

Clinical relevance of ticagrelor monotherapy following 1-month dual antiplatelet therapy after bifurcation percutaneous coronary intervention: Insight from GLOBAL LEADERS trial

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1 **The impact of ticagrelor monotherapy following one-month dual antiplatelet therapy**
2 **after bifurcation percutaneous coronary intervention in a largest all-comers trial:**
3 **insight from GLOBAL LEADERS trial.**

4

5 Short running title: Ticagrelor monotherapy after bifurcation PCI in the GLOBAL
6 LEADERS trial

7

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82

83 **Abstract**

84 **OBJECTIVES:**

85 The aim of this study was to investigate the impact of ticagrelor monotherapy following one-
86 month dual antiplatelet therapy (DAPT) after bifurcation percutaneous coronary intervention
87 (PCI).

88 **BACKGROUND:**

89 The evidence regarding optimal antiplatelet strategy after bifurcation PCI is scarce.

90 **METHODS:**

91 GLOBAL LEADERS was a randomized, superiority, all-comers trial comparing one-month
92 DAPT with ticagrelor and aspirin followed by 23-month ticagrelor monotherapy
93 (experimental treatment) with standard 12-month DAPT followed by 12-month aspirin
94 monotherapy (reference treatment) in patients treated with a biolimus A9-eluting stent.
95 Bifurcation PCI was identified using a dedicated e-CRF based on the MADS classification.
96 The primary endpoint at 2 years was a composite of all-cause death or new Q-wave
97 myocardial infarction (MI).

98 **Results:**

99 A total of 15,845 patients were included in this subgroup analysis. There were 2,498 patients
100 (15.8%) who underwent at least one bifurcation PCI, of whom 489 patients (19.6%) were
101 treated with 2-stent technique. The incidence of primary endpoint at 2 years was similar
102 between bifurcation and non-bifurcation group (4.7% vs 4.0%, $p=0.083$). Two-stent
103 technique for bifurcation PCI was associated with higher incidences of primary endpoint and
104 compared with One-stent technique (primary endpoint: 7.0% vs 4.2%, $p=0.008$). The
105 experimental treatment showed a significant benefit in 2-year definite or probable stent
106 thrombosis in patients with bifurcation PCI (HR: 0.46; 95% CI: 0.22-0.97) compared with
107 those without bifurcation PCI (HR: 1.20; 95% CI: 0.85-1.69; p for interaction = 0.022).

108 **CONCLUSIONS:**

109 PCI for bifurcation lesion with a biolimus A9-eluting stent was associated with worse clinical
110 outcomes than non-bifurcation lesion. When compared with aspirin monotherapy following
111 12-month standard DAPT, ticagrelor monotherapy for 23 month following one-month DAPT
112 after bifurcation PCI showed a significant benefit on definite or probable stent thrombosis but
113 not on the primary endpoint at 2 years.

114

115 Keywords: Percutaneous coronary intervention, drug-eluting stents, bifurcation lesion,
116 antiplatelet treatment

117 **Condensed abstract**

118 The aim of this analysis was to investigate the impact of ticagrelor monotherapy following
119 one-month dual antiplatelet therapy (DAPT) after bifurcation percutaneous coronary
120 intervention. A total of 15,968 all-comer patients were randomly assigned either one-month
121 DAPT with ticagrelor and aspirin followed by 23-month ticagrelor monotherapy as
122 experimental treatment or standard 12-month DAPT followed by 12-month aspirin
123 monotherapy. The difference in a composite of all-cause death and new Q-wave myocardial
124 infarction at 2 years did not reach statistical significance between bifurcation and non-
125 bifurcation group (4.7% vs 4.0%, $p=0.083$). A benefit of experimental treatment was
126 statistically demonstrated in 2-year definite or probable stent thrombosis in patients with
127 bifurcation versus non-bifurcation (p for interaction = 0.022).

128

129 **Abbreviations**

130 ARC = Academic Research Consortium

131 DES = drug-eluting stent

132 e-CRF = electronic case record form

133 MI = myocardial infarction

134 TVR = target vessel revascularization

135 PCI = percutaneous coronary intervention

136 POCE = patient oriented composite endpoint

137 ST = stent thrombosis

138

139 **Introduction**

140 Bifurcation lesions are associated with a lower rate of procedural success and a higher
141 risk of complications compared to non-bifurcation lesions in patients treated with
142 percutaneous coronary intervention (PCI) (1,2). A number of randomized controlled trials
143 have investigated the optimal intervention strategy in patients with bifurcation lesions and
144 showed no benefit in terms of clinical outcomes for the systematic two-stent approach versus
145 main branch-only stenting with provisional stenting of the side branch (2). Therefore, the
146 provisional side branch stenting strategy is recommended for treatment of bifurcation lesions
147 as class IA recommendation by the current guideline (3), whereas in 5 to 25% of cases, a
148 second stent for the side branch may be needed (4-6). When two-stent strategy is necessary,
149 which two-stent technique should be preferred is still debated (3).

150 The complexity and the numerous subtypes of two-stent techniques render their
151 comparison difficult. For that reason, the European bifurcation club (EBC) introduced the
152 MADS classification to standardize reports, to allow comparison between studies, and to
153 facilitate interpretation of published results in the evolving literature (7,8). The MADS
154 classification classifies different stenting techniques according to which segment is initially
155 stented; main proximal first (M), main across side first (A), distal first (D), and side branch
156 first (S), and how many stents are used. In the GLOBAL LEADERS trial, the dedicated
157 electronic case record form (e-CRF) based MADS classification was achieved in all site-
158 reported bifurcation lesions, which represents a unique opportunity to analyze complete case
159 study stratified for presence of bifurcation within the large contemporary PCI trial (9).

160 In terms of antiplatelet therapy after bifurcation PCI, while high PCI complexity
161 including 2-stent technique for bifurcation lesions represent a driver for favoring a prolonged
162 dual antiplatelet therapy (DAPT) over a shorten DAPT, the evidence regarding optimal
163 DAPT duration based on complexity of intervention is limited, especially due to the low

164 prevalence of bifurcation PCI in the previous clinical trials (10,11). Furthermore, the role of
165 potent P2Y12 inhibitor after bifurcation PCI is uncertain.

166 In this prespecified subgroup analysis of the GLOBAL LEADERS trial (12), we
167 sought to investigate the impact of ticagrelor monotherapy following one-month DAPT after
168 bifurcation PCI.

169

170 **Methods**

171 **The GLOBAL LEADERS trial**

172 The design and main results of the GLOBAL LEADERS trial have been published
173 previously (13). Briefly, it was a prospective, multicenter, randomized, open-label,
174 superiority trial comparing two antiplatelet regimens in 15,991 all-comers patients who were
175 exclusively treated with a biolimus A9-eluting stent for stable coronary artery disease or
176 acute coronary syndromes.

177 Patients were randomly assigned in a 1:1 fashion to one-month DAPT with aspirin
178 and ticagrelor followed by 23 months of ticagrelor monotherapy, or standard DAPT with
179 aspirin plus either clopidogrel (for patients with stable coronary artery disease) or ticagrelor
180 (for patients with acute coronary syndromes) for 12 months, followed by aspirin
181 monotherapy for 12 months.

182 In terms of bifurcation PCI, the choice of bifurcation treatment technique was left to
183 the discretion of the operators.

184 The trial was approved by the institutional review board at each investigating center.
185 The study followed the ethical principles of the Declaration of Helsinki. All the participants
186 provided written informed consent at the time of participation in the trial.

187

188 **Study population and data collection**

189 According to the all-comers concept, only a limited number of in- and exclusion
190 criteria were applied in the GLOBAL LEADERS trial (Supplementary methods). There were
191 no restrictions as to the number, severity, or location of lesions to be treated, or number of
192 stents used. Patients in need of chronic anticoagulation were deemed not eligible.

193 In this prespecified subgroup analysis, patients undergoing bifurcation PCI were
194 identified from the dedicated e-CRF based MADS classification reported by investigators.
195 Bifurcation lesions were defined by investigators in accordance with the practical definition
196 of the European Bifurcation Club (7), as “a coronary artery narrowing occurring adjacent to,
197 and/or involving the origin of a significant side branch.” All bifurcation PCI were classified
198 whether treated with 1-stent or 2-stent technique using the results of MADS classification.
199 Three-stent techniques such as “extended V” and “trouser legs and seat” were included in the
200 2-stent technique. The stenting technique for trifurcation lesion is not covered by the MADS
201 classification, therefore trifurcation (7 lesions in 7 patients) was identified according to the
202 definition of SYNTAX Score (14).

203 Total stent length per patient was calculated according to the cumulative nominal
204 length of the stent used in each individual case without consideration for overlapping of
205 stents.

206 As many as seven on-site monitoring visits were done at individual sites, with 20% of
207 reported events checked against source documents. Additionally, the trial was monitored for
208 event under-reporting and event definition consistency. However, no overall central
209 independent adjudication of clinical events was implemented.

210

211 **Endpoint definitions**

212 The primary endpoint was the composite of all-cause death or new Q-wave
213 myocardial infarction (MI) up to two years after randomization. Deaths from any cause were

214 ascertained without adjudication(15), due to the fact that the survival data were derived from
215 thorough site reports and search for vital status obtained from public domains. Q-wave MI
216 was centrally adjudicated and defined in compliance with the Minnesota classification (new
217 major Q-QS wave abnormalities) or by the appearance of a new left bundle branch block in
218 conjunction with abnormal biomarkers.

219 The key secondary endpoint was bleeding defined according to the Bleeding
220 Academic Research Consortium (BARC) criteria (type 3 or 5) up to two years (16). Other
221 secondary endpoints included individual components of the primary endpoint (all-cause death
222 and new Q-wave MI); any stroke; any MI; any revascularization; target vessel
223 revascularization (TVR); definite stent thrombosis (ST) and definite or probable ST (17).

224 In addition, the risk of patient-oriented composite endpoint (POCE) according to the
225 Academic Research Consortium (ARC)-2 was assessed up to two years(17). POCE was
226 defined as the composite of all-cause death, any stroke (ischemic and hemorrhagic), any MI
227 (periprocedural or spontaneous with STEMI or non-ST segment elevation MI (NSTEMI),
228 and any revascularization (repeat PCI or coronary artery bypass graft [CABG] surgery in
229 target or non-target vessel) (17). The third universal definition of MI was the recommended
230 criteria to report MI (18). Composite endpoints were analysed hierarchically. Individual
231 components were reported non-hierarchically (19).

