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ORIGINAL SCIENTIFIC PAPER

'Ticagrelor alone vs. dual antiplatelet therapy from 1 month after drug-eluting coronary stenting among patients with STEMI': a *post hoc* analysis of the randomized GLOBAL LEADERS trial

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Aim

To evaluate the efficacy and safety of ticagrelor monotherapy beyond 1 month and up to 24 months vs. standard 12-month dual antiplatelet therapy (DAPT) with aspirin and ticagrelor followed by aspirin monotherapy among ST-elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI) in the GLOBAL LEADERS trial.

Methods and results

We performed a *post hoc* analysis of STEMI patients in the GLOBAL LEADERS trial comparing experimental ticagrelor monotherapy (1062 patients) with standard 12-month DAPT (1030 patients). We evaluated predefined primary and secondary endpoints in both treatment arms. Rates of net adverse clinical events (NACE), patient-oriented composite endpoints (POCE), and bleeding academic research consortium (BARC)-defined bleeding Type 3 or 5 were also evaluated. At 2 years, there were no significant differences in rates of primary endpoints in patients who had STEMI [0.89 (0.61–1.31)]. There were similar rates of NACE and POCE in both experimental and reference treatment groups at 2 years post-PCI [hazard ratio (HR) 0.96 (0.77–1.20) and 0.96 (0.77–1.21), respectively]. BARC 3 or 5 bleeding events were numerically less in experimental compared to reference treatment groups at 1 year [HR 0.55 (0.27–1.13)] and 2 years [0.61 (0.32–1.16)].

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Conclusion Presentation with STEMI has not influenced the incidence of GLOBAL LEADERS defined primary endpoints. There were no significant differences in rates of NACE, POCE, and BARC bleeding between the two treatment groups up to 2 years of follow-up. Although these findings should be viewed as exploratory, they expand the evidence on potential safety of aspirin-free antiplatelet strategies after PCI in STEMI.

Keywords STEMI • PCI • DAPT • Ticagrelor • GLOBAL LEADERS

Introduction

Several attempts have been made to investigate the need and optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI), either in an elective or acute setting.[1] With specific regard to acute coronary syndrome (ACS), dedicated trials were designed to analyse the benefits of different $P2Y_{12}$ receptor inhibitors, using a 12-month DAPT regimen after PCI in ACS by using prasugrel or ticagrelor instead of clopidogrel.[2,3] The trade-off of these potent and specific antiplatelet agents is that they increase the bleeding risk.[4,5] On this basis, the European DAPT consensus document recommends that these regimens should be tailored according to the high bleeding risk (HBR) score and DAPT duration adapted by stopping the more specific and potent $P2Y_{12}$ agent rather than the less specific and less potent aspirin.[6]

Stents with improved design have prompted the scientific community to reconsider the duration of DAPT, and to propose several trials investigating the benefit and the risks of early DAPT interruption in favour of a $P2Y_{12}$ monotherapy.[6–10] Patients presenting with ST-elevation myocardial infarction (STEMI) were included in all of these trials with the exception of *The Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention* (TWILIGHT) trial. The GLOBAL LEADERS trial is up to now the only trial including STEMI patients treated with a ticagrelor-alone strategy after 1 month of aspirin, whereas the other trials applied such a regimen only after 3 months post-PCI. In particular, the TICO-STEMI sub-study reported promising results of ticagrelor monotherapy compared to the standard 12-month DAPT among STEMI patients, but with lower bleeding events. As a result, the estimates of net adverse clinical events favoured early aspirin interruption even in this specific setting (2.3% vs. 5.2%, $P = 0.01$).[10] Similarly, the *post hoc* analysis of the GLOBAL LEADERS trial related to ACS suggested that continuation of aspirin between 1 month and 12 months after PCI was associated with increased bleeding risk and appeared not to add to the benefit of ticagrelor in reducing ischaemic events occurrences.[11]

We aimed to investigate the benefits and risks of ticagrelor monotherapy beyond 1 month after PCI in STEMI patient population enrolled in the GLOBAL LEADERS trial. We also compared the safety and efficacy of the experimental antiplatelet strategy in STEMI vs. non-STEMI cohorts of the trial.

Study design and participants

The GLOBAL LEADERS trial (NCT01813435) was a randomized, open-label superiority trial conducted at 130 sites in 18 countries.[7] A total of 15 991 all-comers patients were randomized in 1:1 ratio to either 23-month ticagrelor monotherapy (90 mg twice daily) following 1-month DAPT combination with aspirin ≤100 mg once daily (experimental treatment strategy) or 12-month DAPT with either ticagrelor 90 mg twice daily (ACS) or clopidogrel 75 mg once daily [chronic coronary syndrome (CCS)] followed by 12-month aspirin monotherapy ≤100 mg daily (reference treatment strategy) after PCI. Randomization to either treatment arm occurred before intervention in a 1:1 ratio using web-based system. Randomization was concealed, stratified by centre and clinical presentation (stable coronary artery disease vs. ACS), and blocked, with randomly varied block sizes of 2 and 4.[7] A total of 15 968 patients remained in the study because 23 patients withdrew consent and requested data deletion from the database. Out of 15 968 patients, 2092 patients presenting with STEMI at baseline were included in the present *post hoc* analysis. Anatomical SYNTAX score analysis was prespecified in the protocol for the first 4000 consecutive patients in the GLOBAL LEADERS trial: of these, 545 patients presented with STEMI.[12] The MI-SYNTAX scores were analysed off-line by an independent core-laboratory blinded to the treatment allocation.[13,14] Furthermore, complete data in terms of the Updated Clinical Logistic SYNTAX scores were available in 512 patients.[12,13,15] The survival status of the patients lost to follow-up was obtained through public civil registry and 99.95% of the vital status at 2 years was available in the GLOBAL LEADERS trial.[7] All patients provided informed consent. The trial was approved by the institutional review board at each centre and followed the ethical principles of the Declaration of Helsinki.

Study endpoints definitions

We compared rates of primary composite and secondary endpoints between patients with STEMI and without STEMI in the GLOBAL LEADERS study. The primary outcome is the composite of all-cause mortality or non-fatal, new Q wave myocardial infarction (MI). The key secondary safety outcome was site-reported bleeding assessed according to the bleeding academic research consortium (BARC) criteria (Type 3 or 5).[7] The STEMI and chronic coronary syndrome (CCS)/non-ST-elevation MI (NSTEMI) were also compared in rates of other secondary endpoints that were included as individual components of the primary endpoint in the parent study including all-cause death or new Q wave MI, any stroke, any MI, any revascularization, and definite ST.[7]

In addition, in the present exploratory analysis, we evaluated the efficacy and safety of the experimental vs. the reference treatment strategy in reducing the rates of the composite endpoints of net adverse clinical events (NACE), patient-oriented composite endpoints (POCE), and BARC 3 or 5 bleeding up to 2 years after PCI in the STEMI cohort of the GLOBAL LEADERS trial, as well as across different patient subgroups prespecified in the study protocol.[16]

POCE were defined as a composite of all-cause mortality, any stroke, any MI, or any revascularization, as specified by the ARC-2 consensus. NACE included the combination of POCE and BARC bleeding Type 3 or 5. While major bleeding was defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria in the TICO trial, BARC criteria were used to assess bleeding in the GLOBAL LEADERS trial.[7,10]

Rates of NACE, POCE, and BARC 3 and 5 bleeding were further assessed in high-risk STEMI subgroups [age, gender, DM, chronic kidney disease (CKD), complex PCI, previous bleeding and anaemia, HBR patients]. CKD was defined as estimated glomerular filtration rate (eGFR) at time of randomization <60 mL/min/1.73 m^2.[17] Complex PCI was defined 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.[18] As per HBR academic research consortium definition, low haemoglobin is considered a major HBR criterion if <11 g/dL and minor if <11–12.9 g/dL for men and 11–11.9 g/dL for women.[19]

Statistical analysis

Analysis for all adverse events was conducted according to the intention-to-treat principle of all randomized patients as time-to-first-event.[7] The cumulative incidence of adverse events was calculated using the Kaplan–Meier method. In addition to the analysis up to 2 years, we analysed the events occurring at three landmark time points, 0–30, 31–365, and 366–730 days of follow-up among the STEMI patients' cohort of the parent study. Kaplan–Meier survival curves were analysed using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause mortality were determined on the basis of Cox proportional hazards regression. No formal adjustment for multiple testing was conducted due to the *post hoc* nature of the analysis.[20] Continuous variables were expressed as mean ± standard deviation and were compared using the Student's *t*-test or Mann–Whitney *U* test. Categorical variables were reported as numbers and percentages and were compared using the χ^2 or Fisher's exact test as appropriate. A two-sided *P*-value <0.05 was considered statistically significant. Analyses were performed using SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA) and Stata 15 (StataCorp, College Station, TX, USA).

