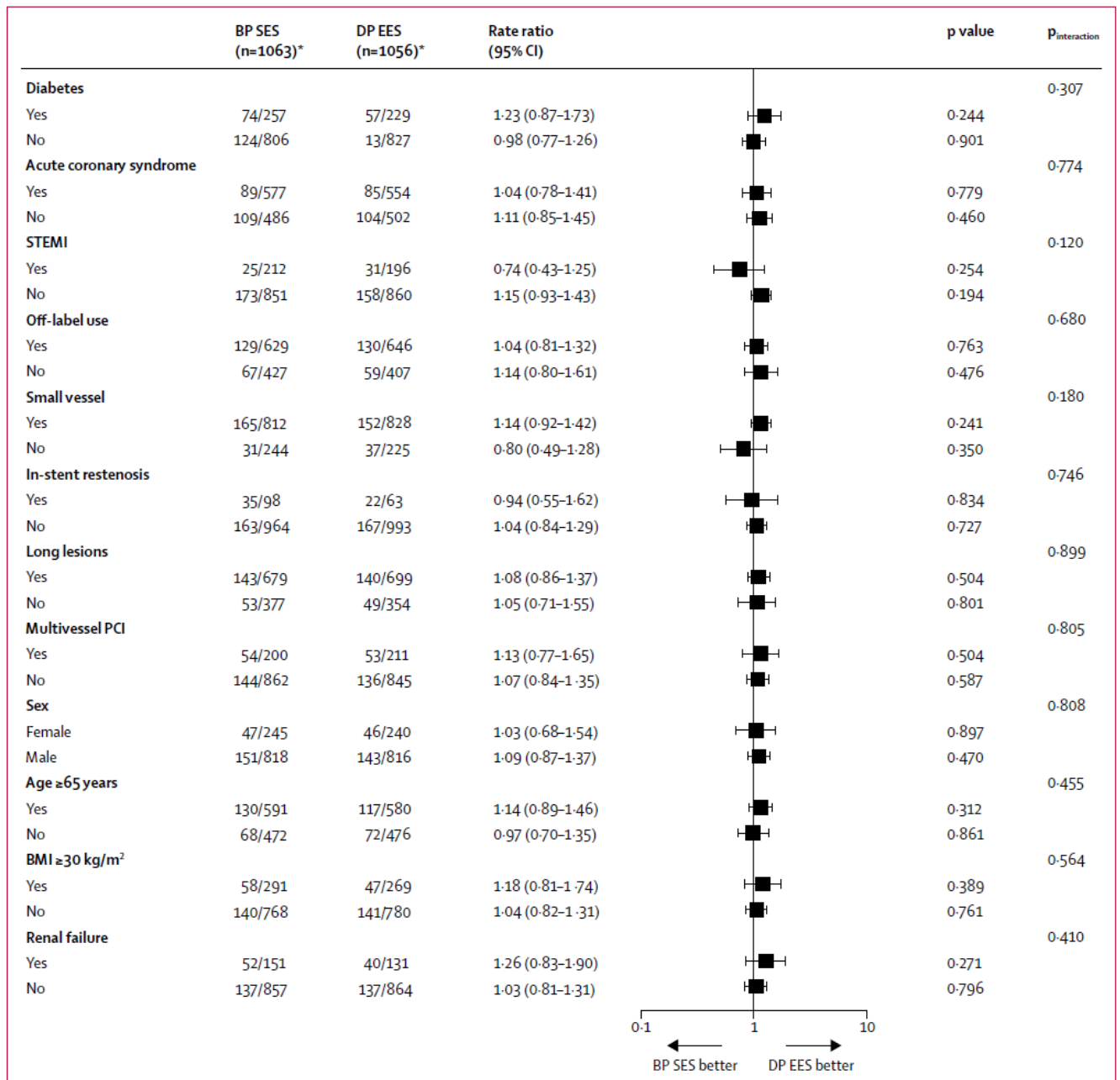
540 **Figure 2:** Time to event curves for the composite primary endpoint of target lesion failure and its  
 541 individual components up to 5 years of follow-up. RR=rate ratio. DP EES=durable-polymer  
 542 everolimus-eluting stent. BP SES=biodegradable-polymer sirolimus-eluting stent. (A) Target lesion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



545

546

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.