232

233 **Statistical Analysis**

234 Clinical outcomes were compared between the following groups:

- 235 1. Patients treated for at least one bifurcation lesions versus patients not treated for any
236 bifurcation lesion (Bifurcation vs. non-bifurcation);
- 237 2. Patients treated for at least one bifurcation lesions with 1-stent technique versus 2-
238 stent technique (1-stent vs. 2-stent);

239 Due to the absence of classification for trifurcation PCI according to the MADS
240 classification, patients with trifurcation PCI (7 lesions in 7 patients) were described
241 separately in supplementary table 3 and were excluded from the analysis comparing 1-stent
242 vs. 2-stent.

243 The effect of experimental versus reference antiplatelet therapy according to
244 presence/absence of bifurcation PCI was estimated with a Cox regression model. In addition,
245 the treatment effect of experimental versus reference treatment according to one or two-stent
246 strategy was estimated with a Cox regression model as exploratory analysis due to too much
247 sub-calcification and small numbers of patients.

248 Categorical variables were compared with the χ^2 test or Fisher's exact test.
249 Continuous variables were compared with Student's t test or Mann-Whitney U test for non-
250 normally distributed data. Composite endpoints were calculated using time-to-first of any of
251 the composite event(s) per patient. Patients started being at risk on the day of index
252 percutaneous coronary intervention, if no procedure was performed, on the day of
253 randomization. Survival curves were constructed using Kaplan-Meier estimates and the log-
254 rank test was used to compare between-group differences. Landmark analyses were
255 performed with prespecified cut-offs at 30 days (at the time of the planned date of
256 discontinuation of aspirin in the experimental treatment) and one year (at the time of the
257 planned dates of discontinuation of a P2Y12 inhibitor in the reference treatment). In total,
258 there were six outpatient protocol visits at 30 days, 3, 6, 12, 18, and 24 months. A two-sided
259 P value of less than 0.05 was considered to indicate statistical significance. All statistical
260 analyses were done in SPSS (version 25.0.0, IBM, New York). The trial is registered with
261 ClinicalTrials.gov, number NCT01813435.

262

263 **Results**

264 The GLOBAL LEADERS trial recruited a total of 15,991 patients(20), of whom 146
265 patients were excluded from this analysis (85 patients were randomised but not treated with
266 PCI; in 38 patients, PCI was attempted but detailed data on PCI procedure were not available;
267 and 23 patients withdrew consent and formally requested the complete deletion of their data
268 from the database), leaving 15,845 patients in this analysis. From the 15,845 patients
269 included in the GLOBAL LEADERS trial, 2,498 patients (15.7%) underwent at least one
270 bifurcation PCI and 7 patients (0.04%) underwent at least one trifurcation PCI. From those
271 2,498 patients with at least one bifurcation PCI, 2002 (80.1%) were treated with 1-stent
272 technique, and 489 (19.6%) with 2-stent technique (Figure 1).

273 **Baseline characteristics**

274 Baseline and procedural characteristics of each comparison are shown in Table 1 and
275 Supplementary table 1.

276 There were some differences between non-bifurcation group and bifurcation group.
277 Patients in the non-bifurcation group had a higher body-mass index and higher prevalence of
278 diabetes mellitus or previous history of PCI and CABG, whereas patients in the bifurcation
279 group presented more often with acute coronary syndrome. In terms of procedural
280 characteristics, patients in the bifurcation group as expected had more lesions, stents, and
281 longer total stent length per patients.

282 Among patients with at least one bifurcation PCI, there were no differences in
283 baseline characteristics between 1-stent group and 2-stent group. In terms of procedural
284 characteristics, patients in 2-stent group were more frequently treated with femoral approach,
285 and had more lesions and stents, and longer total stent length per patients. Bifurcation lesions
286 involving left main stem were more frequently observed in 2-stent group (7.3% vs. 12.2%,
287 $p<0.001$), and also kissing balloon inflation was more frequently performed in 2-stent group

288 (34.3% vs. 73.6%, $p<0.001$). Proximal optimization technique captured in the eCRF was
289 equally performed in both groups (30.6% vs. 34.8%, $p=0.074$).

290 Reflecting proper randomization, allocation of antiplatelet treatment was balanced
291 amongst various subgroups.

292

293 **Clinical outcomes**

294 Clinical outcomes at 30 days, 1 and 2 years, and landmark analysis at 30 days and 1
295 year are shown for each comparison (Table 2, Figure 2, and supplementary table 2).

296 In terms of primary endpoint (a composite of all-cause death or new Q-wave MI) at 2
297 years, there was a trend toward higher incidence in the bifurcation group compared with the
298 non-bifurcation group (4.72% in bifurcation group vs. 3.98% in non-bifurcation group,
299 hazard ratio (HR) 1.19 [95% confidential interval (95%CI): 0.98-1.46], $p=0.083$). This
300 difference was driven by higher incidence of new Q-wave MI in bifurcation group compared
301 with non-bifurcation group (1.84% vs 1.04%, HR 1.78 [95%CI: 1.27-2.48], $p=0.001$). The
302 incidences of 2-year POCE in bifurcation group was higher compared with no bifurcation
303 group (15.05% vs. 13.27%, HR 1.16 [95%CI: 1.03-1.29], $p=0.011$). This difference was
304 driven by higher incidence of any revascularization in bifurcation group compared with non-
305 bifurcation group (11.21% vs 9.19%, HR 1.24 [95%CI: 1.09-1.41], $p=0.001$). In addition, the
306 incidences of 2-year TVR in bifurcation group was higher compared with no bifurcation
307 group (6.69% vs. 4.83%, HR 1.40 [95%CI: 1.18-1.66], $p<0.001$). The differences in TVR
308 were also observed at 30-day and 1-year follow-up, whereas no differences were observed in
309 landmark analysis at 1 year. Bifurcation PCI was not associated with an increased risk of
310 BARC 3 or 5 bleeding at 2 years (2.48% vs. 2.02%, HR 1.23, [95%CI: 0.94-1.63], $p=0.134$).

311 Two-stent group had higher incidences of primary endpoint, all-cause death, POCE,
312 any MI, any revascularization, TVR, and definite or probable stent thrombosis compared with

313 1-stent group at 2-year follow-up. At 30-day follow-up, there was trend toward higher
314 incidences of all-cause death, POCE, and definite or probable stent thrombosis in 2-stent
315 group compared with 1-stent group, whereas a landmark analysis at 30days demonstrated the
316 same trend as 2-year follow-up. At 1-year follow-up, the trend was similar to 2-year follow-
317 up except for all-cause death, whereas a landmark analysis at 1 year demonstrated that there
318 were no significant differences on all endpoints between groups. In terms of BARC 3 or 5
319 bleeding, there were no differences between 2-stent group and 1-stent group in all periods.

320 In terms of trifurcation PCI, the clinical outcomes at 2 years in 7 patients are shown in
321 supplementary table 3.

322

323 **Treatment effect of antiplatelet therapy**

324 Results for experimental versus reference antiplatelet treatment in the bifurcation and
325 non-bifurcation groups are reported in Figure 3 and Table 3. In terms of hard endpoint such
326 as a composite of all-cause death and new-Q wave MI at 2 years, the experimental strategy
327 did not show any benefit in patient undergoing bifurcation PCI against the reference strategy
328 (bifurcation: HR: 0.74; 95% CI: 0.51-1.07, non-bifurcation: HR: 0.90; 95% CI: 0.76-1.07; p
329 for interaction = 0.343). The experimental antiplatelet treatment showed a significant benefit
330 on 2-year definite or probable stent thrombosis in patients with bifurcation PCI (HR: 0.46;
331 95% CI: 0.22-0.97) compared with those without bifurcation PCI (HR: 1.20; 95% CI: 0.85-
332 1.69; p for interaction = 0.022) (Figure 4A). The same trend was observed on 1-year definite
333 or probable stent thrombosis (bifurcation: HR: 0.51; 95% CI: 0.22-1.18, non-bifurcation: HR:
334 1.46; 95% CI: 0.98-2.18; p for interaction = 0.026), whereas this significant benefit of
335 ticagrelor monotherapy against aspirin monotherapy was subsided beyond 1 year
336 (bifurcation: HR: 0.33; 95% CI: 0.07-1.66, non-bifurcation: HR: 0.63; 95% CI: 0.31-1.30; p
337 for interaction = 0.478) (Figure 4B). In addition, the landmark analysis at 30 days did not

338 demonstrate any significant benefit of the experimental antiplatelet treatment against the
339 reference antiplatelet treatment on clinical outcomes (Table 3). In terms of 2-year incidence
340 of stroke, the experimental strategy showed negative effect in patient undergoing bifurcation
341 PCI against the reference strategy (bifurcation: HR: 2.72; 95% CI: 1.06-6.94, non-
342 bifurcation: HR: 0.82; 95% CI: 0.58-1.14; p for interaction = 0.018). This negative effect was
343 observed at 1 year follow-up (bifurcation: HR: 4.07; 95% CI: 1.15-14.43, non-bifurcation:
344 HR: 0.85; 95% CI: 0.55-1.30; p for interaction = 0.021), whereas it was subsided beyond 1
345 year (bifurcation: HR: 1.36; 95% CI: 0.30-6.08, non-bifurcation: HR: 0.77; 95% CI: 0.45-
346 1.32; p for interaction = 0.479).

347 Results for experimental versus reference antiplatelet treatment in 2-stent and 1-stent
348 groups are reported in supplementary figure 1 and supplementary table 4. In terms of 2-year
349 clinical outcomes, there were no effect of experimental antiplatelet treatment against
350 reference antiplatelet treatment. However, the experimental antiplatelet treatment showed a
351 trend toward lower incidence of 1-year primary endpoint in 2-stent group (HR: 0.33; 95% CI:
352 0.12-0.89) compared with 1-stent group (HR: 0.92; 95% CI: 0.51-1.63; p for interaction =
353 0.081). In addition, the experimental antiplatelet treatment showed possibly a trend toward
354 lower incidence of 1-year all-cause death in 2-stent group (HR: 0.21; 95% CI: 0.05-0.96)
355 compared with 1-stent group (HR: 0.87; 95% CI: 0.41-1.82; p for interaction = 0.100),
356 whereas this trend was subsided beyond 1 year. In addition, the experimental antiplatelet
357 treatment showed a trend toward lower incidence of 1 and 2-year definite of probable stent
358 thrombosis in 2-stent group (HR: 0.26; 95% CI: 0.06-1.23, p = 0.089 at 1 year, HR: 0.23;
359 95% CI: 0.05-1.07, p = 0.061 at 2 years).