The details of statistical methods for the metanalysis are included in Supplementary material online.

Results

Out of a total 15 968 patients recruited in the GLOBAL LEADERS trial between 1 July 2013 and 9 November 2015, there were 7487 patients with ACS; of whom 2092 patients presented with STEMI; 1062 patients were assigned to the experimental treatment strategy; and 1030 patients were assigned to the reference treatment strategy (*Figure 1*). Most baseline clinical and angiographic characteristics were well balanced between the two STEMI groups. However, CKD was more frequent in the experimental treatment group (*Tables 1* and *2*).

Analysis of predefined endpoints for GLOBAL LEADERS trial according to clinical presentation at 0–30, 31–365, 365, and 730 days

At 30 days after PCI, there were no significant difference in rates of primary and secondary endpoints between experimental and control arm in STEMI cohort compared to unstable angina (UA), NSTEMI, or CCS. Similarly, the rates of primary and secondary outcomes did not differ significantly between the two treatment groups between 31 and 365 days after PCI regardless of the clinical presentation. At the end of first and second year post-PCI, the rates of primary composite endpoints continued not to be statistically different between the treatment arms in patients with STEMI, UA, NSTEMI, and CCS. No significant difference was observed in rates of secondary bleeding outcomes in either treatment strategy in STEMI compared to UA and NSTEMI cohorts. Nevertheless, there was significant reduction in rates of BARC 3 and 5 bleeding in the experimental vs. the standard strategy in STEMI compared to CCS at 1 year [21 (1.1%) and 12 (2.1%), respectively, HR 0.55; 95% CI 0.27–1.13 in STEMI and 60 (1.4%) and 48 (1.1%), respectively; HR 1.26; 95% CI 0.86–1.85 in CCS; *P* for interaction = 0.04]. Similarly, at 2 years of follow-up, the experimental strategy resulted in significant reduction of secondary bleeding outcome in comparison to the control strategy in STEMI [15 (1.4%) and 24 (2.4%), respectively, HR 0.61; 95% CI 0.32–1.16 in STEMI and 90 (2.2%) and 69 (1.6%), respectively; HR 1.32; 95% CI 0.96–1.81 in CCS; *P* for interaction = 0.03] (*Tables 3–8*).

Additional analyses of rates of other predefined ischaemic and bleeding endpoints for GLOBAL LEADERS trial in STEMI population

Exploratory analyses of additional predefined endpoints did not indicate any significant differences in rates of death, new Q wave MI, all MI, non-fatal stroke, repeat revascularization, or stent thrombosis (definite or probable or both) between the two treatment groups at 1 year or 2 years of follow-up. Rates of BARC 2 bleeding were nearly the same in both treatment groups. There were a numerically lower BARC 3, BARC 5, and BARC 2, 3, and 5 bleeding rates in the experimental arm after follow-up for 1 year and 2 years (*Tables 9* and *10*).

Analysis of rates of NACE, POCE, and BARC 3 or 5 bleeding in experimental and reference treatment groups in STEMI cohort of GLOBAL LEADERS

There was no statistically significant difference in rates of NACE between the reference and experimental groups at 2 years [155

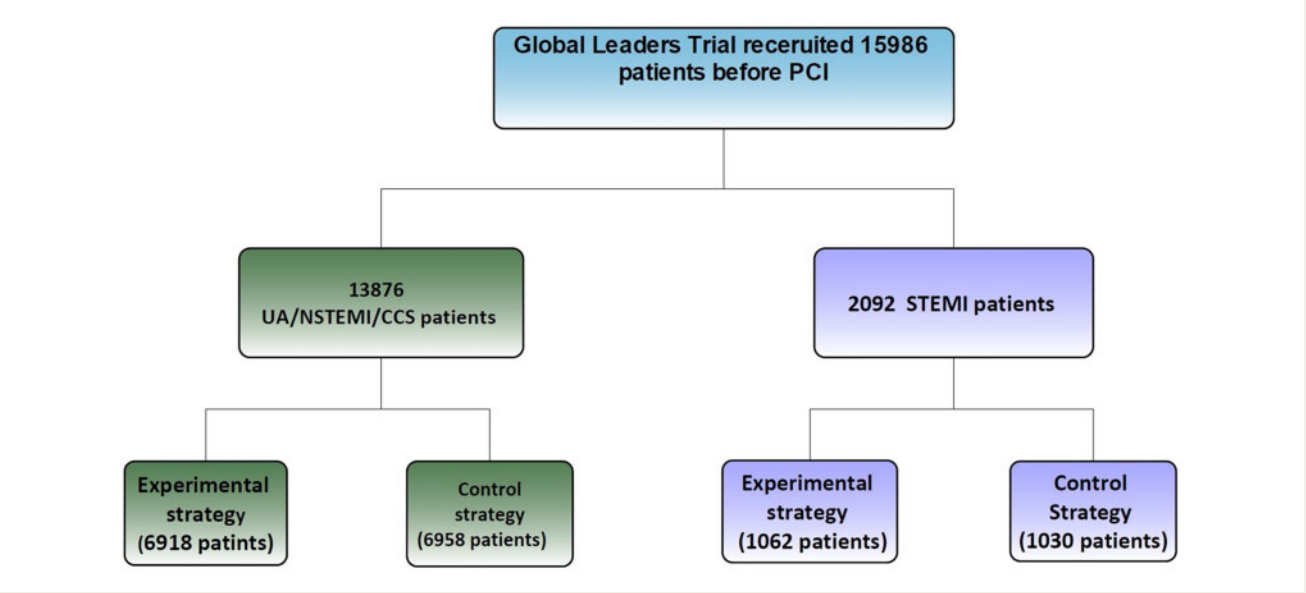


Figure 1 Patients flow diagram of the present study. CCS, chronic coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Table 1 Baseline clinical characteristics

Characteristics	Reference ($n = 1030$)	Experimental ($n = 1062$)	*P*-values
Age	61.08 ± 10.77	62.01 ± 11.05	0.052
Male gender	822 (79.8%)	811 (76.3%)	0.06
Hypertension	600 (58.8%)	642 (61.0%)	0.30
Diabetes	167 (16.2%)	168 (15.8%)	0.81
Current smoker	457 (44.4%)	486 (45.8%)	0.54
Previous myocardial infarction	105 (10.2%)	105 (9.9%)	0.83
Previous percutaneous coronary intervention	126 (12.2%)	126 (11.9%)	0.84
Previous coronary artery bypass grafting	10 (0.97%)	8 (0.75%)	0.64
Previous stroke	17 (1.65%)	13 (1.23%)	0.47
Previous major bleeding	6 (0.58%)	8 (0.75%)	0.79
Peripheral vascular disease	39 (3.8%)	31 (3.0%)	0.28
Chronic obstructive pulmonary disease	31 (3.0%)	41 (3.9%)	0.34
Chronic kidney disease	94 (9.1%)	136 (12.9%)	0.008

Continuous variables were expressed as mean ± standard deviation, and categorical variables were reported as number (percentage).