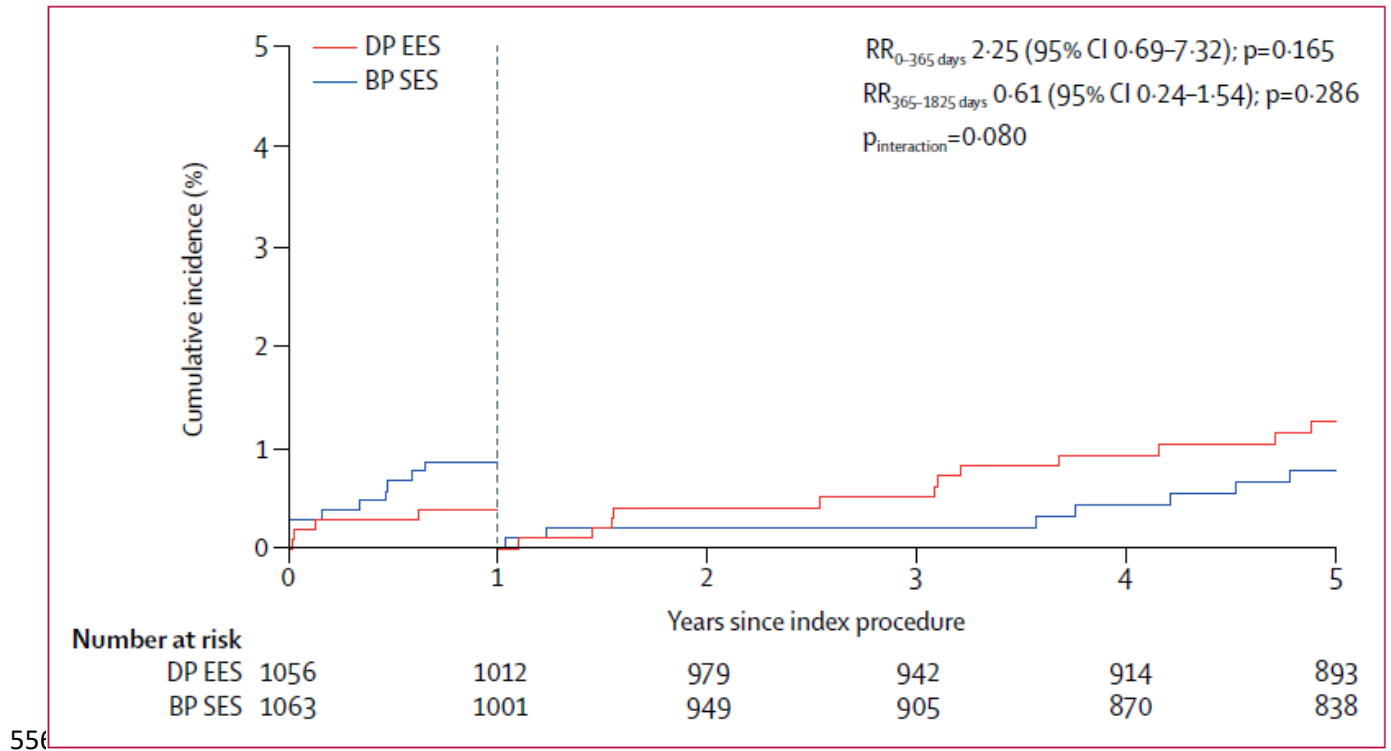


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553 **Figure 4:** Time to event curve for definite stent thrombosis up to 5 years of follow-up. A landmark  
 554 was set at 1 year. RR=rate ratio. DP EES=durable-polymer everolimus-eluting stent. BP  
 555 SES=biodegradable-polymer sirolimus-eluting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



556