360

361 **Discussion**

362 The main findings of the study are following:

- 363 1. PCI for bifurcation lesion with a biolimus A9-eluting stent was associated with worse
364 clinical outcomes compared with non-bifurcation lesion, in terms of POCE, new Q-
365 wave MI, any revascularization and TVR at 2 years, whereas no significant difference
366 was observed on primary endpoint (all-cause death or new Q-wave MI) between
367 groups.
- 368 2. The use of 2-stent technique for bifurcation PCI was associated with higher
369 incidences of primary endpoint, all-cause death, POCE, any MI, any
370 revascularization, TVR, and definite or probable stent thrombosis at 2-years
371 compared with the use of 1-stent technique.
- 372 3. One-month DAPT with aspirin and ticagrelor followed by 23-month ticagrelor
373 monotherapy (experimental treatment) was associated with a significant benefit in the
374 risk of definite or probable stent thrombosis but had no impact on primary endpoint
375 compared with 12-month standard DAPT followed by 12-month aspirin monotherapy
376 (reference treatment) in patients who underwent bifurcation PCI.
- 377 4. The experimental treatment strategy was not associated with an increased risk of
378 BARC 3 or 5 major bleeding in patients who underwent PCI, irrespective of
379 bifurcation and the stenting techniques.

380 **Bifurcation vs. non-bifurcation group**

381 The difference in POCE rate between patients with at least one bifurcation lesion versus
382 patients without any bifurcation lesion was observed up to 1 year and were mainly driven by a
383 difference in any revascularization (bifurcation 8.7% vs. non-bifurcation 6.2%, HR 1.41
384 [95%CI: 1.22-1.64], <0.001), whereas the 2-year all-cause death rate was similar (bifurcation
385 3.0% vs. non-bifurcation 3.0%, p=0.964). The Kaplan-Meier curve showed an early
386 divergency of any revascularization, whereas beyond 1 year patients undergoing bifurcation
387 PCI were no longer at high risk of any revascularization (bifurcation 2.9% vs. non-bifurcation

388 3.3%, p=0.318). The similar trend was also observed on the incidence of TVR. However, the
389 higher incidence of new Q-wave MI in bifurcation group over non-bifurcation group was
390 consistently observed at 1 year and 2 years and landmark analysis at 1 year, whereas the
391 incidence of any MI was similar between groups. This finding may suggest that bifurcation
392 PCI can be associated with the occurrence of more severer MI when compared with non-
393 bifurcation PCI.

394

395 **2-stent vs. 1-stent technique for bifurcation PCI**

396 In the present study, a substantial predominance of 1-stent technique against 2-stent
397 technique was observed for the bifurcation PCI. This finding is in line with the increasing
398 amount of evidence in favor of main branch-only stenting with provisional stenting of the
399 side branch strategy for most of the bifurcation lesions (2). These data reflect the findings of
400 a recently reported pooled analysis of 2 randomized controlled trials comparing simple versus
401 complex stenting for bifurcation lesions (21). However, in absence of the information
402 whether 2-stent technique is provisional or up front these data should be interpreted with
403 caution and considered as hypothesis generating.

404

405 **Optimal antiplatelet strategy for patients undergoing bifurcation PCI**

406 The evidence of optimal antiplatelet strategy after bifurcation PCI is scarce, especially for
407 potent antiplatelet drugs such as ticagrelor and prasugrel. Recent pooled patients-level
408 analysis demonstrated that short DAPT of 3 or 6 months is associated with higher incidence
409 of 1-year major adverse cardiac events mainly driven by MI compared with prolonged DAPT
410 of more than 1 year in patients undergoing PCI for complex lesions including bifurcation
411 treated with 2-stent technique (10). In addition, the multicenter observational study reported
412 that the risks of a composite of all-cause death or MI, MI, and definite or probable ST at 4

413 years were significantly lower in the prolonged DAPT group (≥ 12 months) than shorter
414 DAPT group (< 12 months) after bifurcation PCI with DES (22). From these results, it seems
415 that patients undergoing bifurcation PCI need at least 12-month DAPT. Previously coronary
416 bifurcation lesions were reported as independent risk factor of for stent thrombosis (23-25).
417 Several reasons could explain increased risk of stent thrombosis. Firstly, bifurcation stenting
418 modifies the local hemodynamics and creates low endothelial shear stress and stagnation
419 areas that could result in local thrombogenicity (26). Secondly, pathology study demonstrated
420 that the flow divider zone was associated with a high percentage of uncovered struts and
421 fibrin deposition several months after DES implantation, that could represent a substrate for
422 stent thrombosis (27). Thirdly, two-stent strategies have been suspected of inducing
423 overlapping device segments that could result in local thrombogenicity (28). Finally,
424 bifurcation stenting could also induce stent malapposition due to vessel dimension variation
425 along the different segments and promote future thrombotic events (29).

426 In the present study, ticagrelor monotherapy following very short one-month DAPT
427 demonstrated significant treatment effect on definite or probable stent thrombosis compared
428 with conventional aspirin monotherapy following 12-month DAPT. This benefit was
429 observed up to 1 year and subsided beyond 1 year. Therefore, the effect of ticagrelor
430 monotherapy on definite or probable stent thrombosis may superior to conventional DAPT
431 between 1 and 12 months without increase of major bleeding events. However, similar
432 impact on the composite of all-cause death and new Q-wave MI so called “hard endpoint”
433 was not observed.

434 In terms of early discontinuation of aspirin at 30 days in patients undergoing bifurcation
435 PCI, a landmark analysis at 30 days demonstrated that the incidences of all clinical endpoints
436 were similar between two antiplatelet strategies without any statistically differences in

437 patients with bifurcation PCI (Table 3). This finding may suggest that aspirin can be stopped
438 at 30 days without safety concerns even in patients undergoing bifurcation PCI.

439

440 **Study limitations**

441 This prespecified subgroup analysis has several limitations.

442 Firstly, no formal power calculation was performed and there was numerical
443 mismatch between groups. Together with the inherent limitations of sub-analyses including
444 multiple testing, the study findings should be considered as hypothesis-generating (30).

445 Secondly, clinical outcomes were not adjudicated by an independent clinical event
446 committee. All events were identified and confirmed by the investigators of each hospital.
447 There might be inaccuracies in determining cause of death (cardiac versus noncardiac) or
448 target vessel MI. Therefore, we chose all-cause death or new Q-wave MI centrally
449 adjudicated by core lab instead of cardiac death or target vessel MI as the primary outcome.

450 Thirdly, a biolimus A9-eluting stent has a relatively thicker strut of 120 μm compared
451 with other current generation DES. This might result in the worse outcomes in bifurcation
452 lesions treated with 2-stent technique using a biolimus A9-eluting stent due to the overlap of
453 relatively thicker struts. However, in the present study, all patients were exclusively treated
454 with a biolimus A9-eluting stent, and this makes the effect of antiplatelet drug more likely.

455 Finally, in the context of a trial in which the primary endpoint was not met, these
456 findings need to be considered as hypothesis generating and further investigations are
457 warranted in future specific trials on bifurcation PCI.

458

459 **Conclusion**

460 In the present study, bifurcation PCI with a biolimus A9 eluting stent was associated
461 with worse clinical outcomes at 2 years compared with non-bifurcation PCI in all-comers

462 population. Ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone
463 for 23months was more beneficial on definite or probable stent thrombosis compared with
464 12-month standard DAPT followed by 12-month aspirin monotherapy without increase of
465 major bleeding events. However, the experimental strategy did not show any benefit on hard
466 endpoint such as a composite of all-cause mortality or new Q-wave MI when compared with
467 the reference strategy in patients undergoing bifurcation PCI.

468

469 **Perspectives**

470 **What is known?**

471 The evidence regarding optimal DAPT duration after bifurcation PCI is limited. These
472 limited evidences suggested that patients undergoing bifurcation PCI need at least 12-month
473 DAPT. However, the role of potent P2Y12 inhibitor after bifurcation PCI is uncertain.

474

475 **What is new?**

476 The present all-comer study included the largest cohort exclusively treated with a biolimus
477 A9 eluting stent. One-month DAPT followed by 23-month potent P2Y12 inhibitor
478 demonstrated clinical benefit on stent thrombosis but not on a composite of all-cause death or
479 new Q-wave MI when compared with 12-month standard DAPT followed by 12-month
480 aspirin monotherapy without increase of major bleeding events.

481

482 **What is next?**

483 Very short DAPT followed by monotherapy of potent P2Y12 inhibitor to optimize outcomes
484 after bifurcation PCI may warrant prospective randomized investigation.