(15.1%) and 154 (14.6%), respectively, HR 0.96, 95% CI 0.77–1.20; $P = 0.74$] or 1 year [109 (10.6%) and 112 (10.6%), respectively; HR 1.0, 95% CI 0.76–1.30; $P = 0.98$] of follow-up (*Table 11* and *Figure 2*). Rates of POCE were also similar for both groups. During the first year, 95 POCE events (9.3%) occurred in the control group vs. 101 (9.6%) in the experimental one; HR 1.03, 95% CI 0.78–1.37; $P = 0.82$. At 2-year follow-up, a total of 144 POCE events (13.7%) had occurred in the experimental group compared to 145 events (14.2%) in the control one; HR 0.96, 95% CI 0.77–1.21; $P = 0.76$ (*Table 11* and *Figure 2*).

However, rates of BARC 3 or 5 bleeding were numerically less frequent in the experimental group at both 1 year and 2 years follow-up; 21 (2.1%) in control vs. 12 (1.1%) in experimental group; HR 0.55, 95% CI 0.27–1.13; $P = 0.63$ at 365 days and 24 (2.4%) vs. 15 (1.4%); HR 0.61, 95% CI 0.32–1.16; $P = 0.13$ at 730 days of follow-up (*Table 11* and *Figure 2*).

Table 2 Baseline angiographic characteristics

Characteristics	Reference (*n* = 1030 patients)	Experimental (*n* = 1062 patients)	*P*-values
Percutaneous coronary intervention done	1027 (99.7%)	1057 (99.5%) patients	0.73
Vascular access site:			
Radial	814 (79.3%)	807 (76.3%)	0.11
Femoral	215 (20.9%)	250 (23.7%)	0.14
Brachial	2 (0.2%)	3 (0.3%)	0.68
MI-SYNTAX score	14.6 ± 9.6, *n* = 240	14.9 ± 9.3, *n* = 272	0.76
Updated clinical logistic SYNTAX score	-0.36 ± 0.90, *n* = 240	-0.22 ± 0.86, *n* = 272	0.09
	Reference (*n* = 1255 lesions)	**Experimental (*n* = 1316 lesions)**	***P*-values**
Bifurcational lesions	134 (10.7%)	139 (10.6%)	0.95
Lesions location			0.56
LMS	18 (1.4%)	14 (1.1%)	
LAD	508 (40.8%)	513 (39.0%)	
LCX	225 (17.9%)	256 (19.5%)	
RCA	501 (39.9%)	532 (40.4%)	
Bypass grafts	3 (0.2%)	1 (0.1%)	
Number of stented lesions	1230 (98.0%)	1295 (98.4%)	0.46
Number of stents per lesion	1.23 ± 0.57	1.22 ± 0.58	0.64
Mean diameter of stents	3.07 ± 0.47 mm	3.05 ± 0.47 mm	0.23
Total length of stents	27.07 ± 13.73 mm	26.01 ± 14.15 mm	0.55

Continuous variables were expressed as mean ± standard deviation, and categorical variables were reported as number (percentage). The MI-SYNTAX score was defined as the initial diagnostic angiogram, which considers the patency of the IRA. Thus, an IRA with a TIMI flow of 0 or 1 is scored as a total occlusion with thrombus. The updated clinical logistic SYNTAX score was calculated based on the following formula: 0.0187 × (MI-SYNTAX score) + 0.1667 × (SYNTAX-like characteristic) + 0.0425 × (age) + 0.0174 × (90-CrCl) + 0.0522 × (50-EF) + 0.0312 × (BMI) + 0.57 × (PVD) + 0.3463 × (diabetes) - 4.521 (19).
BMI, body mass index; IRA, infarct-related artery; LAD, left anterior descending; LCX, left circumflex; LMS, left main stem; PVD, peripheral vascular disease; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

Table 3 Rates of primary composite endpoints (composite of death and new Q myocardial infarction) between ST-elevation myocardial infarction and non-ST-elevation myocardial infarction cohorts in the GLOBAL LEADERS study at 30, 31–365, 365, and 730 days of follow-up

	STEMI cohort of the study			NSTEMI cohort of the study			*P*-value for interaction
	Control (1030)	Experimental (1062)	Hazard ratio (95% CI)	Control (1018)	Experimental (1004)	Hazard ratio (95% CI)	
0–30 days	15 (1.5%)	15 (1.4%)	0.97 (0.47–1.98)	9 (0.5%)	6 (0.4%)	0.67 (0.24–1.88)	0.56
31–365 days	17 (1.7%)	12 (1.1%)	0.62 (0.24–1.59)	42 (2.5%)	31 (1.8%)	0.74 (0.46–1.17)	0.86
At 365 days	32 (4.1%)	27 (2.5%)	0.82 (0.49–1.36)	51 (3.0%)	37 (2.2%)	0.73 (0.47–1.11)	0.73
At 730 days	54 (5.2%)	50 (4.7%)	0.89 (0.61–1.31)	84 (5.0%)	72 (4.3%)	0.86 (0.62–1.17)	0.86

CI, confidence interval; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 4 Rates of secondary endpoints (bleeding academic research consortium 3 or 5 bleeding) between ST-elevation myocardial infarction and non-ST-elevation myocardial infarction cohorts in the GLOBAL LEADERS study at 30, 31–365, 365, and 730 days of follow-up

	STEMI cohort of the study			NSTEMI cohort of the study			*P*-value for interaction
	Control (1030)	Experimental (1062)	Hazard ratio (95% CI)	Control (1018)	Experimental (1004)	Hazard ratio (95% CI)	
0–30 days	11 (1.1%)	7 (0.7%)	0.62 (0.24–1.59)	12 (0.7%)	17 (1.0%)	1.42 (0.68–2.98)	0.17
31–365 days	10 (1.0%)	5 (0.5%)	0.48 (0.17–1.42)	29 (1.8%)	16 (1.0%)	0.55 (0.30–1.02)	0.83
At 365 days	21 (2.1%)	12 (1.1%)	0.55 (0.27–1.13)	41 (2.5%)	33 (2.0%)	0.81 (0.51–1.28)	0.38
At 730 days	24 (2.4%)	15 (1.4%)	0.61 (0.32–1.16)	49 (3.0%)	44 (2.7%)	0.90 (0.60–1.53)	0.31

CI, confidence interval; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 5 Rates of primary composite endpoints (composite of death and new Q myocardial infarction) between ST-elevation myocardial infarction and unstable angina cohorts in the GLOBAL LEADERS study at 30, 31–365, 365, and 730 days of follow-up

	STEMI cohort of the study			UA cohort of the study			*P*-value for interaction
	Control (1030)	Experimental (1062)	Hazard ratio (95% CI)	Control (1018)	Experimental (1004)	Hazard ratio (95% CI)	
0–30 days	15 (1.5%)	15 (1.4%)	0.97 (0.47–1.98)	4 (0.4%)	1 (0.1%)	0.25 (0.03–2.27)	0.25
31–365 days	17 (1.7%)	12 (1.1%)	0.62 (0.24–1.59)	16 (1.6%)	12 (1.2%)	1.42 (0.68–2.98)	0.85
At 365 days	32 (4.1%)	27 (2.5%)	0.82 (0.49–1.36)	20 (2.0%)	13 (1.3%)	0.65 (0.33–1.32)	0.62
At 730 days	54 (5.2%)	50 (4.7%)	0.89 (0.61–1.31)	31 (3.0%)	25 (2.5%)	0.82 (0.48–1.37)	0.77

CI, confidence interval; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Table 6 Rates of secondary endpoints (bleeding academic research consortium 3 or 5 bleeding) between ST-elevation myocardial infarction and unstable angina cohorts in the GLOBAL LEADERS study at 30, 31–365, 365, and 730 days of follow-up

	STEMI cohort of the study			UA cohort of the study			*P*-value for interaction
	Control (1030)	Experimental (1062)	Hazard ratio (95% CI)	Control (1018)	Experimental (1004)	Hazard ratio (95% CI)	
0–30 days	11 (1.1%)	7 (0.7%)	0.62 (0.24–1.59)	11 (1.1%)	5 (0.5%)	0.46 (0.16–1.32)	0.68
31–365 days	10 (1.0%)	5 (0.5%)	0.48 (0.17–1.42)	15 (1.5)	7 (0.7%)	0.47 (0.19–1.15)	0.96
At 365 days	21 (2.1%)	12 (1.1%)	0.55 (0.27–1.13)	26 (2.6%)	12 (1.2%)	0.46 (0.23–0.92)	0.73
At 730 days	24 (2.4%)	15 (1.4%)	0.61 (0.32–1.16)	27 (2.7%)	14 (1.4%)	0.52 (0.27–0.99)	0.75

CI, confidence interval; STEMI, ST-elevation myocardial infarction, UA, unstable angina.

