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Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial

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Aims To evaluate the impact of an experimental strategy [23-month ticagrelor monotherapy following 1-month dual antiplatelet therapy (DAPT)] vs. a reference regimen (12-month aspirin monotherapy following 12-month DAPT) after complex percutaneous coronary intervention (PCI).

Methods and results In the present post hoc analysis of the Global Leaders trial, the primary endpoint [composite of all-cause death or new Q-wave myocardial infarction (MI)] at 2 years was assessed in patients with complex PCI, which includes at least one of the following characteristics: multivessel PCI, ≥3 stents implanted, ≥3 lesions treated, bifurcation PCI with ≥2 stents, or total stent length >60 mm. In addition, patient-oriented composite endpoint (POCE) (composite of all-cause death, any stroke, any MI, or any revascularization) and net adverse clinical events (NACE) [composite of POCE or Bleeding Academic Research Consortium (BARC) Type 3 or 5 bleeding] were explored. Among

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15 450 patients included in this analysis, 4570 who underwent complex PCI had a higher risk of ischaemic and bleeding events. In patients with complex PCI, the experimental strategy significantly reduced risks of the primary endpoint [hazard ratio (HR): 0.64, 95% confidence interval (CI): 0.48–0.85] and POCE (HR: 0.80, 95% CI: 0.69–0.93), but not in those with non-complex PCI ($P_{interaction}$ = 0.015 and 0.017, respectively). The risk of BARC Type 3 or 5 bleeding was comparable (HR: 0.97, 95% CI: 0.67–1.40), resulting in a significant risk reduction in NACE (HR: 0.80, 95% CI: 0.69–0.92; $P_{interaction}$ = 0.011).

Conclusion Ticagrelor monotherapy following 1-month DAPT could provide a net clinical benefit for patients with complex PCI. However, in view of the overall neutral results of the trial, these findings of a post hoc analysis should be considered as hypothesis generating.

Keywords Complex percutaneous coronary intervention • Drug-eluting stent • Dual antiplatelet therapy • Ticagrelor monotherapy

Introduction

Coronary artery disease (CAD) is responsible for myocardial ischaemia, including angina pectoris, myocardial infarction, and ischaemic heart failure and is the leading cause of morbidity and mortality in the world.[1] Although the rates of coronary revascularization procedures have continued to decline over the past decade,[2] especially in patients with stable CAD, complexity of percutaneous coronary intervention (PCI) has increased.[3] Given the association between extent and complexity of CAD and subsequent higher rates of adverse events,[4] the need to identify and provide patients at higher risk of ischaemic events with an optimal treatment, is of paramount importance.

The concept of complex and higher risk indicated patient has recently been proposed.[5] However, there is no universal definition of complex PCI in terms of angiographic and lesion characteristics, resulting in a variety of outcome assessments reported in previous studies that precludes comparisons of study results.[6] Furthermore, data on optimal adjunctive antiplatelet regimens to improve outcomes in this high ischaemic risk population are scarce.[7,8] Recently, Giustino *et al.*[7] analysed a pooled patient-level data (n = 9577) from six randomized controlled trials (RCT), comparing ≥ 12-month dual antiplatelet therapy (DAPT) vs. 3- or 6-month DAPT in patients who underwent complex PCI. The investigators found that 1680 patients with complex PCI had a significantly increased risk of major adverse cardiac events (MACE) compared with the non-complex PCI group [adjusted hazard ratio (HR): 1.98, 95% confidence interval (CI): 1.50–2.60; $P < 0.0001$] at a median follow-up of 392 days. With a prolonged DAPT, patients who underwent complex PCI had a significantly reduced risk of MACE as compared with abbreviated DAPT (adjusted HR: 0.56; 95% CI: 0.35–0.89; $P_{interaction}$ = 0.01). However, as anticipated, this significant benefit was achieved at the expense of an increased risk of major bleeding.

As newer antiplatelet agents (e.g. prasugrel or ticagrelor)—that have faster action, more potent, and more consistent effect—have become available, an abbreviated DAPT strategy followed by potent P2Y12 monotherapy may be a potential alternative to standard DAPT regimens, aiming to reduce an excess of bleeding risk mainly associated with the addition of aspirin while maintaining a potent anti-ischaemic efficacy.[9] Therefore, the present substudy of the Global Leaders trial sought to investigate the impact of 1-month DAPT followed by 23-month ticagrelor monotherapy in patients with complex PCI.

Methods

Study design

This study is a post hoc analysis of the Global Leaders trial,[10] a multicentre, prospective, open-label RCT (NCT01813435). Details of the study design and protocol have been reported elsewhere.[10] In brief, the trial randomly assigned patients before PCI to either (i) the experimental strategy with 1-month DAPT (aspirin and ticagrelor) followed by 23-month ticagrelor monotherapy, or (ii) the reference regimen with 12-month DAPT [aspirin and either ticagrelor for acute coronary syndrome (ACS) or clopidogrel for stable CAD] followed by 12-month aspirin monotherapy, respectively. The trial randomized a total of 15 991 patients at 130 hospitals in 18 countries between 1 July 2013 and 9 November 2015.

The trial was approved by the institutional review board at each centre and followed the ethical principles of the Declaration of Helsinki. All the patients gave written informed consent prior to participation in the trial.

Study proceedings

The protocol of the trial defined a significant lesion as the presence of one or more coronary artery stenosis of 50% or more, in a native coronary artery, in stent restenosis, or bypass graft (saphenous venous or arterial bypass conduit) suitable for coronary stent implantation.[10] All target lesions were treated by default with a Biolimus A9-eluting stents (BES) (BioMatrix, Biosensors, Europe). The protocol allowed multiple target vessel treatment either within the index procedure or as a staged procedure with a maximal allocated time window of 90 days. Beyond this time window, staged procedures were counted as events (revascularization) according to the protocol.