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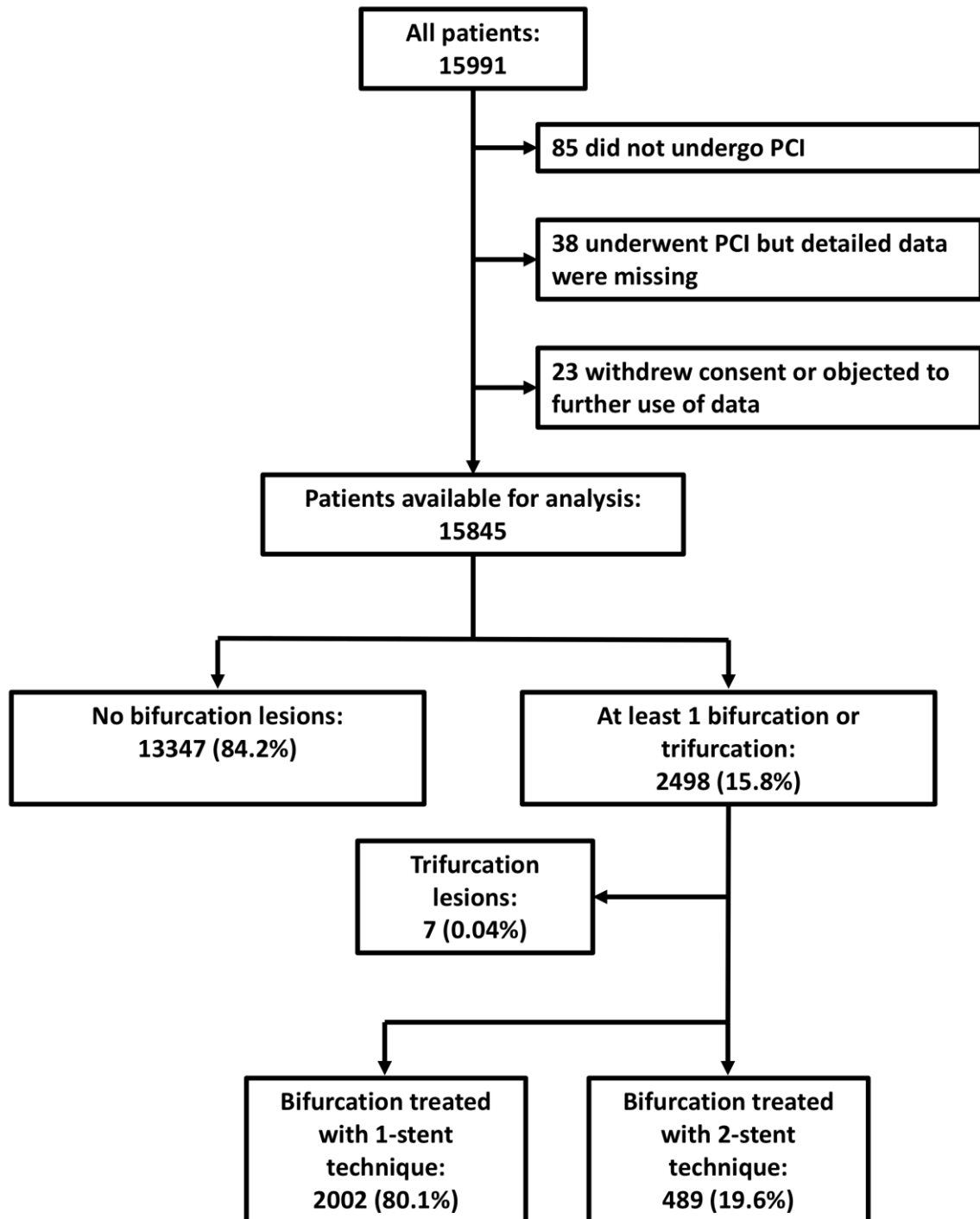
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583 **Figure legends**

584

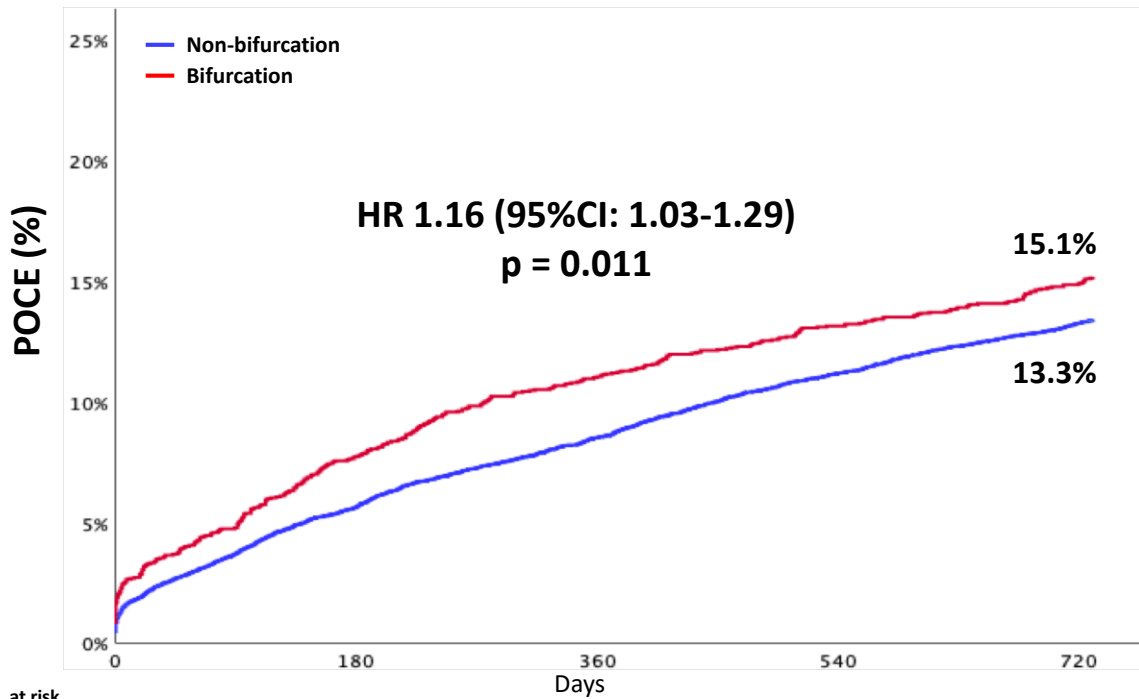
585 **Figure 1. Study flow chart.**



586

587 **Figure 2. Kaplan–Meier estimates for clinical endpoints over 730 days of follow-up**
588 **among patients with or without bifurcation PCI.**
589 Kaplan–Meier curves show the cumulative incidence of patient oriented composite endpoint
590 (POCE) -a composite of all-cause death, stroke, any myocardial infarction, or any
591 revascularization- (Panel A); all-cause death (Panel B); stroke (Panel C); any myocardial
592 infarction (Panel D); any revascularization (Panel E).

A

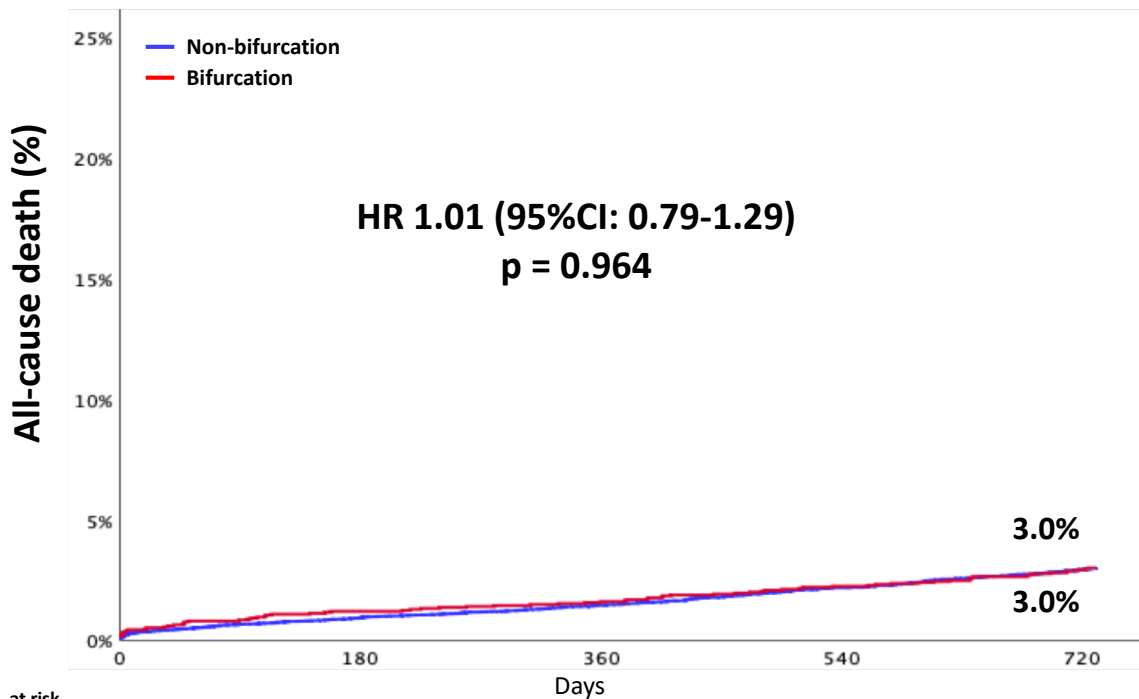


No. at risk

| | | | | | | | | | |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Non-bifurcation | 13347 | 12735 | 12452 | 12232 | 12064 | 11832 | 11678 | 11512 | 11278 |
| Bifurcation | 2498 | 2358 | 2281 | 2225 | 2193 | 2165 | 2136 | 2113 | 2069 |

593

B

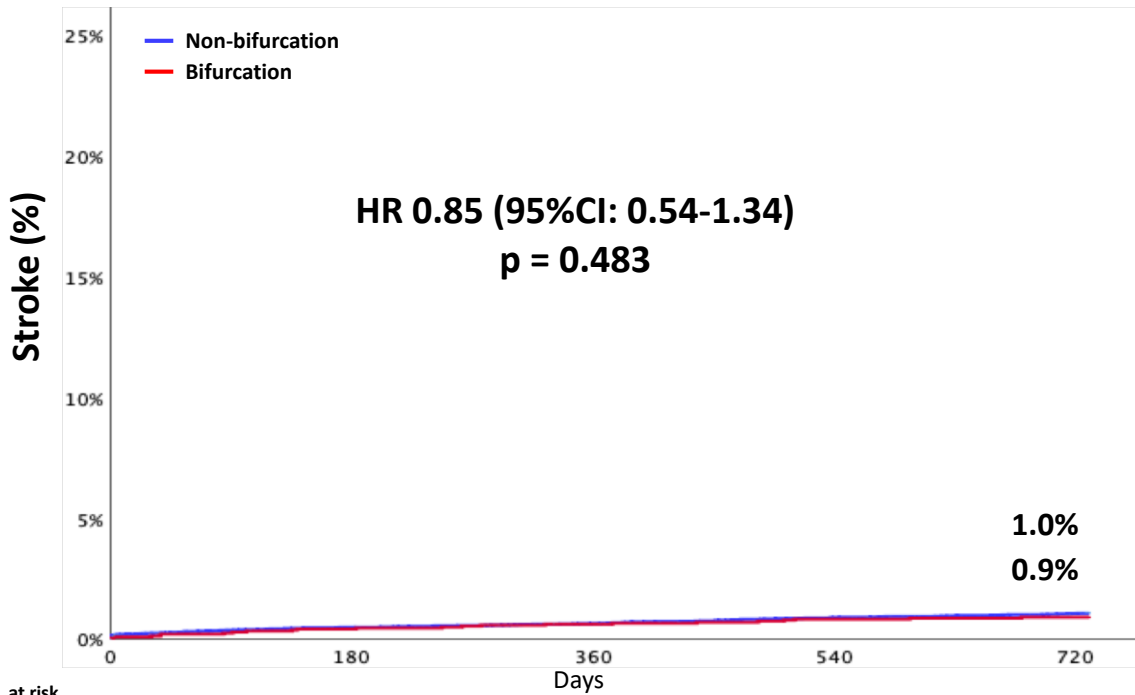


No. at risk

| | | | | | | | | | |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Non-bifurcation | 13347 | 13251 | 13212 | 13184 | 13144 | 13093 | 13043 | 12987 | 12842 |
| Bifurcation | 2498 | 2476 | 2466 | 2461 | 2456 | 2448 | 2439 | 2429 | 2403 |