Table 7 Rates of primary composite endpoints (composite of death and new Q myocardial infarction) between ST-elevation myocardial infarction and chronic coronary syndrome cohorts in the GLOBAL LEADERS study at 30, 31–365, 365, and 730 days of follow-up

	STEMI cohort of the study			CCS cohort of the study			*P*-value for interaction
	Control (1030)	Experimental (1062)	Hazard ratio (95% CI)	Control (4251)	Experimental (4230)	Hazard ratio (95% CI)	
0–30 days	15 (1.5%)	15 (1.4%)	0.97 (0.47–1.98)	14 (0.3%)	12 (0.3%)	0.86 (0.40–1.86)	0.83
31–365 days	17 (1.7%)	12 (1.1%)	0.62 (0.24–1.59)	80 (1.9%)	67 (1.6%)	0.84 (0.61–1.16)	0.61
At 365 days	32 (4.1%)	27 (2.5%)	0.82 (0.49–1.36)	94 (2.2%)	79 (1.9%)	0.84 (0.63–1.14)	0.91
At 730 days	54 (5.2%)	50 (4.7%)	0.89 (0.61–1.31)	180 (3.9%)	157 (3.3%)	0.82 (0.48–1.37)	0.93

CCS, chronic coronary syndrome; CI, confidence interval; STEMI, ST-elevation myocardial infarction,.

Table 8 Rates of secondary endpoints (bleeding academic research consortium 3 or 5 bleeding) and between ST-elevation myocardial infarction and chronic coronary syndrome cohorts in the GLOBAL LEADERS study at 30, 31–365, 365, and 730 days of follow-up

	STEMI cohort of the study			CCS cohort of the study			*P*-value for interaction
	Control (1030)	Experimental (1062)	Hazard ratio (95% CI)	Control (4251)	Experimental (4230)	Hazard ratio (95% CI)	
0–30 days	11 (1.1%)	7 (0.7%)	0.62 (0.24–1.59)	14 (0.3%)	22 (0.5%)	1.58 (0.81–3.09)	0.11
31–365 days	10 (1.0%)	5 (0.5%)	0.48 (0.17–1.42)	34 (0.8%)	38 (0.9%)	1.13 (0.71–1.80)	0.15
At 365 days	21 (2.1%)	12 (1.1%)	0.55 (0.27–1.13)	48 (1.1%)	60 (1.4%)	1.26 (0.86–1.85)	0.04
At 730 days	24 (2.4%)	15 (1.4%)	0.61 (0.32–1.16)	69 (1.6%)	90 (2.2%)	1.32 (0.96–1.81)	0.03

CCS, chronic coronary syndrome; CI, confidence interval; STEMI, ST-elevation myocardial infarction.

Additional *post hoc* subgroup analyses using exploratory outcomes

In a *post hoc* analysis, there was no significant difference in rates of NACE across all high-risk STEMI subgroups in both control and experimental treatment groups at 1 year and 2 years follow-up (*Tables 12* and *13*).

At 2 years, STEMI patients who underwent complex PCI experienced significant reduction in rates of POCE when treated with the experimental strategy. Rates of POCE did not vary significantly in other high-risk subgroups treated with either treatment strategy after 1 year and 2 years (*Tables 14* and *15*).

At 1-year follow-up, the experimental strategy was associated with significant reduction in the rates of BARC 3 or 5 bleeding in males and in patients with no history of CKD as compared to the reference group. The benefit of ticagrelor monotherapy in reducing the risks of bleeding in these STEMI patients' subgroups persisted up to 2 years of the follow-up. Nevertheless, at 1 year and 2 years of follow-up there were no significant differences in rates of BARC bleeding for both treatment arms in all other patients' subsets (*Tables 16* and *17*).

Discussion

Here, we present a *post hoc* analysis evaluating the efficacy and safety of aspirin cessation after 1 month course of DAPT, followed by the sole use of the potent $P2Y_{12}$ receptor antagonist—ticagrelor in the subgroup of STEMI patients undergoing primary PCI.

Table 9 Rates of other GLOBAL LEADERS predefined ischaemic and bleeding endpoints in ST-elevation myocardial infarction population at 1 year

Characteristics	Reference group (1030)	Experimental group (1062)	Hazard ratio (95% CI)	*P*-value
Death	24 (2.3%)	24 (2.3%)	0.97 (0.55–1.71)	0.91
New Q wave MI	9 (0.9%)	3 (0.3%)	0.32 (0.90–1.20)	0.90
All MI	21 (2.1%)	28 (2.7%)	1.30 (0.74–2.29)	0.36
Stroke	6 (0.6%)	7 (0.7%)	1.31 (0.38–3.37)	0.82
Repeat revascularization	67 (6.6%)	74 (7.1%)	1.08 (0.77–1.50)	0.66
BARC 5 bleeding	4 (0.4%)	2 (0.2%)	0.49 (0.09–2.65)	0.40
BARC 3 bleeding	19 (1.9%)	11 (1.1%)	0.56 (0.27–1.18)	0.13
BARC 2 bleeding	41 (4.1%)	42 (4.0%)	1.00 (0.65–1.54)	1.00
BARC 2, 3, and 5	59 (5.8%)	52 (5.0%)	0.86 (0.59–1.25)	0.42
Definite stent thrombosis	14 (1.4%)	14 (1.3%)	0.97 (0.46–2.04)	0.94
Probable stent thrombosis	7 (0.7%)	7 (0.7%)	0.97 (0.34–2.77)	0.96
Stent thrombosis (both probable and definite)	21 (2.0%)	21 (2.0%)	0.97 (0.53–1.78)	0.92

BARC, bleeding academic research consortium; CI, confidence interval; MI, myocardial infarction.

Table 10 Rates of other GLOBAL LEADERS predefined ischaemic and bleeding endpoints in ST-elevation myocardial infarction population at 2 years

Characteristics	Reference group (1030)	Experimental group (1062)	Hazard ratio (95% CI)	*P*-value
Death	46 (4.5%)	41 (3.9%)	0.86 (0.57–1.31)	0.50
New Q wave MI	10 (1.0%)	9 (0.9%)	0.87 (0.35–2.14)	0.76
All MI	37 (3.7%)	39 (3.8%)	1.03 (0.66–1.61)	0.90
Stroke	12 (1.2%)	8 (0.8%)	0.65 (0.26–1.59)	0.34
Repeat revascularization	92 (9.1%)	97 (9.4%)	1.03 (0.77–1.37)	0.85
BARC 5 bleeding	5 (0.5%)	4 (0.4%)	0.78 (0.21–2.90)	0.71
BARC 3 bleeding	22 (2.2%)	13 (1.3%)	0.57 (0.29–1.14)	0.11
BARC 2 bleeding	46 (4.6%)	47 (4.5%)	1.00 (0.66–1.50)	0.99
BARC 2, 3, and 5	66 (6.5%)	60 (5.8%)	0.88 (0.62–1.26)	0.49
Definite stent thrombosis	20 (2.0%)	15 (1.4%)	0.73 (0.37–1.42)	0.35
Probable stent thrombosis	7 (0.7%)	7 (0.7%)	0.97 (0.34–2.77)	0.96
Stent thrombosis (both probable and definite)	27 (2.6%)	22 (2.1%)	0.79 (0.45–1.39)	0.41

BARC, bleeding academic research consortium; CI, confidence interval; MI, myocardial infarction.