In the present analysis, PCI was defined as complex PCI when at least one of the following features were met; multivessel PCI, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation PCI with ≥ 2 stents, and total stent length >60 mm. These five high-risk features of complex percutaneous procedure for ischaemic events have been described in the guidelines of the ESC on myocardial revascularization.[1] Multivessel PCI was defined as PCI performed to treat two or three separate major coronary territories. An isolated left main lesion was classified as two-vessel disease

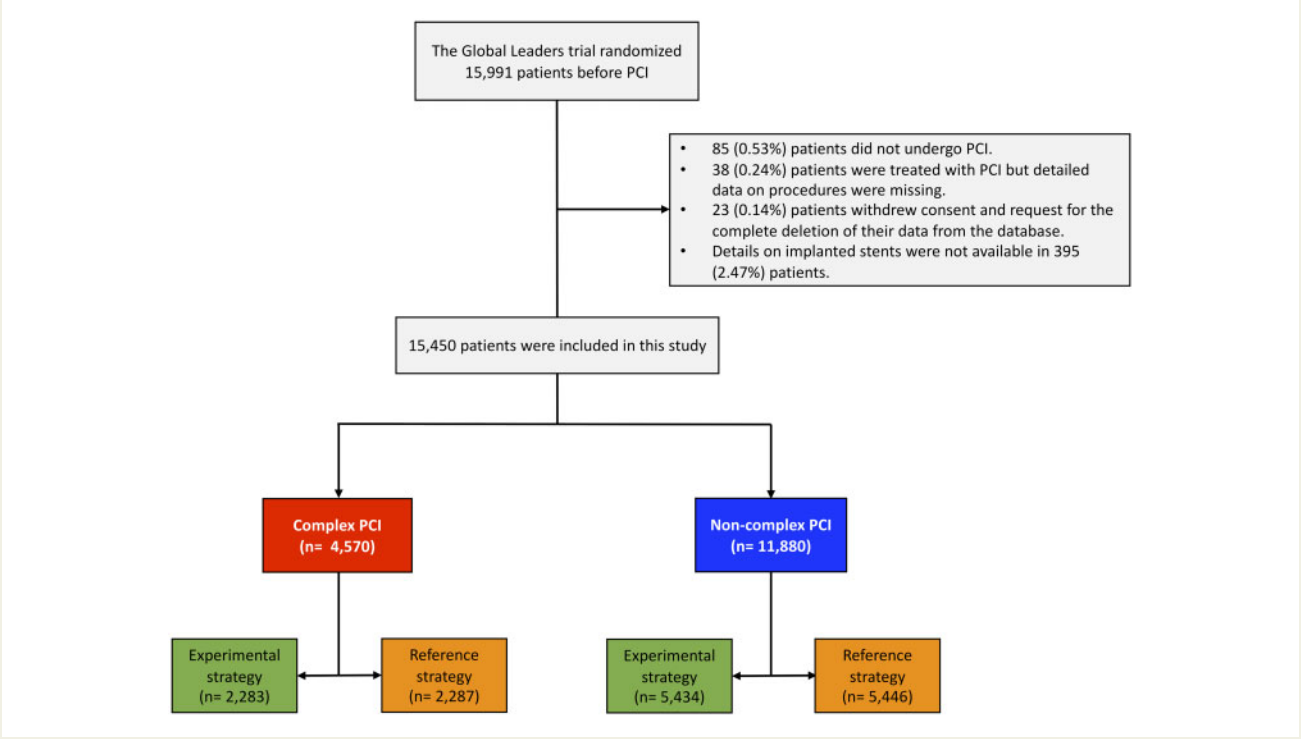


Figure 1 Patient flow diagram of the present study.

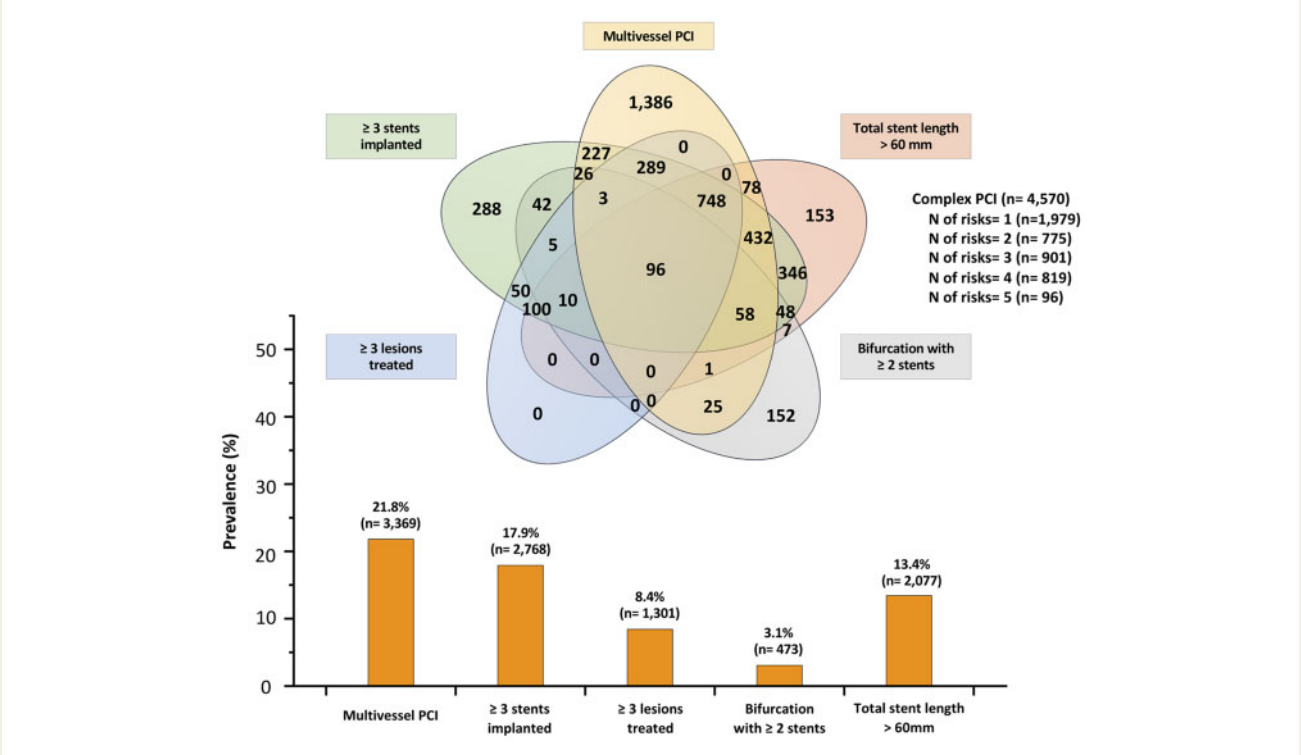


Figure 2 Prevalence of complex percutaneous coronary intervention components [mutually exclusive (upper panel) and not mutually exclusive (lower panel)]. Data are presented as % (*n*).