594

C

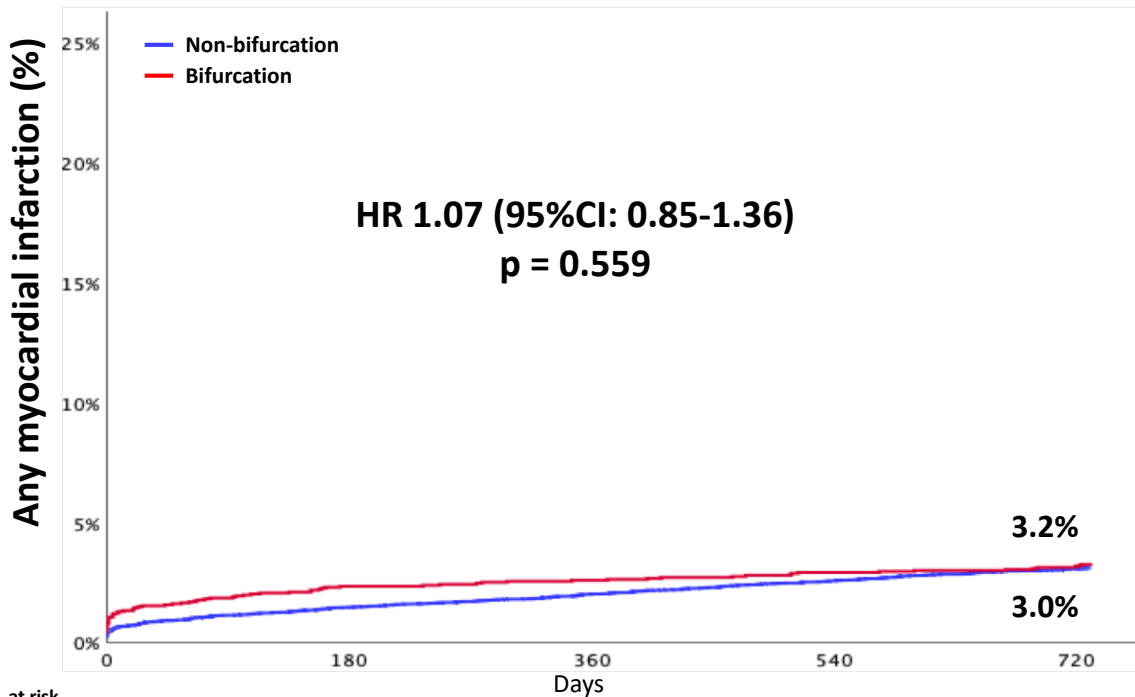


No. at risk

| | | | | | | | | | |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Non-bifurcation | 13347 | 13089 | 13018 | 12972 | 12916 | 12834 | 12769 | 12691 | 12524 |
| Bifurcation | 2498 | 2455 | 2436 | 2425 | 2417 | 2405 | 2391 | 2377 | 2350 |

595

D

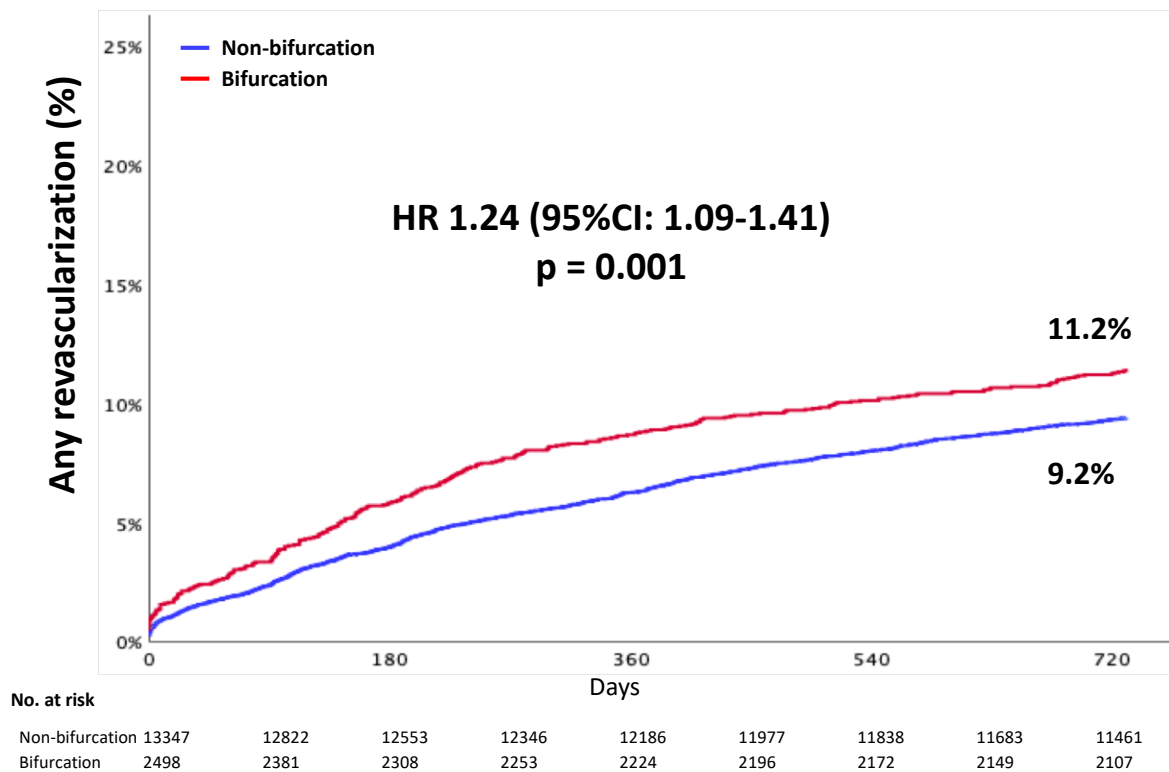


No. at risk

| | | | | | | | | | |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Non-bifurcation | 13347 | 12993 | 12891 | 12822 | 12743 | 12637 | 12551 | 12453 | 12274 |
| Bifurcation | 2498 | 2416 | 2389 | 2379 | 2370 | 2360 | 2344 | 2329 | 2298 |

596

E



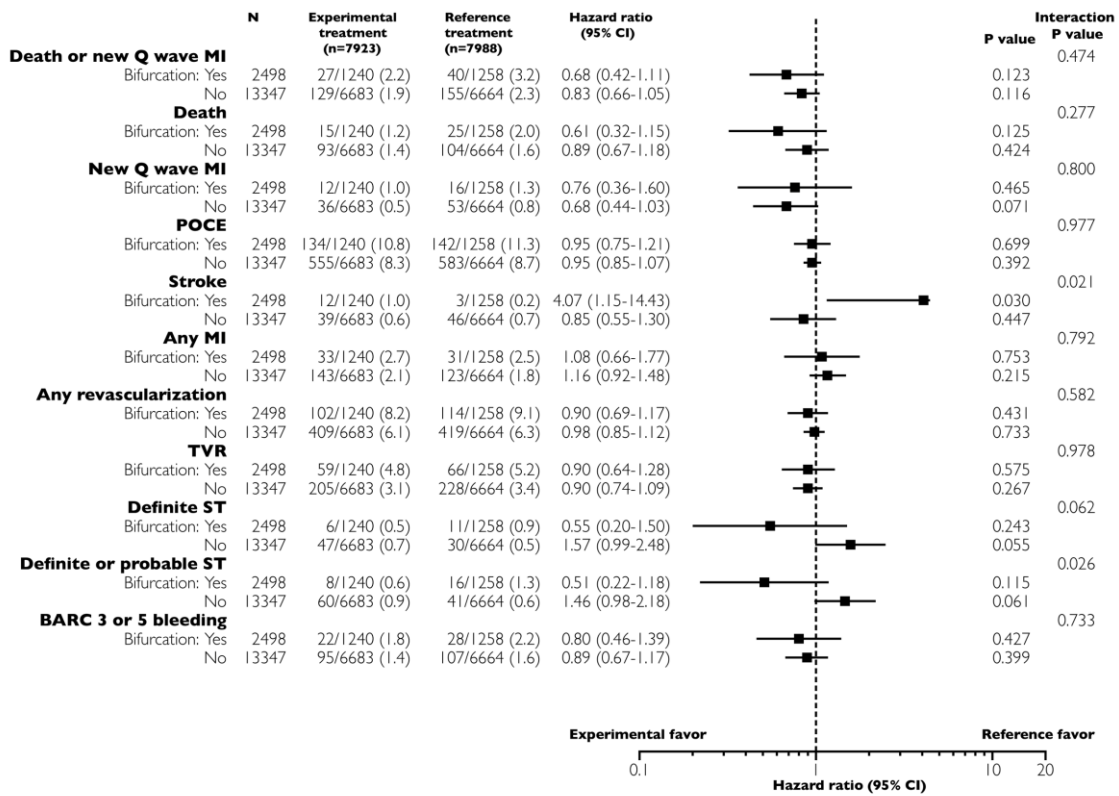
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598 **Figure 3. Treatment comparison of experimental versus reference antiplatelet strategy**
599 **in randomized patients with versus without bifurcation PCI at 1 year (A) and 2 years**
600 **(B) follow-up**