The salient findings of this study can be summarized as follows:

(1) In GLOBAL LEADERS trial, rates of predefined primary and secondary endpoints were similar in patients with STEMI.
(2) The rates of NACE and POCE did not differ between the experimental and the reference treatment strategy over the 2-year follow-up period.
(3) The experimental treatment strategy tended to reduce the rates of clinically relevant bleeding (BARC-defined bleeding Type 3 or 5), compared with the reference strategy. While landmark analyses indicated that the observed bleeding risk reduction was confined primarily to the first year of therapy, the benefit of ticagrelor monotherapy in reducing the bleeding risk appeared to be maintained during the second year of follow-up without additional divergence of the cumulative event curves during the second year.
(4) In a series of analyses performed among STEMI subjects with particularly high-risk clinical features such as patients at advanced age, diabetics or patients with CKD, HBR, we observed comparable rates of ischaemic and bleeding events in the reference and experimental arms.

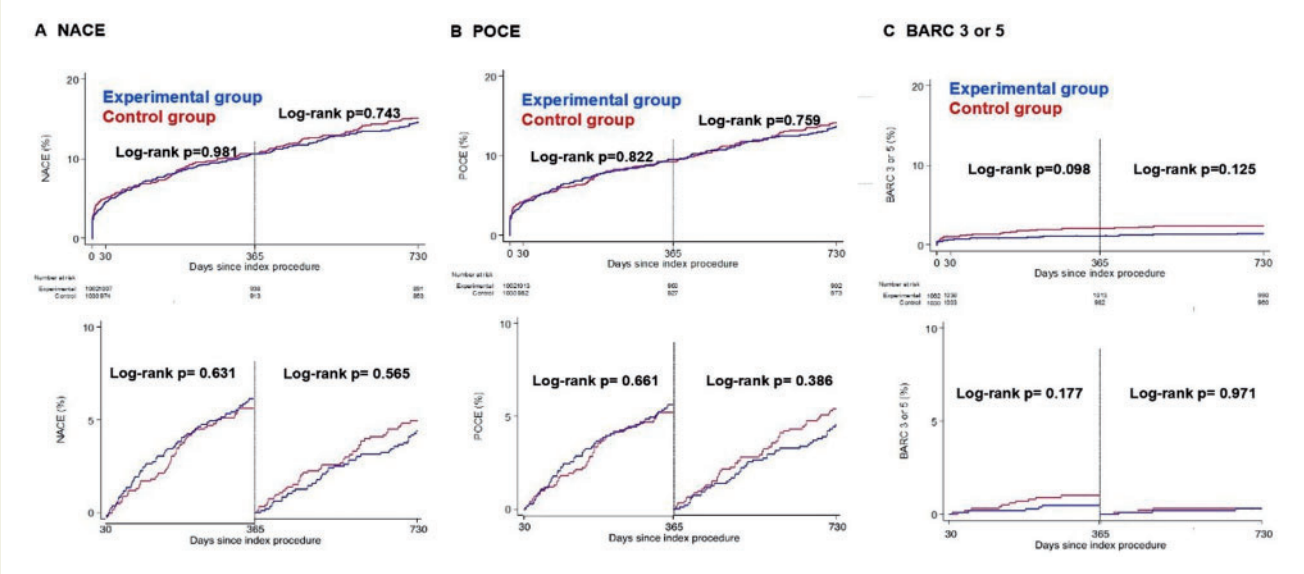


Figure 2 Clinical events in ST-elevation myocardial infarction patients. BARC, bleeding academic research consortium; NACE, net adverse clinical events; POCE, patient-oriented composite endpoints.

Table 11 Comparison of rates of net adverse clinical events, patient-oriented composite endpoints, and bleeding academic research consortium 3 or 5 bleeding in both experimental and control groups at 1 year and 2 years follow-up

Event	Reference (n = 1030)	Experimental (n = 1062)	Hazard ratio (95% CI)	P-value
NACE				
From 0 to 365 days	109 (10.6%)	112 (10.6%)	1.0 (0.76–1.30)	0.98
From 366 to 730 days	46 (5.0%)	42 (4.5%)	0.88 (0.58–1.34)	0.56
Overall (from 0 to 730 days)	155 (15.1%)	154 (14.6%)	0.96 (0.77–1.20)	0.74
POCE				
From 0 to 365 days	95 (9.3%)	101 (9.6%)	1.03 (0.78–1.37)	0.82
From 366 to 730 days	50 (5.4%)	43 (4.5%)	0.83 (0.56–1.25)	0.39
Overall (from 0 to 730 days)	145 (14.2%)	144 (13.7%)	0.96 (0.77–1.21)	0.76
BARC 3 or 5				
From 0 to 365 days	21 (2.1%)	12 (1.1%)	0.55 (0.27–1.13)	0.63
From 366 to 730 days	3 (0.3%)	3 (0.3%)	0.97 (0.20–4.8)	0.97
Overall (from 0 to 730 days)	24 (2.4%)	15 (1.4%)	0.61 (0.32–1.16)	0.13

BARC, bleeding academic research consortium; CI, confidence interval; NACE, net adverse clinical events; POCE, patient-oriented composite endpoints.

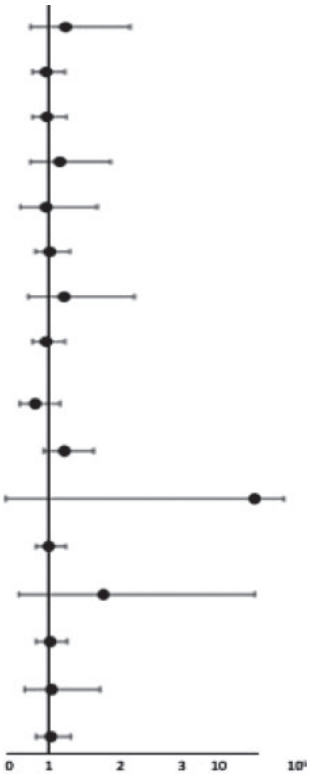
(5) In terms of the bleeding events, ticagrelor monotherapy was more favourable in males and in those with no CKD.

(6) At 2 years, ticagrelor monotherapy resulted in significant reduction of POCE in STEMI patients who had complex PCI.

These findings need to be interpreted with caution since these analyses were not prespecified and the parent trial did not meet its primary endpoint.[7] Although the present findings suggest a potentially higher risk of bleeding in the control treatment strategy in males and in patients with no history of renal impairment, this could be the play of chance given the infrequent bleeding events in the studied cohort and the multiple treatment comparisons. Furthermore, comprehensive evaluation of net clinical benefit of antiplatelet regimens remains challenging; it should be noted that the resulting expected relative risk reduction of NACE—combining efficacy and safety into a single measure—is usually lower than the separate impact of evaluated

Table 12 Subgroup analysis for net adverse clinical events in ST-elevation myocardial infarction patients at 1 year