Table 1 Baseline characteristics stratified according to the complex percutaneous coronary intervention and the randomized regimens

	Complex PCI (n = 4570)			Non-complex PCI (n = 10 880)		
	Experimental strategy (n = 2283)	Reference strategy (n = 2287)	P-value	Experimental strategy (n = 5434)	Reference strategy (n = 5446)	P-value
Age (years)	65.3 ± 10.3	65.2 ± 10.1	0.750	64.2 ± 10.3	64.3 ± 10.3	0.812
Sex			0.473			0.945
Male	78.2 (1786/2283)	79.1 (1809/2287)		75.8 (4121/5434)	75.8 (4127/5446)	
Female	21.8 (497/2283)	20.9 (478/2287)		24.2 (1313/5434)	24.2 (1319/5446)	
Body mass index	28.0 ± 4.4	28.1 ± 4.6	0.617	28.2 ± 4.6	28.2 ± 4.6	0.876
Diabetes	27.5 (627/2280)	25.1 (573/2286)	0.062	24.7 (1342/5431)	24.6 (1338/5442)	0.881
Insulin-dependent diabetes mellitus	8.7 (198/2276)	7.7 (175/2283)	0.203	7.0 (380/5416)	7.7 (419/5429)	0.162
Hypertension	74.5 (1698/2278)	73.0 (1664/2278)	0.252	73.5 (3976/5413)	73.4 (3986/5427)	0.995
Hypercholesterolaemia	69.8 (1545/2215)	71.2 (1583/2224)	0.298	69.2 (3633/5251)	69.6 (3667/5272)	0.681
Current smoker	26.9 (613/2283)	26.5 (605/2287)	0.762	25.4 (1378/5434)	26.4 (1440/5446)	0.197
Peripheral vascular disease	6.4 (145/2267)	7.3 (166/2269)	0.220	5.8 (311/5376)	6.3 (340/5395)	0.260
Chronic obstructive pulmonary disease	5.2 (119/2274)	5.8 (132/2279)	0.409	4.9 (263/5411)	5.0 (270/5419)	0.769
Previous major bleeding	0.7 (15/2278)	0.6 (14/2284)	0.847	0.5 (29/5427)	0.7 (38/5440)	0.274
Impaired renal failure[a]	14.1 (322/2279)	14.0 (319/2275)	0.917	13.8 (743/5392)	13.3 (720/5421)	0.449
Previous stroke	2.7 (61/2279)	2.9 (66/2281)	0.656	2.6 (141/5425)	2.5 (134/5442)	0.650
Previous myocardial infarction	20.9 (476/2276)	21.8 (497/2278)	0.457	23.5 (1273/5418)	24.1 (1308/5433)	0.479
Previous percutaneous coronary intervention	29.3 (670/2283)	29.4 (671/2282)	0.966	33.7 (1830/5428)	33.7 (1837/5443)	0.969
Previous coronary artery bypass grafting	6.0 (138/2281)	6.0 (138/2284)	0.991	5.3 (290/5430)	6.2 (338/5443)	0.052
Clinical presentation			0.975			0.780
Stable coronary artery disease	51.4 (1174/2283)	51.4 (1175/2287)		53.6 (2910/5434)	53.8 (2931/5446)	
Acute coronary syndrome	48.6 (1109/2283)	48.6 (1112/2287)		46.4 (2524/5434)	46.2 (2515/5446)	
Overall			0.842			0.569
Unstable angina	11.3 (259/2283)	11.8 (271/2287)		13.1 (710/5434)	13.3 (723/5446)	
Non-ST-elevation myocardial infarction	23.3 (533/2283)	22.9 (524/2287)		20.3 (1104/5434)	20.5 (1118/5446)	
ST-elevation myocardial infarction	13.9 (317/2283)	13.9 (317/2287)		13.1 (710/5434)	12.4 (674/5446)	
Vascular access site						
Femoral	30.6 (691/2256)	32.0 (724/2261)	0.313	25.6 (1370/5362)	24.9 (1342/5381)	0.466
Brachial	0.8 (18/2256)	0.8 (18/2261)	0.995	0.6 (33/5362)	0.7 (35/5381)	0.819
Radial	75.6 (1705/2256)	73.9 (1671/2261)	0.196	74.6 (4001/5362)	75.2 (4045/5381)	0.508
Lesion treated per patient			0.451			0.440
One lesion	16.9 (386/2283)	17.4 (399/2287)		90.7 (4931/5434)	91.2 (4965/5446)	
Two lesions	55.3 (1262/2283)	53.4 (1222/2287)		9.3 (503/5434)	8.8 (481/5446)	
≥Three lesions	27.8 (635/2283)	29.1 (666/2287)				
Mean stents per lesion	1.3 ± 0.7	1.3 ± 0.7	0.974	1.1 ± 0.3	1.1 ± 0.3	0.167
Mean total stent length per lesion	28.2 ± 17.5	28.3 ± 17.6	0.696	22.3 ± 9.7	22.2 ± 9.5	0.567
Mean stent diameter per lesion	2.9 ± 0.5	3.0 ± 0.5	0.183	3.0 ± 0.5	3.0 ± 0.5	0.404
Treated lesions			0.904			0.283
Left main coronary artery	4.2 (212/5009)	3.9 (198/5047)		0 (0/5937)	0 (0/5927)	
Left anterior descending artery	37.4 (1871/5009)	37.2 (1878/5047)		43.5 (2583/5937)	45.1 (2673/5927)	
Left circumflex artery	26.1 (1305/5009)	26.3 (1329/5047)		23.1 (1371/5937)	23.0 (1361/5927)	
Right coronary artery	31.7 (1590/5009)	32.0 (1615/5047)		32.1 (1904/5937)	30.6 (1813/5927)	
Bypass graft	0.6 (31/5009)	0.5 (27/5047)		1.3 (79/5937)	1.3 (80/5927)	
Biomatrix stent	91.8 (4599/5009)	90.9 (4590/5047)	0.120	95.6 (5676/5937)	95.3 (5649/5927)	0.442
Other stent	9.8 (492/5009)	10.8 (546/5047)	0.101	5.2 (306/5937)	5.2 (310/5927)	0.852
Direct stenting	29.4 (1474/5009)	28.9 (1458/5047)	0.552	35.6 (2115/5937)	36.0 (2132/5927)	0.693
Bifurcation	15.1 (757/5009)	14.8 (749/5047)	0.702	9.3 (555/5937)	10.1 (597/5927)	0.183
Thrombus aspiration	2.9 (145/5009)	3.8 (192/5047)	0.011	5.5 (326/5937)	5.9 (348/5927)	0.371