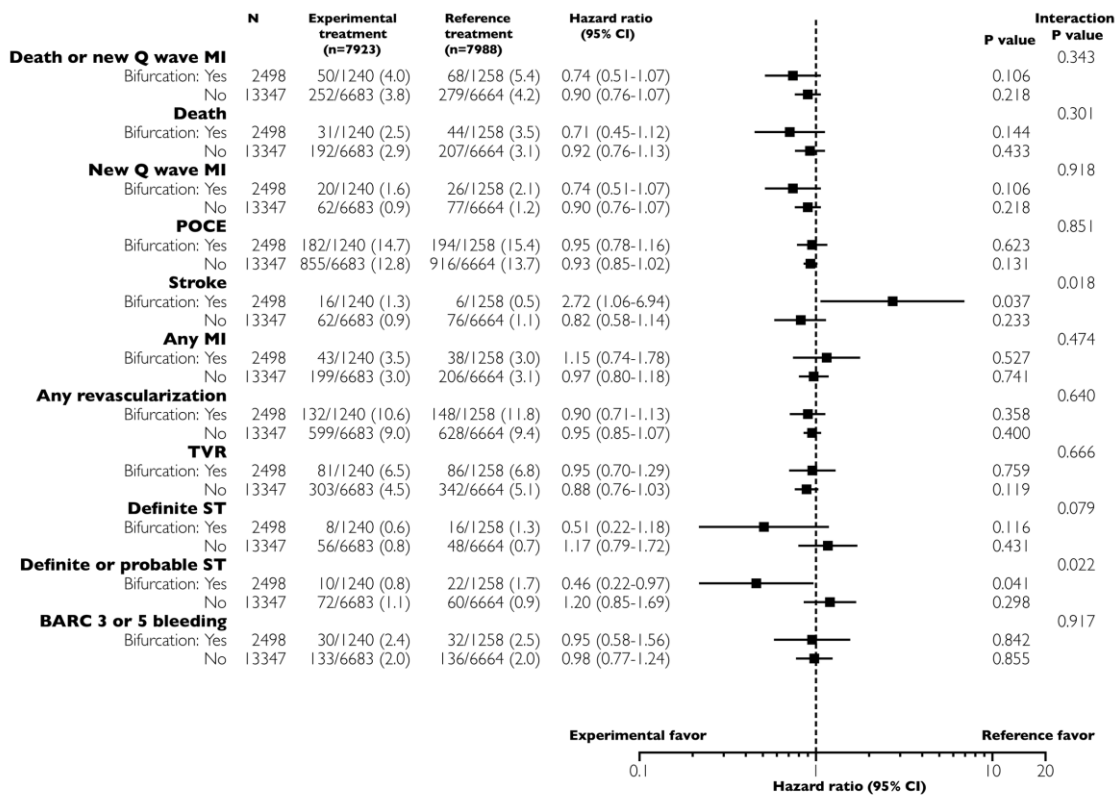
601 *POCE was defined as a composite of all-cause death, any stroke, any MI, and any
602 revascularization.

603 #Values were compared with Fisher's exact test.

604 BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; POCE =
605 patient-oriented composite endpoint; ST = stent thrombosis; TVR = target vessel
606 revascularization.



607

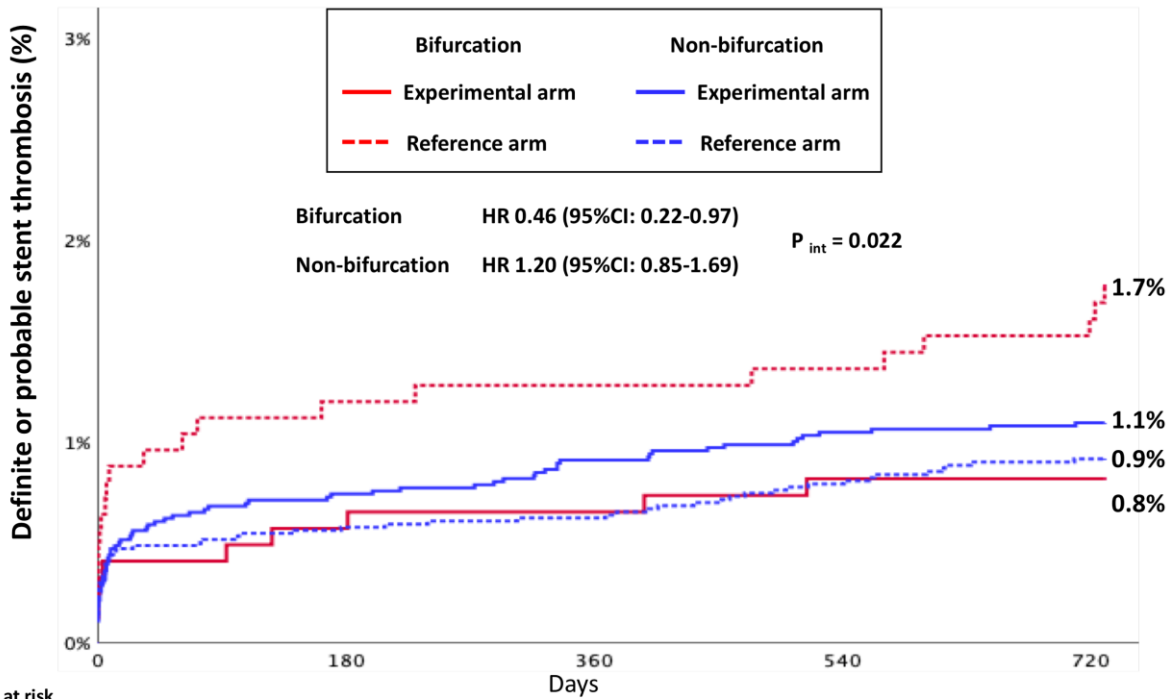


608

609 **Figure 4. Kaplan–Meier estimates of cumulative incidence of definite or probable stent**
610 **thrombosis for experimental versus reference antiplatelet strategy in patients with or**
611 **without bifurcation up to 730 days (A) and up to 365 days and landmark analysis at 365**
612 **days (B)**

613 Kaplan–Meier curves show the cumulative incidence of definite or probable stent thrombosis.

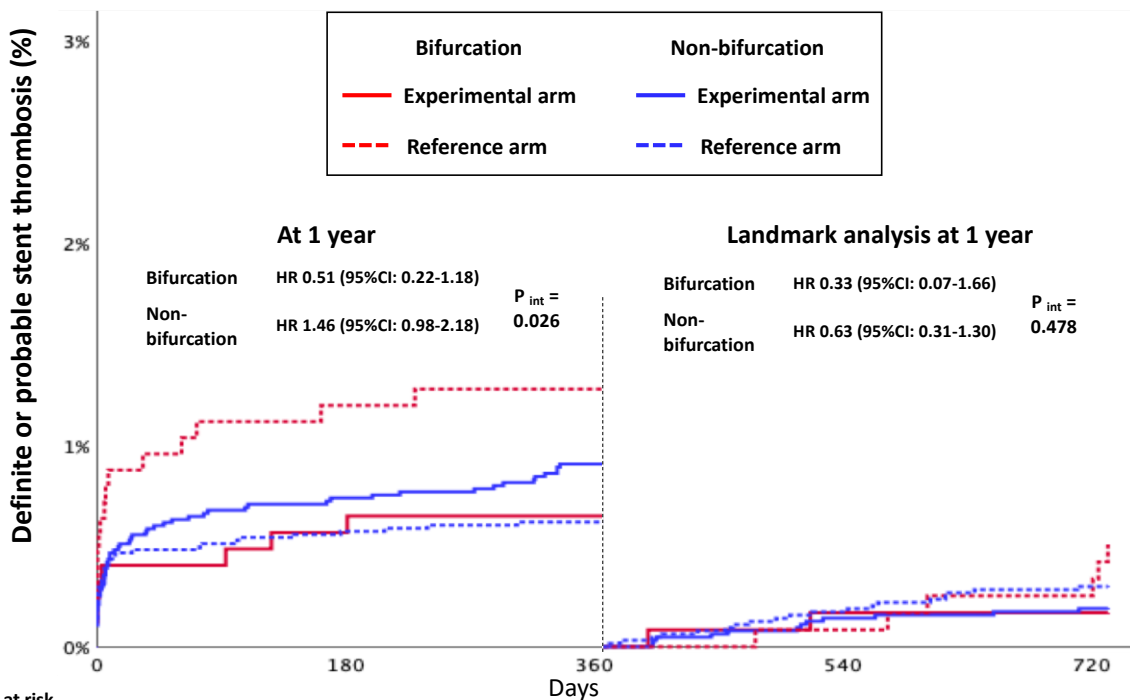
A



| No. at risk | 0 | 180 | 360 | 540 | 720 |
|-------------|------|------|------|------|------|
| Bifur-Exp | 1240 | 1225 | 1216 | 1214 | 1212 |
| Bifur-Ref | 1258 | 1234 | 1226 | 1221 | 1219 |
| Non-B-Exp | 6683 | 6547 | 6517 | 6498 | 6476 |
| Non-B-Ref | 6664 | 6564 | 6531 | 6510 | 6483 |

614

B



| No. at risk | 0 | 180 | 360 | 540 | 720 |
|-------------|------|------|------|------|------|
| Bifur-Exp | 1240 | 1225 | 1216 | 1214 | 1212 |
| Bifur-Ref | 1258 | 1234 | 1226 | 1221 | 1219 |
| Non-B-Exp | 6683 | 6547 | 6517 | 6498 | 6476 |
| Non-B-Ref | 6664 | 6564 | 6531 | 6510 | 6483 |