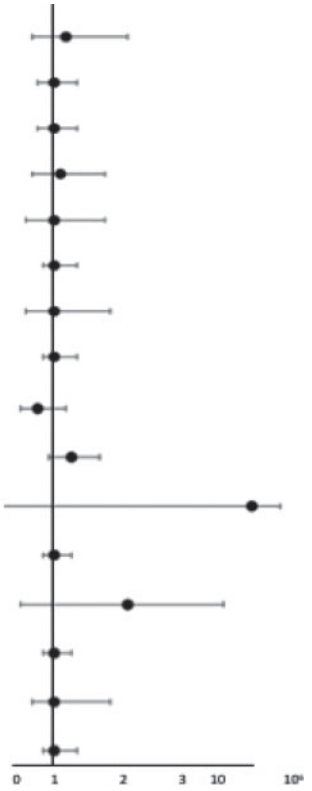
Characteristics	1 year NACE, *n* (%)		Hazard ratio (95% CI)	*P*-value	*P*-value for interaction	Favors ticagrelor monotherapy after 1-month DAPT	Favors DAPT for 12 months
	Reference strategy (*n* = 1030)	Experimental strategy (*n* = 1062)					
Age (years)							
>75	16 (14.3)	24 (17.4)	1.26 (0.67–2.37)	0.48	0.40		
≤75	93 (10.2)	88 (9.6)	0.93 (0.70–1.25)	0.65			
Gender							
Male	88 (10.7)	83 (10.3)	0.95 (0.70–1.28)	0.73	0.81		
Female	21 (10.2)	29 (11.6)	1.17 (0.67–2.05)	0.58			
DM							
Yes	20 (12.1)	19 (11.4)	0.94 (0.50–1.76)	0.85	0.87		
No	89 (10.4)	92	1.0 (0.75–1.34)	0.99			
CKD							
Yes	13 (13.8)	23 (16.9)	1.24 (0.63–2.45)	0.53	0.45		
No	96 (10.3)	89 (9.7)	0.94 (0.70–1.25)	0.66			
Complex PCI							
Yes	43 (13.6)	32 (10.1)	0.73 (0.46–1.15)	0.17	0.07		
No	58 (8.6)	74 (10.5)	1.23 (0.87–1.73)	0.24			
Prev. bleeding							
Yes	0 (0)	3 (37.5)	57.33 (0.005–647617.31)	0.39	0.91		
No	109 (10.7)	108 (10.3)	0.96 (0.74–1.25)	0.77			
HB ≤11 g/dL							
Yes	3 (12.5)	5 (22.0)	1.89 (0.45–7.92)	0.38	0.37		
No	103 (10.6)	105 (10.4)	0.98 (0.74–1.28)	0.86			
Mild anaemia[a]							
Yes	21 (17.7)	22 (17.7)	1.01 (0.55–1.84)	0.97	0.97		
No	85 (9.7)	88 (9.7)	0.99 (0.74–1.34)	0.97			



Number of reported first events and their percentages.
CI, confidence interval; CKD, chronic kidney disease; DM, Diabetes mellitus; HB, haemoglobin; NACE, net adverse clinical events; PCI, percutaneous coronary intervention.
[a]Mild anaemia refers to haemoglobin <11–12.9 g/dL for men and 11–11.9 g/dL for women.

Table 13 Subgroup analysis for net adverse clinical events in ST-elevation myocardial infarction patients at 2 years

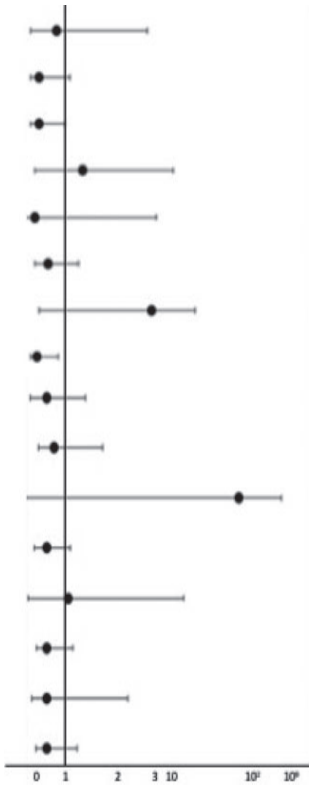
Characteristics	2 years NACE, *n* (%)		Hazard ratio (95% CI)	*P*-value	*P*-value for interaction	Favors ticagrelor monotherapy after 1-month DAPT	Favors DAPT for 12 months
	Reference strategy (*n* = 1030)	Experimental strategy (*n* = 1062)					
Age (years)							
>75	27 (24.2)	29 (21.1)	0.90 (0.53–1.51)	0.68	0.80		
≤75	128 (14.0)	125 (13.6)	0.96 (0.75–1.23)	0.78			
Gender							
Male	123 (15.0)	117 (14.6)	0.96 (0.74–1.23)	0.74	0.48		
Female	32 (15.7)	37 (14.9)	0.97 (0.61–1.56)	0.91			
DM							
Yes	37 (22.5)	28 (16.8)	0.74 (0.45–1.20)	0.22	0.24		
No	117 (13.6)	125 (14.1)	1.03 (0.80–1.33)	0.80			
CKD							
Yes	22 (23.4)	27 (19.9)	0.86 (0.49–1.51)	0.59	0.71		
No	123 (14.3)	127 (13.9)	0.96 (0.76–1.23)	0.78			
Complex PCI							
Yes	61 (19.4)	46 (14.6)	0.73 (0.50–1.07)	0.10	0.07		
No	85 (12.7)	100 (14.2)	1.14 (0.85–1.52)	0.38			
Prev. bleeding							
Yes	1 (16.7)	3 (37.5)	2.83 (0.29–27.42)	0.37	0.32		
No	154 (15.1)	150 (14.4)	0.94 (0.75–1.18)	0.62			
HB ≤11 g/dL							
Yes	7 (29.2)	7 (31.2)	1.19 (0.42–3.39)	0.75	0.73		
No	143 (14.7)	144 (14.2)	0.96 (0.76–1.21)	0.75			
Mild anaemia[a]							
Yes	29 (24.5)	27 (21.8)	0.90 (0.53–1.52)	0.69	0.76		
No	121 (13.8)	124 (13.6)	0.98 (0.77–1.26)	0.90			



Number of reported first events and their percentages.
CI, confidence interval; CKD, chronic kidney disease; DM, Diabetes mellitus; HB, haemoglobin; NACE, net adverse clinical events; PCI, percutaneous coronary intervention.
[a]Mild anaemia refers to haemoglobin <11–12.9 g/dL for men and 11–11.9 g/dL for women.

Table 14 Subgroup analysis for patient-oriented composite endpoints in ST-elevation myocardial infarction patients at 1 year

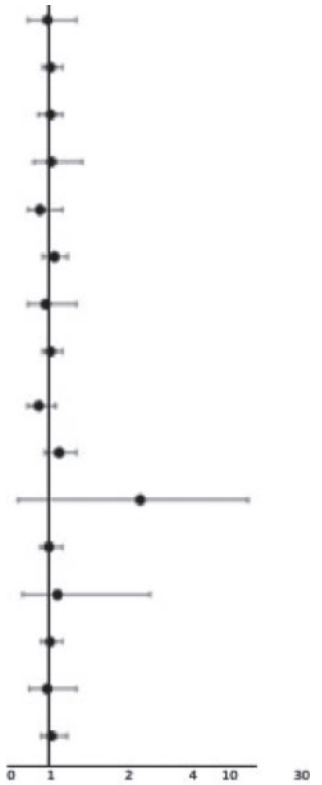
Characteristics	1 year POCE, *n* (%)		Hazard ratio (95% CI)	*P*-value	*P*-value for interaction	Favors ticagrelor monotherapy after 1-month DAPT	Favors DAPT for 12 months
	Reference strategy (*n* = 1030)	Experimental strategy (*n* = 1062)					
Age (years)							
>75	15 (13.4)	21 (15.3)	1.16 (0.60–2.25)	0.66	0.67		
≤75	80 (8.8)	80 (8.7)	0.99 (0.73–1.35)	0.96			
Gender							
Male	75 (9.1)	75 (9.3)	1.01 (0.73–1.39)	0.95	0.79		
Female	20 (9.7)	26 (10.4)	1.09 (0.61–1.96)	0.76			
DM							
Yes	19 (11.5)	19 (11.4)	0.99 (0.53–1.87)	0.98	0.92		
No	76 (8.8)	81 (9.1)	1.03 (0.75–1.41)	0.85			
CKD							
Yes	13 (13.8)	19 (14.0)	1.01 (0.50–2.04)	0.98	0.99		
No	82 (8.8)	82 (9.0)	1.01 (0.75–1.38)	0.93			
Complex PCI							
Yes	35 (11.0)	26 (8.2)	0.72 (0.44–1.20)	0.21	0.08		
No	53 (7.9)	69 (9.8)	1.25 (0.88–1.79)	0.22			
Prev. bleeding							
Yes	0 (0)	2 (25.0)	53.49 (0.001–5165358.80)	0.50	0.90		
No	95 (9.3)	98 (9.4)	1.003 (0.76–1.33)	0.98			
HB ≤11 g/dL							
Yes	2 (8.3)	4 (17.7)	2.34 (0.43–12.80)	0.33	0.35		
No	90 (9.2)	95 (9.4)	1.01 (0.76–1.35)	0.94			
Mild anaemia[a]							
Yes	17 (14.3)	19 (15.3)	1.08 (0.56–2.08)	0.81	0.89		
No	75 (8.5)	80 (8.8)	1.02 (0.75–1.40)	0.88			



Number of reported first events and their percentages.
CI, confidence interval; CKD, chronic kidney disease; DM, Diabetes mellitus; HB, haemoglobin; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoints.
[a]Mild anaemia refers to haemoglobin <11–12.9 g/dL for men and 11–11.9 g/dL for women.