Continued

Table 1 *Continued*

	Complex PCI ($n = 4570$)			Non-complex PCI ($n = 10\,880$)		
	Experimental strategy ($n = 2283$)	Reference strategy ($n = 2287$)	*P*-value	Experimental strategy ($n = 5434$)	Reference strategy ($n = 5446$)	*P*-value
TIMI flow						
Pre-procedure			0.506			0.406
0 or 1	13.0 (508/3903)	13.1 (517/3956)		12.9 (722/5605)	12.8 (721/5637)	
2	10.3 (401/3903)	11.1 (438/3956)		13.3 (745/5605)	12.5 (703/5637)	
3	76.7 (2994/3903)	75.9 (3001/3956)		73.8 (4138/5605)	74.7 (4213/5637)	
Post-procedure			0.588			0.691
0 or 1	0.1 (4/4003)	0.1 (6/4101)		0.1 (5/5724)	0.1 (3/5744)	
2	0.6 (24/4003)	0.5 (19/4101)		0.4 (22/5724)	0.3 (19/5744)	
3	99.3 (3975/4003)	99.4 (4076/4101)		99.5 (5697/5724)	99.6 (5722/5744)	

Data are presented as mean ± standard deviation or % (*n*).
TIMI: thrombolysis in myocardial infarction.
[a]Based on creatinine-estimated GFR (eGFR) clearance of <60 mL/min/1.73 m^2, using the Modification of Diet in Renal Disease (MDRD) formula.

in the presence of right dominance and three-vessel disease in the presence of left dominance. To calculate the total stent length, the sum of the nominal stent lengths was used as per patient.

Study endpoints

The primary endpoint was the composite of all-cause death or new Q-wave MI at 2 years. Deaths from any cause were ascertained without adjudication.[11] Q-wave MI was centrally adjudicated and defined in compliance with the Minnesota classification (new major Q-QS wave abnormalities) or by the appearance of a new left bundle branch block in conjunction with symptoms, abnormal cardiac biomarkers, or loss of myocardial viability. The key secondary safety endpoint was bleeding according to the Bleeding Academic Research Consortium (BARC) criteria (Type 3 or 5) up to 2 years.[12] Other secondary endpoints included individual components of the primary endpoint (all-cause death or new Q-wave MI), any stroke, any MI, any revascularization, and definite ST.

In addition, patient-oriented cardiovascular events (POCE) and net adverse clinical endpoints (NACE) were evaluated at 2 years according to the Academic Research Consortium (ARC)-2 definition.[13,14] Patient-oriented composite endpoint is the composite of all-cause death, any stroke (ischaemic or haemorrhagic), any MI [periprocedural or spontaneous with ST-segment elevation MI (STEMI) or non-STEMI], or any revascularization [repeated PCI or coronary artery bypass graft (CABG) surgery in target or non-target vessel]. The third universal definition of MI at the time of the trial design was the criteria recommended to the investigators to report MI. Net adverse clinical event is the composite of POCE or BARC Type 3 or 5 bleeding. Composite endpoints were analysed hierarchically. Individual components of the composite endpoints as well as definite ST according to ARC definition,[15] were reported non-hierarchically.

Furthermore, the pre-specified 1-year landmark analysis was performed to assess rates of clinical outcomes in the second year according to the two antiplatelet regimens.

Statistical analysis

Continuous variables were reported as mean ± standard deviations or median and IQR, and were compared using Student's *t*-tests or Mann–Whitney *U* test, respectively. Categorical variables were reported as percentages and numbers, and were compared using χ^2 or Fisher's exact test as appropriate.

The cumulative incidence of clinical events up to 2 years was calculated using the Kaplan–Meier method and compared using the log-rank test. HR with 95% CI was derived from a Cox regression model. The treatment effect of the experimental strategy vs. the reference regimen between the subgroups was also derived from a Cox regression model. These analyses were repeated, stratifying patients according to the number of high-risk features of complex PCI (0, 1–3, or 4 or more features). All tests were two-sided and a *P*-value of <0.05 was considered to be statistically significant. All the analyses were performed using SPSS Statistics, version 25 (IBM Corp., Armonk, 281 NY, USA).

Results

The Global Leaders trial randomized a total of 15 991 patients, of whom 15 450 patients were included in the present analysis [85 (0.53%) did not undergo PCI and were treated with medical therapy alone or urgent CABG; 38 (0.24%) were treated with PCI but detailed data on procedures were missing; 23 (0.14%) withdrew consent and requested the deletion of their data from the database; in 395 (2.47%) patients, details on implanted stents were not available] (*Figure 1*). Among these patients, 4570 underwent complex PCI, whereas 11 880 underwent a non-complex PCI. The prevalence of extent and complexity of PCI features is presented in *Figure 2* and Supplementary material online, *Table S1*.

Baseline characteristics in patients with complex PCI vs. non-complex PCI are presented in Supplementary material online, *Table S2*. Patients with complex PCI were more likely to be elderly and male and have acute indication for PCI as compared with the non-complex PCI group. The complex PCI group had a higher proportion of diabetes and a lower proportion of previous MI and PCI.

Angiographically, the complex PCI group had a greater number of treated lesions with more prevalence of bifurcation and received a