615

616 **Table 1. Baseline and procedural characteristics**

| | Bifurcation n = 2498 | Non-bifurcation n = 13347 | p Value |
|--|---------------------------------|--------------------------------------|----------------|
| Age, years | 64.4 ± 10.4 | 64.6 ± 10.3 | 0.601 |
| Male | 1950/2498 (78.1) | 10205/13347 (76.5) | 0.082 |
| Body-mass index, kg/m ² | 28.0 ± 4.5 | 28.2 ± 4.6 | 0.034 |
| Medical history | | | |
| Diabetes mellitus | 590/2495 (23.6) | 3414/13339 (25.6) | 0.040 |
| Insulin-dependent diabetes mellitus | 169/2490 (6.8) | 1043/13308 (7.8) | 0.071 |
| Hypertension | 1856/2491 (74.5) | 9774/13300 (73.5) | 0.289 |
| Hypercholesterolemia | 1722/2429 (70.9) | 8965/12915 (69.4) | 0.146 |
| Current smoker | 638/2498 (25.5) | 3501/13347 (26.2) | 0.471 |
| Peripheral vascular disease | 137/2469 (5.5) | 857/13230 (6.5) | 0.082 |
| Chronic obstructive pulmonary disease | 109/2482 (4.4) | 702/13292 (5.3) | 0.065 |
| Previous major bleeding | 15/2498 (0.6) | 83/13326 (0.6) | 0.896 |
| Impaired renal function* | 322/2488 (12.9) | 1836/13273 (13.8) | 0.236 |
| Previous stroke | 70/2497 (2.8) | 348/13325 (2.6) | 0.584 |
| Previous myocardial infarction | 554/2494 (22.2) | 3125/13305 (23.5) | 0.167 |
| Previous percutaneous coronary intervention | 774/2498 (31.0) | 4407/13333 (33.1) | 0.043 |
| Previous coronary artery bypass grafting | 108/2498 (4.3) | 830/13334 (6.2) | <0.001 |
| Clinical presentation | | | |
| Stable coronary artery disease | 1277/2498 (51.1) | 7127/13347 (53.4) | 0.036 |
| Acute coronary syndrome | 1221/2498 (48.9) | 6220/13347 (46.6) | 0.036 |
| Unstable angina | 348/2498 (13.9) | 1659/13347 (12.4) | 0.038 |
| Non-ST-elevation myocardial infarction | 559/2498 (22.4) | 2797/13347 (21.0) | 0.110 |
| ST-elevation myocardial infarction | 314/2498 (12.6) | 1764/13347 (13.2) | 0.380 |
| Procedural characteristics | | | |
| Vascular access site | | | |
| Femoral | 679/2458 (27.6) | 3589/13188 (27.2) | 0.675 |
| Brachial | 15/2458 (0.6) | 91/13188 (0.7) | 0.658 |
| Radial | 1872/2458 (76.2) | 9827/13188 (74.5) | 0.085 |
| Number of lesions treated | 1.7 ± 0.9 | 1.4 ± 0.7 | <0.001 |
| Number of stents | 2.2 ± 1.4 | 1.6 ± 1.0 | <0.001 |
| Total stent length | 47.3 ± 31.6 | 33.2 ± 23.2 | <0.001 |
| Randomization of antiplatelet therapy | | | |
| Experimental treatment (one-month DAPT followed by 23-month ticagrelor monotherapy) | 1240/2498 (49.6) | 6683/13347 (50.1) | 0.692 |
| Reference treatment (12-month DAPT followed by 12-month aspirin monotherapy) | 1258/2498 (50.4) | 6664/13347 (49.9) | |

617 Data are mean ± SD or counts (percentage).

618 *Impaired renal function is defined as estimated glomerular filtration rate of creatinine
619 clearance of 60 mL/min per 1.73 m² based on the Modification of Diet in Renal Disease
620 formula.

621 **Table 2. Clinical outcomes at 30 days, one, two years follow-up and landmark analysis**
 622 **at 30 days and 1 year stratified by presence or absence of bifurcation.**

| | Bifurcation n = 2498 | Non-bifurcation n = 13347 | HR (95%CI) | p Value |
|----------------------------------|---------------------------------|--------------------------------------|-------------------|----------------|
| 30-day outcomes | | | | |
| All-cause death or new Q-wave MI | 15 (0.60%) | 61 (0.46%) | 1.32 (0.75-2.31) | 0.340 |
| All-cause death | 13 (0.52%) | 54 (0.40%) | 1.29 (0.70-2.36) | 0.412 |
| New Q-wave MI | 2 (0.08%) | 8 (0.06%) | 1.34 (0.28-6.30) | 0.712 |
| POCE* | 86 (3.44%) | 311 (2.33%) | 1.49 (1.17-1.89) | 0.001 |
| Stroke | 3 (0.12%) | 31 (0.23%) | 0.52 (0.16-1.69) | 0.267 |
| Any MI | 38 (1.52%) | 112 (0.84%) | 1.82 (1.26-2.63) | 0.001 |
| Any revascularization | 55 (2.20%) | 189 (1.42%) | 1.56 (1.16-2.11) | 0.003 |
| TVR | 35 (1.40%) | 124 (0.93%) | 1.51 (1.04-2.20) | 0.030 |
| Definite ST | 10 (0.40%) | 49 (0.37%) | 1.09 (0.55-2.15) | 0.802 |
| Definite or probable ST | 16 (0.64%) | 69 (0.52%) | 1.24 (0.72-2.13) | 0.438 |
| BARC 3 or 5 bleeding | 16 (0.64%) | 82 (0.61%) | 1.04 (0.61-1.78) | 0.876 |
| 1-year outcomes | | | | |
| All-cause death or new Q-wave MI | 67 (2.68%) | 284 (2.13%) | 1.27 (0.97-1.65) | 0.082 |
| All-cause death | 40 (1.60%) | 197 (1.48%) | 1.09 (0.77-1.53) | 0.630 |
| New Q-wave MI | 28 (1.12%) | 89 (0.67%) | 1.69 (1.10-2.58) | 0.015 |
| POCE* | 276 (11.05%) | 1138 (8.53%) | 1.32 (1.15-1.50) | <0.001 |
| Stroke | 15 (0.60%) | 85 (0.64%) | 0.94 (0.54-1.63) | 0.833 |
| Any MI | 64 (2.56%) | 266 (1.99%) | 1.29 (0.98-1.70) | 0.064 |
| Any revascularization | 216 (8.65%) | 828 (6.20%) | 1.41 (1.22-1.64) | <0.001 |
| TVR | 125 (5.00%) | 433 (3.24%) | 1.55 (1.27-1.90) | <0.001 |
| Definite ST | 17 (0.68%) | 77 (0.58%) | 1.18 (0.70-2.00) | 0.535 |
| Definite or probable ST | 24 (0.96%) | 101 (0.76%) | 1.27 (0.81-1.98) | 0.292 |
| BARC 3 or 5 bleeding | 50 (2.00%) | 202 (1.51%) | 1.33 (0.97-1.81) | 0.073 |
| 2-year outcomes | | | | |
| All-cause death or new Q-wave MI | 118 (4.72%) | 531 (3.98%) | 1.19 (0.98-1.46) | 0.083 |
| All-cause death | 75 (3.00%) | 399 (2.99%) | 1.01 (0.79-1.29) | 0.964 |
| New Q-wave MI | 46 (1.84%) | 139 (1.04%) | 1.78 (1.27-2.48) | 0.001 |
| POCE* | 376 (15.05%) | 1771 (13.27%) | 1.16 (1.03-1.29) | 0.011 |
| Stroke | 22 (0.88%) | 138 (1.03%) | 0.85 (0.54-1.34) | 0.483 |
| Any MI | 81 (3.24%) | 405 (3.03%) | 1.07 (0.85-1.36) | 0.559 |
| Any revascularization | 280 (11.21%) | 1227 (9.19%) | 1.24 (1.09-1.41) | 0.001 |
| TVR | 167 (6.69%) | 645 (4.83%) | 1.40 (1.18-1.66) | <0.001 |
| Definite ST | 24 (0.96%) | 104 (0.78%) | 1.23 (0.79-1.92) | 0.353 |
| Definite or probable ST | 32 (1.28%) | 132 (0.99%) | 1.29 (0.88-1.90) | 0.189 |

| | | | | |
|-------------------------------------|--------------|---------------|------------------|-------|
| BARC 3 or 5 bleeding | 62 (2.48%) | 269 (2.02%) | 1.23 (0.94-1.63) | 0.134 |
| Landmark analysis at 30 days | | | | |
| All-cause death or new Q-wave MI | 103 (4.15%) | 470 (3.54%) | 1.18 (0.95-1.46) | 0.134 |
| All-cause death | 62 (2.50%) | 345 (2.60%) | 0.96 (0.73-1.26) | 0.776 |
| New Q-wave MI | 44 (1.77%) | 131 (0.99%) | 1.80 (1.28-2.54) | 0.001 |
| POCE* | 290 (12.08%) | 1460 (11.26%) | 1.08 (0.96-1.23) | 0.210 |
| Stroke | 19 (0.77%) | 107 (0.81%) | 0.95 (0.58-1.54) | 0.831 |
| Any MI | 43 (1.76%) | 293 (2.23%) | 0.79 (0.57-1.09) | 0.145 |
| Any revascularization | 225 (9.29%) | 1038 (7.96%) | 1.18 (1.02-1.36) | 0.025 |
| TVR | 132 (5.40%) | 521 (3.98%) | 1.37 (1.13-1.66) | 0.001 |
| Definite ST | 14 (0.57%) | 55 (0.42%) | 1.36 (0.76-2.45) | 0.301 |
| Definite or probable ST | 16 (0.65%) | 63 (0.48%) | 1.35 (0.78-2.35) | 0.276 |
| BARC 3 or 5 bleeding | 46 (1.87%) | 187 (1.42%) | 1.32 (0.96-1.82) | 0.092 |
| Landmark analysis at 1 year | | | | |
| All-cause death or new Q-wave MI | 51 (2.10%) | 247 (1.89%) | 1.11 (0.82-1.50) | 0.500 |
| All-cause death | 35 (1.43%) | 202 (1.54%) | 0.93 (0.65-1.33) | 0.676 |
| New Q-wave MI | 18 (0.74%) | 50 (0.38%) | 1.94 (1.13-3.32) | 0.014 |
| POCE* | 100 (4.56%) | 633 (5.25%) | 0.86 (0.70-1.07) | 0.171 |
| Stroke | 7 (0.29%) | 53 (0.41%) | 0.70 (0.32-1.55) | 0.382 |
| Any MI | 17 (0.72%) | 139 (1.09%) | 0.65 (0.40-1.08) | 0.097 |
| Any revascularization | 64 (2.88%) | 399 (3.28%) | 0.87 (0.67-1.14) | 0.318 |
| TVR | 42 (1.82%) | 212 (1.69%) | 1.07 (0.77-1.50) | 0.672 |
| Definite ST | 7 (0.29%) | 27 (0.21%) | 1.39 (0.60-3.18) | 0.440 |
| Definite or probable ST | 8 (0.33%) | 31 (0.24%) | 1.38 (0.63-2.99) | 0.419 |
| BARC 3 or 5 bleeding | 12 (0.50%) | 67 (0.52%) | 0.96 (0.52-1.78) | 0.897 |

623 Data are counts (percentage).

624 *POCE was defined as a composite of all-cause death, any stroke, any MI, and any

625 revascularization.