Table 15 Subgroup analysis for patient-oriented composite endpoints in ST-elevation myocardial infarction patients at 2 years

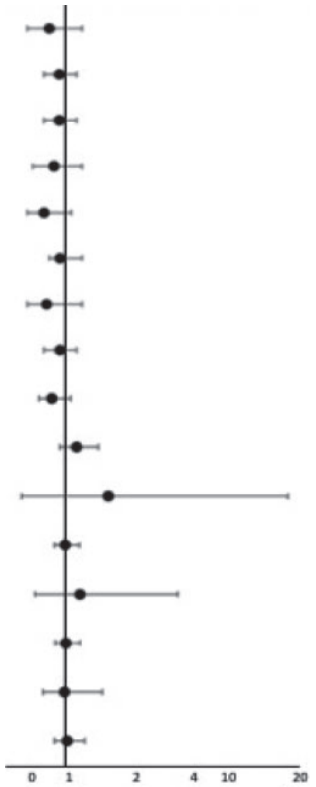
Characteristics	2 years POCE, *n* (%)		Hazard ratio (95% CI)	*P*-value	*P*-value for interaction	Favors ticagrelor monotherapy after 1-month DAPT	Favors DAPT for 12 months
	Reference strategy (*n* = 1030)	Experimental strategy (*n* = 1062)					
Age (years)							
>75	25 (22.4)	25 (18.2)	0.82 (0.47–1.43)	0.49	0.57		
≤75	120 (13.1)	119 (13.0)	0.98 (0.76–1.27)	0.90			
Gender							
Male	114 (13.9)	111 (13.8)	0.98 (0.76–1.28)	0.91	0.22		
Female	31 (15.2)	33 (13.3)	0.89 (0.55–1.45)	0.64			
DM							
Yes	37 (22.5)	27 (16.2)	0.71 (0.43–1.17)	0.18	0.18		
No	107 (12.5)	116 (13.1)	1.05 (0.81–1.37)	0.71			
CKD							
Yes	21 (22.3)	23 (16.9)	0.75 (0.41–1.35)	0.34	0.40		
No	124 (13.3)	121 (13.3)	0.99 (0.77–1.27)	0.94			
Complex PCI							
Yes	57 (18.1)	41 (13.0)	0.70 (0.47–1.04)	0.08	0.050		
No	80 (11.9)	95 (13.5)	1.15 (0.85–1.54)	0.36			
Prev. bleeding							
Yes	1 (16.7)	2 (25.0)	1.73 (0.16–19.15)	0.65	0.61		
No	144 (14.1)	141 (13.5)	0.95 (0.75–1.20)	0.68			
HB ≤11 g/dL							
Yes	6 (25.0)	6 (26.8)	1.21 (0.39–3.75)	0.74	0.74		
No	134 (13.8)	135 (13.3)	0.96 (0.76–1.22)	0.77			
Mild anaemia[a]							
Yes	26 (22.0)	25 (20.2)	0.94 (0.54–1.62)	0.81	0.96		
No	114 (13.0)	116 (12.7)	0.98 (0.75–1.27)	0.86			



Number of reported first events and their percentages.
CI, confidence interval; CKD, chronic kidney disease; DM, Diabetes mellitus; HB, haemoglobin; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoints.
[a]Mild anaemia refers to haemoglobin <11–12.9 g/dL for men and 11–11.9 g/dL for women.

Table 16 Subgroup analysis for bleeding academic research consortium 3 or 5 bleeding in ST-elevation myocardial infarction patients at 1 year

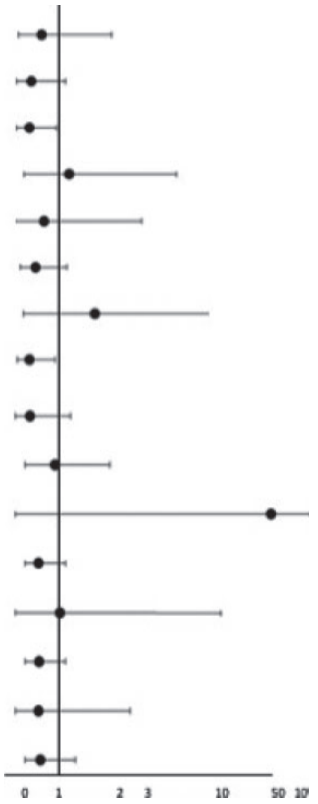
Characteristics	1 year BARC 3 or 5, *n* (%)		Hazard ratio (95% CI)	*P*-value	*P*-value for interaction	Favors ticagrelor monotherapy after 1-month DAPT	Favors DAPT for 12 months
	Reference strategy (*n* = 1030)	Experimental strategy (*n* = 1062)					
Age (years)							
>75	5 (4.6)	5 (3.6)	0.83 (0.24–2.85)	0.76	0.40		
≤75	16 (1.8)	7 (0.8)	0.43 (0.18–1.05)	0.06			
Gender							
Male	18 (2.2)	7 (0.9)	0.39 (0.16–0.94)	0.036[a]	0.14		
Female	3 (1.5)	5 (2.0)	1.39 (0.33–5.80)	0.65			
DM							
Yes	3 (1.8)	1 (0.6)	0.34 (0.04–3.24)	0.35	0.64		
No	18 (2.1)	11 (1.2)	0.59 (0.28–1.25)	0.17			
CKD							
Yes	1 (1.1)	5 (3.7)	3.51 (0.41–30.09)	0.25	0.051		
No	20 (2.2)	7 (0.8)	0.35 (0.15–0.84)	0.02[a]			
Complex PCI							
Yes	10 (3.2)	5 (1.6)	0.49 (0.17–1.44)	0.19	0.67		
No	10 (1.5)	7 (1.0)	0.67 (0.25–1.76)	0.42			
Prev. bleeding							
Yes	0 (0)	1 (12.5)	50.52 (0.00–621500322.71)	0.64	0.94		
No	21 (2.1)	11 (1.1)	0.51 (0.24–1.05)	0.07			
HB ≤11 g/dL							
Yes	1 (4.2)	1 (4.3)	1.00 (0.06–15.99)	1.00	0.63		
No	20 (2.1)	11 (1.1)	0.53 (0.25–1.10)	0.09			
Mild anaemia[a]							
Yes	5 (4.3)	3 (2.4)	0.57 (.14–2.39)	0.44	0.95		
No	16 (1.8)	9 (1.0)	0.54 (0.24–1.22)	0.14			



Number of reported first events and their percentages.
BARC, bleeding academic research consortium; CI, confidence interval; CKD, chronic kidney disease; DM, Diabetes mellitus; HB, haemoglobin; PCI, percutaneous coronary intervention.
[a]Mild anaemia refers to haemoglobin <11–12.9 g/dL for men and 11–11.9 g/dL for women.