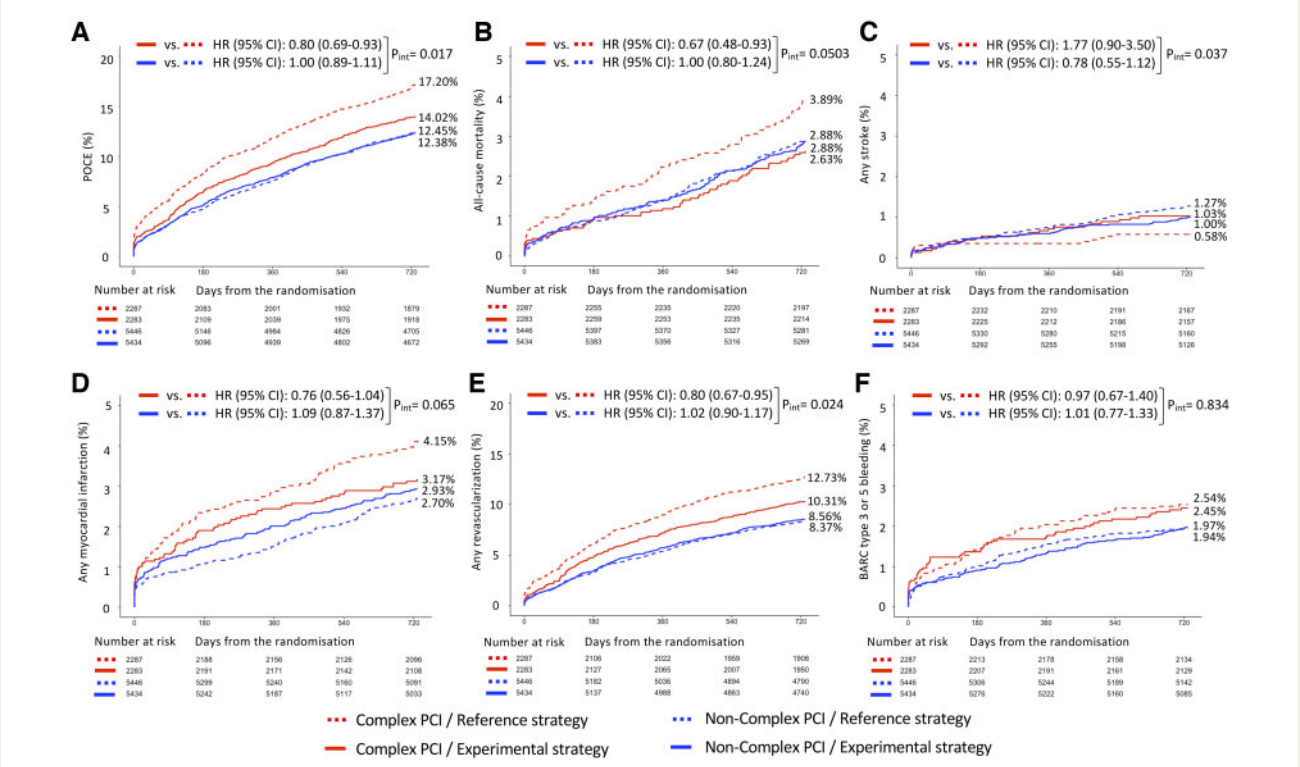


Figure 3 The impact of the two different antiplatelet regimens on clinical outcomes at 2 years in patients with and without complex percutaneous coronary intervention. Kaplan–Meier curves show a cumulative incidence of patient-oriented composite endpoint (*A*), all-cause mortality (*B*), any stroke (*C*), any myocardial infarction (*D*), any revascularization (*E*), and BARC Type 3 or 5 bleeding (*F*) at 2 years in patients with and without complex percutaneous coronary intervention. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoint.

greater number of stents implanted, leading to a greater total stent length per lesion. Mean stent diameter in the complex PCI group was smaller than that in the non-complex PCI group. The complex PCI group was treated with less use of direct stenting. The complex PCI group more frequently had TIMI 3 flow pre-procedure, whereas TIMI flow post-procedure did not differ significantly.

Clinical outcomes in patients with complex percutaneous coronary intervention

Two-year clinical outcomes in patients with complex PCI are presented in Supplementary material online, *Figure S1* and *Table S3*. The risk of the primary endpoint was numerically higher but statistically non-significant in the complex PCI group (4.47% vs. 3.94%; HR: 1.14, 95% CI: 0.96–1.35; $P = 0.124$), but complex PCI was associated with a significantly increased risk of POCE (15.62% vs. 12.41%; HR: 1.29, 95% CI: 1.18–1.41; $P < 0.001$), which was driven by an increased risk of any MI and any revascularization. The risk of BARC Type 3 or 5 bleeding was also higher in the complex PCI group at 2 years (2.49% vs. 1.96%; HR: 1.28, 95% CI: 1.02–1.61; $P = 0.034$), leading to a significantly increased risk of NACE (17.05% vs. 13.61%; HR: 1.29, 95% CI: 1.18–1.40; $P < 0.001$). The 1-year landmark analysis showed a similar risk of POCE, BARC Type 3 or 5 bleeding, and NACE in the second year, while these differences were highly significant at the time of 1 year and remained unchanged therefore significant at 2 years (Supplementary material online, *Table S3*).

Clinical outcomes according to the two antiplatelet regimens in patients with complex percutaneous coronary intervention

Baseline characteristics according to the two antiplatelet regimens in patients with complex PCI are presented in *Table 1*. All variables are well-balanced between groups, except the rate of thrombus aspiration which was less frequently performed in the experimental strategy.

Two-year clinical outcomes according to the allocated antiplatelet strategies in patients with complex PCI are presented in *Figure 3* and Supplementary material online, *Table S4*. The treatment effect of the experimental strategy vs. the reference regimen between the complex and non-complex PCI is presented in *Figure 4*. The experimental strategy significantly reduced the risk of the primary endpoint (3.51% vs. 5.43%, HR: 0.64; 95% CI: 0.48–0.85; $P = 0.002$) with a significant treatment effect ($P_{interaction} = 0.015$) in favour of the complex PCI group. Similarly, the experimental treatment was associated with a significant risk reduction in POCE (14.02% vs. 17.20%; HR: 0.80; 95% CI: 0.69–0.93; $P = 0.003$) with a significant