626 BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; POCE =

627 patient-oriented composite endpoint; ST = stent thrombosis; TVR = target vessel

628 revascularization

629 **Table 3. Clinical outcomes in all patients according to prevalence of bifurcation and allocated antiplatelet regimen at 30days, and**

630 **Landmark analysis at 30 days and 1 year**

| | Bifurcation | | | | Non-bifurcation | | | | p for interaction |
|----------------------------------|-------------------------------|----------------------------|-------------------|--------------------|-------------------------------|----------------------------|-------------------|----------------|--------------------------|
| | Experimental treatment | Reference treatment | HR (95%CI) | p value | Experimental treatment | Reference treatment | HR (95%CI) | p value | |
| 30 days | | | | | | | | | |
| All-cause death or new Q-wave MI | 3/1240 (0.2) | 12/1258 (1.0) | 0.25 (0.07-0.90) | 0.033 | 31/6683 (0.5) | 30/6664 (0.5) | 1.03 (0.62-1.70) | 0.906 | 0.043 |
| All-cause death | 3/1240 (0.2) | 10/1258 (0.8) | 0.30 (0.08-1.10) | 0.070 | 29/6683 (0.4) | 25/6664 (0.4) | 1.16 (0.68-1.98) | 0.592 | 0.060 |
| New Q-wave MI | 0/1240 (0.0) | 2/1258 (0.2) | NA | 0.254 [#] | 2/6683 (0.02) | 6/6664 (0.1) | 0.33 (0.07-1.65) | 0.177 | NA |
| POCE* | 34/1240 (2.7) | 52/1258 (4.1) | 0.66 (0.43-1.02) | 0.060 | 151/6683 (2.3) | 160/6664 (2.4) | 0.94 (0.75-1.18) | 0.592 | 0.153 |
| Stroke | 2/1240 (0.2) | 1/1258 (0.1) | 2.02 (0.18-22.33) | 0.565 | 14/6683 (0.2) | 17/6664 (0.3) | 0.82 (0.41-1.67) | 0.587 | 0.480 |
| Any MI | 21/1240 (1.7) | 17/1258 (1.4) | 1.25 (0.66-2.38) | 0.488 | 61/6683 (0.9) | 51/6664 (0.8) | 1.19 (0.82-1.73) | 0.349 | 0.897 |
| Any revascularization | 17/1240 (1.4) | 38/1258 (3.0) | 0.45 (0.25-0.80) | 0.006 | 93/6683 (1.4) | 96/6664 (1.4) | 0.97 (0.73-1.29) | 0.815 | 0.019 |
| TVR | 11/1240 (0.9) | 24/1258 (1.9) | 0.46 (0.23-0.95) | 0.035 | 61/6683 (0.9) | 63/6664 (0.9) | 0.97 (0.68-1.37) | 0.848 | 0.070 |
| Definite ST | 3/1240 (0.2) | 7/1258 (0.6) | 0.43 (0.11-1.68) | 0.227 | 27/6683 (0.4) | 22/6664 (0.3) | 1.22 (0.70-2.15) | 0.480 | 0.165 |
| Definite or probable ST | 5/1240 (0.4) | 11/1258 (0.9) | 0.46 (0.16-1.33) | 0.150 | 37/6683 (0.6) | 32/6664 (0.5) | 1.15 (0.72-1.85) | 0.553 | 0.120 |
| BARC 3 or 5 bleeding | 8/1240 (0.6) | 8/1258 (0.6) | 1.01 (0.38-2.70) | 0.978 | 43/6683 (0.6) | 39/6664 (0.6) | 1.10 (0.71-1.70) | 0.664 | 0.881 |
| Landmark at 30 days | | | | | | | | | |
| All-cause death or new Q-wave MI | 47/1236 (3.8) | 56/1246 (4.5) | 0.84 (0.57-1.24) | 0.390 | 221/6651 (3.3) | 249/6632 (3.8) | 0.88 (0.74-1.06) | 0.177 | 0.835 |
| All-cause death | 28/1236 (2.3) | 34/1248 (2.7) | 0.83 (0.50-1.37) | 0.464 | 163/6653 (2.5) | 182/6637 (2.7) | 0.89 (0.72-1.10) | 0.291 | 0.791 |
| New Q-wave MI | 20/1236 (1.6) | 24/1246 (1.9) | 0.84 (0.46-1.52) | 0.561 | 60/6651 (0.9) | 71/6632 (1.1) | 0.84 (0.60-1.19) | 0.325 | 0.992 |
| POCE* | 148/1198 (12.4) | 142/1202 (11.8) | 1.06 (0.84-1.33) | 0.638 | 704/6497 (10.8) | 756/6474 (11.7) | 0.93 (0.84-1.03) | 0.157 | 0.313 |
| Stroke | 14/1228 (1.1) | 5/1243 (0.4) | 2.86 (1.03-7.93) | 0.044 | 48/6602 (0.7) | 59/6591 (0.9) | 0.81 (0.56-1.19) | 0.289 | 0.024 |
| Any MI | 22/1209 (1.8) | 21/1228 (1.7) | 1.07 (0.59-1.94) | 0.829 | 138/6556 (2.1) | 155/6559 (2.4) | 0.89 (0.71-1.12) | 0.333 | 0.584 |
| Any revascularization | 115/1214 (9.5) | 110/1209 (9.1) | 1.05 (0.81-1.36) | 0.718 | 506/6523 (7.8) | 532/6515 (8.2) | 0.95 (0.84-1.07) | 0.414 | 0.501 |
| TVR | 70/1220 (5.7) | 62/1223 (5.1) | 1.14 (0.81-1.61) | 0.441 | 242/6555 (3.7) | 279/6546 (4.3) | 0.87 (0.73-1.03) | 0.101 | 0.154 |
| Definite ST | 5/1227 (0.4) | 9/1239 (0.7) | 0.56 (0.19-1.68) | 0.303 | 29/6587 (0.4) | 26/6588 (0.4) | 1.12 (0.66-1.90) | 0.677 | 0.267 |

| | | | | | | | | | |
|----------------------------------|---------------|---------------|------------------|-------|----------------|----------------|------------------|-------|-------|
| Definite or probable ST | 5/1231 (0.4) | 11/1241 (0.9) | 0.46 (0.16-1.32) | 0.147 | 35/6598 (0.5) | 28/6598 (0.4) | 1.25 (0.76-2.06) | 0.376 | 0.091 |
| BARC 3 or 5 bleeding | 22/1223 (1.8) | 24/1238 (1.9) | 0.93 (0.52-1.66) | 0.804 | 90/6579 (1.4) | 97/6576 (1.5) | 0.93 (0.70-1.24) | 0.612 | 0.999 |
| Landmark at 1Y | | | | | | | | | |
| All-cause death or new Q-wave MI | 23/1211 (1.9) | 28/1218 (2.3) | 0.82 (0.47-1.43) | 0.490 | 123/6549 (1.9) | 124/6507 (1.9) | 0.99 (0.77-1.26) | 0.907 | 0.562 |
| All-cause death | 16/1223 (1.3) | 19/1233 (1.5) | 0.85 (0.44-1.65) | 0.625 | 99/6585 (1.5) | 103/6558 (1.6) | 0.96 (0.73-1.26) | 0.754 | 0.740 |
| New Q-wave MI | 8/1211 (0.7) | 10/1218 (0.8) | 0.80 (0.32-2.03) | 0.642 | 26/6549 (0.4) | 24/6507 (0.4) | 1.08 (0.62-1.88) | 0.791 | 0.593 |
| POCE* | 48/1087 (4.4) | 52/1106 (4.7) | 0.94 (0.63-1.39) | 0.755 | 300/6039 (5.0) | 333/6018 (5.5) | 0.90 (0.77-1.05) | 0.168 | 0.826 |
| Stroke | 4/1196 (0.3) | 3/1220 (0.2) | 1.36 (0.30-6.08) | 0.686 | 23/6460 (0.4) | 30/6452 (0.5) | 0.77 (0.45-1.32) | 0.336 | 0.479 |
| Any MI | 10/1175 (0.9) | 7/1195 (0.6) | 1.46 (0.56-3.84) | 0.442 | 56/6363 (0.9) | 83/6377 (1.3) | 0.68 (0.48-0.95) | 0.023 | 0.140 |
| Any revascularization | 30/1108 (2.7) | 34/1115 (3.0) | 0.89 (0.54-1.45) | 0.636 | 190/6096 (3.1) | 209/6084 (3.4) | 0.91 (0.74-1.10) | 0.325 | 0.942 |
| TVR | 22/1150 (1.9) | 20/1163 (1.7) | 1.12 (0.61-2.05) | 0.721 | 98/6296 (1.6) | 114/6271 (1.8) | 0.86 (0.65-1.12) | 0.258 | 0.432 |
| Definite ST | 2/1200 (0.2) | 5/1214 (0.4) | 0.41 (0.08-2.09) | 0.280 | 9/6448 (0.1) | 18/6466 (0.3) | 0.50 (0.23-1.12) | 0.091 | 0.818 |
| Definite or probable ST | 2/1211 (0.2) | 6/1219 (0.5) | 0.33 (0.07-1.66) | 0.180 | 12/6475 (0.2) | 19/6482 (0.3) | 0.63 (0.31-1.30) | 0.214 | 0.478 |
| BARC 3 or 5 bleeding | 8/1188 (0.7) | 4/1198 (0.3) | 2.02 (0.61-6.71) | 0.251 | 38/6411 (0.6) | 29/6403 (0.5) | 1.31 (0.81-2.13) | 0.272 | 0.512 |

631 Data are counts (percentage).

632 *POCE was defined as a composite of all-cause death, any stroke, any MI, and any revascularization.

633 #Values were compared with Fisher's exact test.

634 BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; NA = not available; POCE = patient-oriented composite

635 endpoint; ST = stent thrombosis; TVR = target vessel revascularization.