Table 17 Subgroup analysis for bleeding academic research consortium 3 or 5 bleeding in ST-elevation myocardial infarction patients at 2 years

Characteristics	2 years BARC 3 or 5, *n* (%)		Hazard ratio (95% CI)	*P*-value	*P*-value for interaction	Favors ticagrelor monotherapy after 1-month DAPT	Favors DAPT for 12 months
	Reference strategy (*n* = 1030)	Experimental strategy (*n* = 1062)					
Age (years)							
>75	7 (6.5)	6 (4.4)	0.71 (0.24–2.12)	0.54	0.66		
≤75	17 (1.9)	9 (1.0)	0.52 (0.23–1.18)	0.12			
Gender:							
Male	20 (2.5)	9 (1.1)	0.46 (0.21–1.00)	0.05	0.19		
Female	4 (2.0)	6 (2.4)	1.25 (0.35–4.42)	0.73			
DM							
Yes	4 (2.5)	3 (1.9)	0.75 (0.17–3.37)	0.71	0.75		
No	20 (2.4)	12 (1.4)	0.58 (0.28–1.18)	0.13			
CKD							
Yes	2 (2.2)	5 (3.7)	1.76 (0.34–9.09)	0.50	0.14		
No	22 (2.4)	10 (1.1)	0.46 (0.22–0.97)	0.04[a]			
Complex PCI							
Yes	12 (3.9)	5 (1.6)	0.41 (0.14–1.16)	0.09	0.27		
No	11 (1.6)	10 (1.4)	0.87 (0.37–2.05)	0.75			
Prev. bleeding							
Yes	0 (0)	1 (12.5)	50.52 (0.00–621500322.71)	0.64	0.94		
No	24 (2.4)	14 (1.4)	0.57 (0.29–1.10)	0.09			
HB ≤11 g/dL							
Yes	1 (4.2)	1 (4.3)	1.00 (0.06–15.99)	1.00	0.67		
No	23 (2.4)	14 (1.4)	0.58 (0.30–1.13)	0.11			
Mild anaemia[a]							
Yes	5 (4.3)	3 (2.4)	0.57 (0.14–2.39)	0.44	0.95		
No	19 (2.2)	12 (1.3)	0.61 (0.29–1.25)	0.18			



Number of reported first events and their percentages.
BARC, bleeding academic research consortium; CI, confidence interval; CKD, chronic kidney disease; DM, Diabetes mellitus; HB, haemoglobin; PCI, percutaneous coronary intervention.
[a]Mild anaemia refers to haemoglobin <11–12.9 g/dL for men and 11–11.9 g/dL for women.

treatment strategies on either efficacy or safety, considering antiplatelet agents have opposite effects on these outcomes. Notwithstanding these limitations, our report extends the understanding of the safety and efficacy of aspirin-free antiplatelet regimens in the early phase after primary PCI.[21]

The results of large randomized clinical trial have recently suggested that stopping aspirin after 3 months of uneventful DAPT comprising $P2Y_{12}$ antagonist and aspirin could reduce the risk of clinically relevant bleeding, with no higher risk of death, MI, or stroke, as compared to standard 12-month DAPT regimen.[8,22] Clinical presentation with STEMI is considered, however, as a highly prothrombotic condition often associated with recurrent ischaemic events.

Notably, our study provides unique insights on the risk–benefit ratio of aspirin use in this specific patients subset, given that in some trials like TWILIGHT, STEMI patients were a priori excluded by trial protocol.[22] Previously reported *post hoc* landmark analyses of the GLOBAL LEADERS trial did not include any analysis pertaining specifically to STEMI population, known for its distinct pathophysiology such as acute thrombotic setting, with usually high thrombus burden, more pronounced inflammatory response, and reportedly more pronounced prothrombotic tendency of circulating blood.[11]

Only one study has evaluated aspirin-free antiplatelet strategy in STEMI to date: the TICO-STEMI sub-analysis, which showed that STEMI patients treated with ultrathin bioresorbable polymer sirolimus-eluting stents and receiving ticagrelor monotherapy after 3-month DAPT had reduced risk of major bleeding compared with patients who received ticagrelor-based 12-month DAPT. Our findings are consistent with these observations and suggest that even an earlier cessation of DAPT at 1 month post-primary PCI, with continuation of a potent $P2Y_{12}$ antagonist monotherapy, could be safe and avoids an excess of bleeding risk in the STEMI setting.

Importantly, differences in bleeding endpoints definitions between the trials need to be considered; the key safety endpoint in GLOBAL LEADERS and TWILIGHT included BARC 3 or 5 type and BARC 2, 3, or 5 type bleeding, respectively, whereas the TICO trial defined its bleeding endpoint according to the TIMI criteria (fatal bleeding, overt bleeding with drop in haemoglobin ≥5 g/dL or a 15% drop in haematocrit, and any intracranial haemorrhage).[7,10,16,22]

The strength of GLOBAL LEADERS—conducted at 130 sites in 18 countries from 5 continents with majority from Europe—resides in external generalizability of its findings.[14] This contrasts with the TICO, STOP-DAPT 2, or SMART CHOICE trials restricted to specific Japanese or Korean patient populations, and caution is needed in extrapolating results outside of these investigating countries.[10,23,24]

Finally, our results need to be put in perspective of recent *post hoc* analysis of the ISAR REACT-5 trial suggesting similar event rates in STEMI patients treated DAPT including either ticagrelor or prasugrel, yet ticagrelor was associated with a significant increase in the risk for recurrent MI. Therefore, prasugrel might well be considered in future studies addressing aspirin—free strategies in STEMI setting. Aspirin-free prasugrel monotherapy following successful PCI has already demonstrated feasibility and safety without any stent thrombosis in selected low-risk patients with stable CAD.[9,25,26]

Limitations

The following limitations need to be considered while interpreting the results of this study. It is a *post hoc* analysis not prespecified in the GLOBAL LEADERS study design. Given the *post hoc* nature of the analysis, our findings should not necessitate changes in recommendations for practice by professional associations and regulatory agencies but all reported findings should rather be considered only as hypothesis-generating and need to be replicated in dedicated large-scale randomized trials.[20,27] In the primary endpoint analysis, GLOBAL LEADERS trial failed to reach its primary endpoint, and the presented secondary analysis, as in the parent trial, was not powered to detect between-group differences in clinical event rates.[7] Similarly, according to the present sample size (1030 vs. 1062 patients), the events comparison analysis between the two treatment arms has to be considered underpowered. Indeed, as regards the statistical difference of BARC 3 or 5 rates, with a probability of a Type 1 error of 0.05, power of 80%, and the reported event rates, the required sample sizes would be 4940 (2470 per arm) and 5850 (2925 per arm) at 1 year and 2 years, respectively.

Although the clinical profile of GLOBAL LEADERS patients was generally less severe compared with the patients enrolled in PLATO, ticagrelor monotherapy significantly reduced the risk of ischaemic events without increasing the risk of bleeding in high-risk patients subgroups such as subjects undergoing complex PCI, multivessel PCI, PCI of proximal LAD, or interventions with overall high total length of stents implanted.[18,28–30] Similarly, the current exploratory sensitivity analyses performed in our STEMI patients with widely recognized clinical high-risk features indicated consistent efficacy and safety of ticagrelor monotherapy in those patients with very high ischaemic risk.

Investigator reporting was used without central adjudication for secondary outcomes. This aspect should be considered in particular when interpreting bleeding event rates due to more complex definitions related to bleeding subtypes and numerous classifications like BARC, GUSTO, TIMI, etc., which are more prone to be confused by the investigators. Nevertheless, use of site-reported endpoints is a valid method in clinical research, especially when involving large cohorts and well-defined and restricted categories within a classification (i.e. BARC-defined bleeding Type 3–5 as compared with Type 1 and 2) are expected to provide higher concordance among sites and a central clinical event adjudication committee, as well as higher reproducibility.[31] Of note, the trial was monitored for event definition consistency and underreporting of the clinical endpoint, with onsite monitoring visits done at individual sites and one-fifth of events verified based on the source documentation. The GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) was performed to implement an independent adjudication process of reported as well as unreported potential adverse events in patients from the 20 top-enrolling participating sites in the GLOBAL LEADERS trial.[32]

GLASSY demonstrated that there were no significant differences between site-reported and adjudicated rates of stroke, MI, and BARC 3 or 5 type bleeding.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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