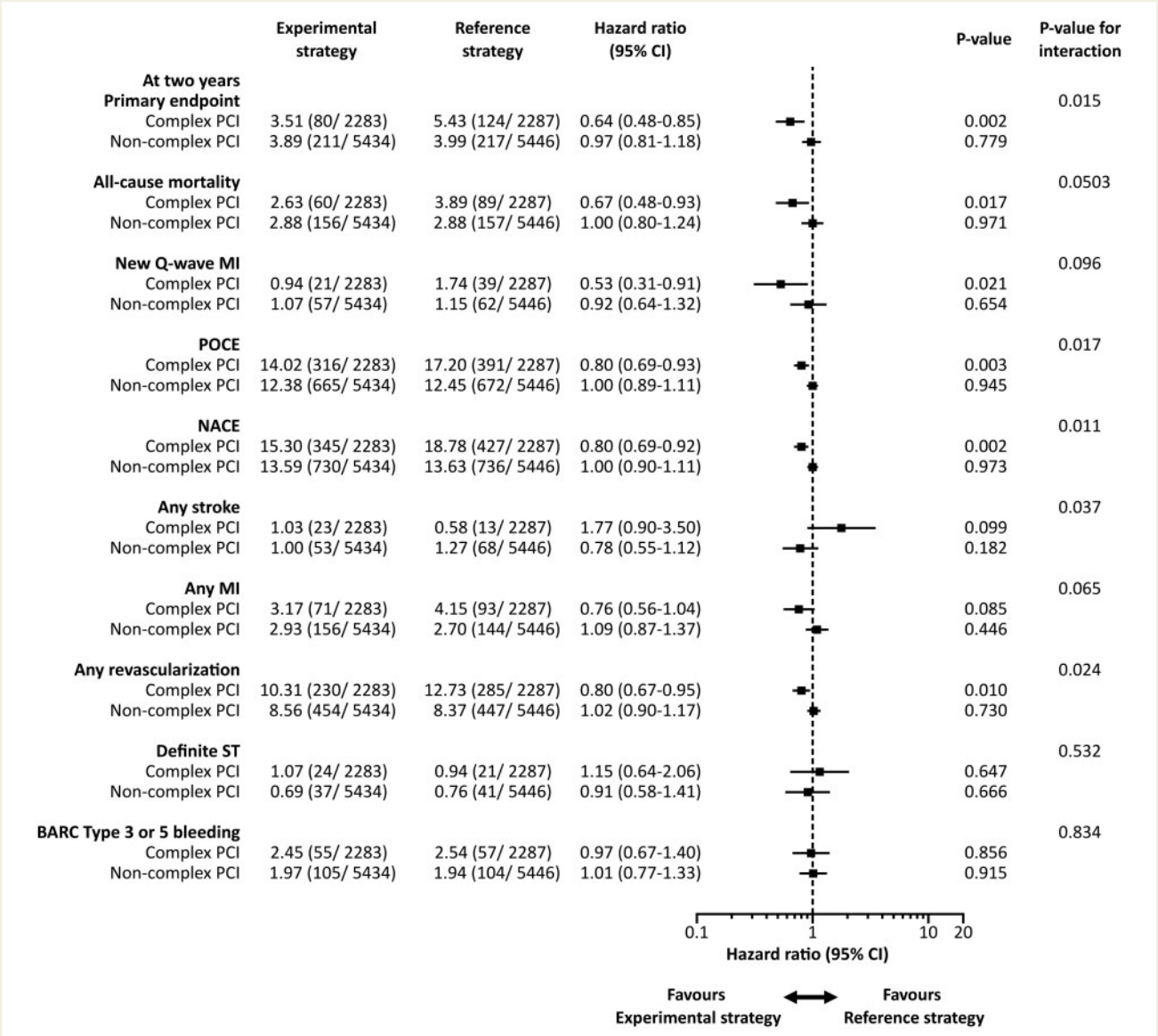


Figure 4 The treatment effect of the experimental strategy vs. the reference regimen stratified according to complex percutaneous coronary intervention. The favourable treatment effect of the experimental strategy vs. the reference regimen was observed in terms of patient-oriented composite endpoint, net adverse clinical events, and any revascularization at 2 years in favour of patients with complex percutaneous coronary intervention.

treatment effect ($P_{interaction}$ = 0.017), favouring patients who received complex PCI. There was a large risk reduction in individual components, including a 33% risk reduction in all-cause mortality (2.63% vs. 3.89%; HR: 0.67, P = 0.017; $P_{interaction}$ = 0.0503) and a 20% risk reduction in any revascularization (10.31% vs. 12.73%; HR: 0.80, 95% CI: 0.67–0.95; P = 0.010; $P_{interaction}$ = 0.024). Importantly, the benefit of long-term ticagrelor monotherapy was greater as the number of high-risk features increased (*Take home figure*). In contrast, the risk of BARC Type 3 or 5 bleeding did not differ significantly between the two regimens in patients with complex PCI (2.45% vs. 2.54%; HR: 0.97; 95% CI: 0.67–1.40; P = 0.856; $P_{interaction}$ = 0.834). Consequently, the experimental strategy achieved a significantly lower risk of NACE (15.30% vs. 18.78%; HR: 0.80, 95% CI: 0.69–0.92; P = 0.002) with a significant treatment effect ($P_{interaction}$ = 0.011) in favour of the complex PCI group.

The prespecified 1-year landmark analysis has shown that ticagrelor monotherapy, when compared with aspirin monotherapy, had no significant effect in any ischaemic and bleeding endpoints during the second year of follow-up (*Figure 5* and Supplementary material online, *Table S4*).

Stratified analyses according to clinical presentation (stable coronary artery disease or acute coronary syndrome)

In stable CAD patients with complex PCI, the experimental treatment had a non-significant effect on the primary endpoint and POCE, whereas

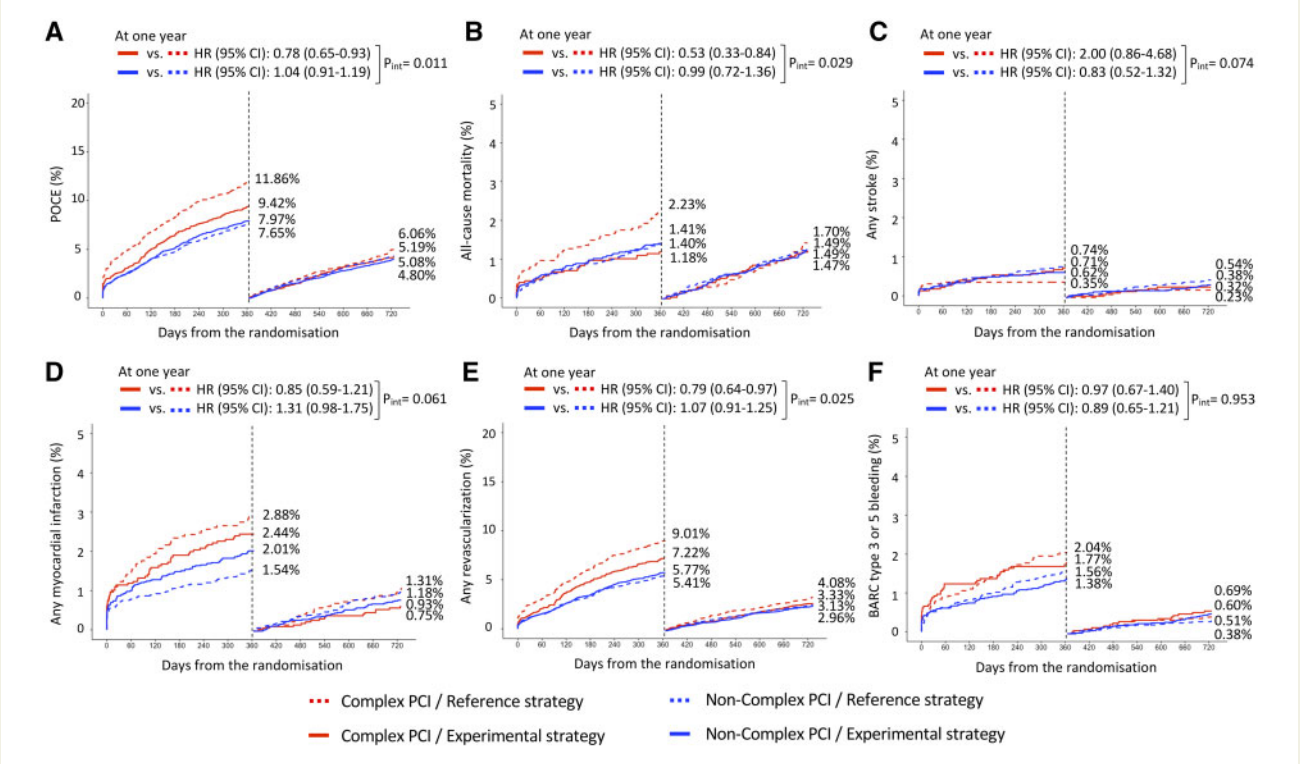


Figure 5 The impact of the two different antiplatelet regimens on clinical outcomes up to and beyond 1 year in patients with and without complex percutaneous coronary intervention. The 1-year landmark analyses have demonstrated that the benefit of the experimental strategy vs. the reference regimen was largely obtained at 1 year. BARC, Bleeding Academic Research Consortium; NACE, net adverse clinical events; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoint.

the risk of BARC Type 3 or 5 bleeding was numerically higher in the experimental group (2.56% vs. 1.62%, HR: 1.60, 95% CI: 0.90–2.84; $P = 0.109$, $P_{interaction} = 0.481$) (Supplementary material online, *Table S5*).

In contrast, in ACS patients with complex PCI, the experimental strategy was associated with a significant risk reduction in the primary endpoint (3.07% vs. 5.85%, HR: 0.52, 95% CI: 0.34–0.78; $P = 0.002$, $P_{interaction} = 0.003$) and POCE (12.80% vs. 16.46%, HR: 0.76, 95% CI: 0.61–0.95; $P = 0.008$, $P_{interaction} = 0.009$). The risk of BARC Type 3 or 5 bleeding was numerically lower in the experimental group (2.25% vs. 3.42%, HR: 0.65, 95% CI: 0.39–1.08; $P = 0.098$, $P_{interaction} = 0.474$), resulting in a significantly reduced risk of NACE (14.07% vs. 18.71%, HR: 0.73, 95% CI: 0.59–0.90; $P = 0.003$, $P_{interaction} = 0.010$) (Supplementary material online, *Table S6*).

Discussion

The main findings of this study could be summarized as follows.

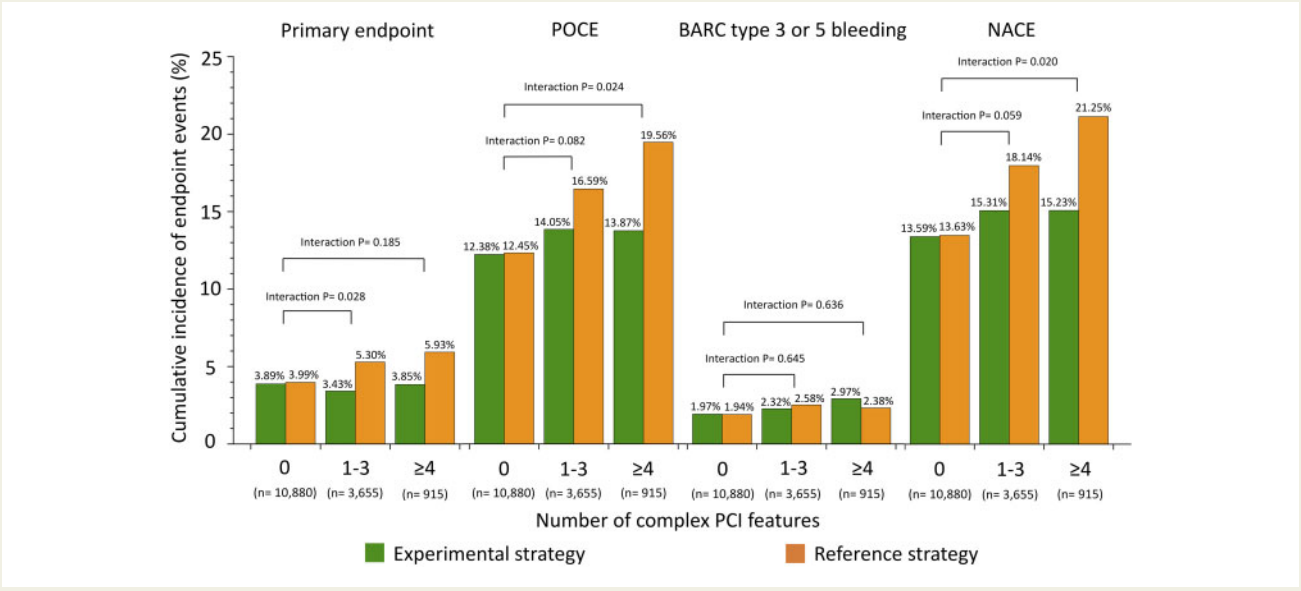
(1) Compared with non-complex PCI, complex PCI was associated with a greater risk of ischaemic and bleeding events at 2 years, mainly observed in the first year.

(2) With the experimental strategy, patients with complex PCI had a significant risk reduction in the primary endpoint as well as POCE while maintaining a similar risk of bleeding, thereby resulting in a net clinical benefit at 2 years. These benefits of the experimental strategy were mainly derived from the first year of treatment.

(3) Stratified analyses according to clinical presentation (stable CAD or ACS) have shown that the real benefit of the ticagrelor monotherapy after early cessation of aspirin seems to be mainly related to ACS patients who underwent complex PCI owing to a reduction in bleeding risk, without trade-off in anti-ischaemic efficacy, thereby achieving an increased net clinical benefit.

Although the extent and complexity of complex CAD is significantly associated with stent-related and non-stent-related adverse ischaemic events,[4] there has been no universal definition of complex PCI, resulting in different criteria with a combination of angiographic and lesion-related characteristics applied in previous studies[6] (Supplementary material online, *Table S7*). In the present study, taking into account the current ESC guideline-endorsed criteria,[1] we applied the modified version of the definition proposed by Giustino *et al.*,[7] and demonstrated that the complex PCI group ($n = 4570$) had a higher risk of recurrent ischaemic events as compared with the non-complex PCI group. Of note, consistent with a previous report,[16] the risk of BARC Type 3 or 5 bleeding was also significantly higher in the complex PCI group. These findings confront us with the dilemma of either a prolonged or abbreviated course of DAPT, since a long-term duration of DAPT could reduce the ischaemic risk but increase the bleeding risk significantly.

As the advent of a new generation drug-eluting stent (DES) has significantly reduced the risk of early, late, and very late ST, the incremental benefit of extended DAPT in terms of prevention of stent-related ischaemic events observed especially in the first-generation



Take home figure Long-term ticagrelor monotherapy with complex percutaneous coronary intervention: cumulative incidence of endpoint events at 2 years. The endpoint events were stratified by the number of complex percutaneous coronary intervention characteristics and randomized treatment strategies. Outcomes were analysed comparing randomized treatments among subgroups of patients with 0, 1–3, or 4 or more complex percutaneous coronary intervention features. The magnitude of the anti-ischaemic effect of long-term ticagrelor monotherapy vs. standard dual antiplatelet therapy regimen tended to be greater as the number of complex percutaneous coronary intervention features increased. BARC, Bleeding Academic Research Consortium; NACE, net adverse clinical events; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoint.

DES era is likely no longer significant in patients treated with contemporary devices. Consequently, the protection against recurrent MI in a non-stent-related segment may be the predominant reason for prescribing long-term DAPT for many physicians. Unsurprisingly, its benefit is coupled with an increased bleeding risk, which alters quality of life and is associated with morbidity, mortality, and medical cost.[17,18] To overcome this drawback of long-term DAPT, a novel antiplatelet regimen with an initial short-term duration of DAPT to prevent stent-related thrombotic events followed by a long-term course of a potent P2Y12 inhibitor alone has been expected to reduce the excess of aspirin-related bleeding without reducing anti-ischaemic efficacy of the potent P2Y12 inhibitor.[9] Indeed, the present study has found that, with a new antiplatelet regimen, the complex PCI group did not experience an increased risk of bleeding, while maintaining a significant risk reduction in ischaemic events, thereby achieving a maximized net clinical benefit at 2 years.

Interestingly, the 1-year landmark analysis suggested that the significant ischaemic efficacy of ticagrelor monotherapy at 2 years were largely obtained in the first year. In other words, the similar rates of events during the second year between the complex and non-complex PCI group may suggest that potent antiplatelet inhibition is no longer necessary in the second year. A sub-study of the DAPT trial investigated the impact of 30- vs. 12-month DAPT according to lesion complexity in patients who were free from ischaemic and bleeding events within the first year after DAPT initiation. The investigators found that patients who underwent complex PCI ($n = 3730$) had a similar risk of ischaemic events compared with non-complex group after 1 year and that a greater anti-ischaemic efficacy of prolonged DAPT was consistently observed in both the complex and non-complex PCI group without evidence of interaction,[8] which might be attributed to the fact that most of stent-related ischaemic events are known to occur within weeks or months after coronary stenting. However, a recent report has shown different patterns of these events between 0–6 months and 6–24 months according to types of lesions or procedures.[19] Specifically, for ≥3 stents implanted and bifurcation PCI, the risk of MACE was higher within 6 months but not after 6 months, whereas for saphenous vein graft PCI, the risk was higher over 2 years.[19] These findings might suggest that a personalized duration or intensity of antiplatelet inhibition should be taken into account the time course of ischaemic risks according to types of lesions treated or procedures performed in an individual patient.

On the other hand, there might be a potential concern of a higher risk of any stroke in the experimental strategy vs. the reference regimen in patients who underwent complex PCI (*Figure 4*). However, this is likely to be the play of chance in the setting of infrequent events, because both complex and non-complex PCI groups allocated to the experimental strategy had a similar rate of any stroke, while the non-complex PCI group with reference regimen had a much higher risk of any stroke as compared to the complex PCI group.

The present results in the context of complex PCI have to be weighed against surgical revascularization. The recent studies comparing the new generation DES with CABG in patients with multivessel disease have found that surgery was associated with a lower risk of MI and repeat revascularization albeit an increased risk of stroke in

early phase.[20] Both stenting and surgery can provide revascularization to vascular territories caused by flow-limiting stenoses. Given the majority of new infarctions occurs at the site of non-significant stenoses, only CABG can be expected to protect these events arising from non-significant stenoses by providing flow distal to unstable plaque burden, thereby potentially contributing to a reduced risk of mortality during a long-term follow-up. Indeed, long-term ticagrelor monotherapy, as compared with standard DAPT regimen, could achieve a net clinical benefit in patients who underwent complex PCI, however, this benefit was mainly driven by the risk reduction in repeat revascularization, but not MI. In view of this gap between CABG and PCI even with a second-generation DES implantation followed by a novel adjunctive antiplatelet regimen, a meticulous assessment regarding the optimal revascularization strategy (PCI or CABG) is of paramount importance.[5] Once PCI is considered the preferred revascularization approach, the use of state-of-art PCI including physiological assessment and intravascular imaging in conjunction with a novel adjunctive antiplatelet therapy could be helpful to optimize outcomes in patients undergoing complex PCI.

Limitations

The present results need to be interpreted in light of the following limitations. First, the present study was not pre-specified in the protocol, however, high-risk features of complex PCI were not formally described in the guidelines of the ESC at the time of the trial design. Nevertheless, together with the inherent limitations of sub-analyses including multiple testing,[21] our findings need to be interpreted only as hypothesis-generating and call for confirmatory randomized trials. Second, we did not collect the anatomic SYNTAX score in all patients, chronic total occlusion (requiring 3-month duration of angiographic or clinical evidence), and calcified lesions requiring rotational atherectomy, which were not documented in the electronic case report form. Third, these missing individual items of complex PCI characteristics might also interact with the treatment effect of the experimental strategy. However, each component had a limited power to detect this heterogeneity due to the reduced size of each subgroup. Fourth, all endpoints were site-reported, as the trial did not have a clinical adjudication committee for serious adverse events due to limited financial resources. However, seven on-site monitoring visits were performed in each participating centre, and 20% of the reported events were checked according to source documents. In addition, the trial was monitored for event under-reporting and event definition consistency.

Conclusion

Patients who underwent complex PCI had a higher risk of ischaemic and bleeding events at 2 years as compared with the non-complex PCI group. Compared with standard DAPT regimen, 1-month DAPT followed by long-term ticagrelor monotherapy significantly reduced ischaemic risks without an increase in bleeding risk in patients with complex PCI. In view of the fact that the primary endpoint was neutral in the overall population, our findings need to be considered as hypothesis-generating and should be tested in a dedicated prospective trial on complex PCI.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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