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Impact of proton pump inhibitors on efficacy of antiplatelet strategies with ticagrelor or aspirin after percutaneous coronary intervention: Insights from the GLOBAL LEADERS trial

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Abbreviations: ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CAD, coronary artery disease; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; NACE, net adverse clinical events; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoint; PPI, proton pump inhibitor.

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Abstract

Background: Several studies have suggested that proton pump inhibitors (PPIs) may reduce the antiplatelet effects of clopidogrel and/or aspirin, possibly leading to cardiovascular events.

Aims: We aimed to investigate the association between PPI and clinical outcomes in patients treated with ticagrelor monotherapy or conventional antiplatelet therapy after percutaneous coronary intervention (PCI).

Methods: This is a subanalysis of the randomized GLOBAL LEADERS trial, comparing the experimental antiplatelet arm (23-month ticagrelor monotherapy following 1-month dual antiplatelet therapy [DAPT]) with the reference arm (12-month aspirin monotherapy following 12-month DAPT) after PCI. Patient-oriented composite endpoints (POCEs: all-cause mortality, myocardial infarction, stroke, or repeat revascularization) and its components were assessed stratified by PPI use as a time-dependent covariate in patients with the experiment or reference antiplatelet arm.

Results: Among 15,839 patients, 2115 patients (13.5%) experienced POCE at 2 years. In the reference arm, the use of PPIs was independently associated with POCE (hazard ratio [HR]: 1.27; 95% confidence interval [CI]: 1.12–1.44) and its individual components, whereas it was not in the experimental arm (HR: 1.04; 95% CI: 0.92–1.19; $p_{\text{interaction}} = 0.035$). During the second-year follow-up, patients taking aspirin with PPIs had a significantly higher risk of POCE compared to those on aspirin without PPIs (HR: 1.57; 95% CI: 1.27–1.94), whereas the risk did not differ significantly irrespective of PPI in ticagrelor monotherapy group (HR: 1.03; 95% CI: 0.83–1.28; $p_{\text{interaction}} = 0.008$).

Conclusions: In contrast to conventional antiplatelet strategy, there were no evidence suggesting the interaction between ticagrelor monotherapy and PPIs on increased cardiovascular events, which should be confirmed in further studies.

Clinical Trial Registration: URL: https://clinicaltrials.gov

KEYWORDS
drug interaction, dual antiplatelet therapy, percutaneous coronary intervention, proton pump inhibitor, ticagrelor monotherapy

1 | INTRODUCTION

Antiplatelet therapy has been established as a standard of care in patients with coronary artery disease (CAD), especially after percutaneous coronary intervention (PCI), to reduce the risk of adverse ischemic events, although potent antiplatelet therapies augment the risk of bleeding.[1,2] In daily clinical practice, proton pump inhibitors (PPIs) are often prescribed together with antiplatelet agents to prevent upper gastrointestinal bleeding. However, previous studies have suggested that PPIs may reduce the antiplatelet effects of clopidogrel and/or aspirin, possibly leading to an increase in serious cardiovascular events.[3,4]

Numerous studies have reported conflicting results about the drug interaction between those antiplatelet agents and PPIs.[5–9] Thus far, a few randomized controlled trials comparing antiplatelet therapy with concomitant PPI in patients with cardiovascular disease have questioned whether any significant association exists between PPIs and adverse clinical outcomes when used together with clopidogrel or aspirin after PCI; however, there are scarce data on the interaction between PPIs and more potent $P2Y_{12}$ inhibitors, such as ticagrelor.[7]

Guideline recommendations on the use of PPIs in patients on dual antiplatelet therapy (DAPT) differ on both sides of the Atlantic. The European guidelines on DAPT recommend the routine use of PPIs when treated with DAPT (Class I), however they did not endorse extended use after discontinuation of DAPT.[10] The 2016 ACC/AHA guidelines on DAPT only gave a Class I recommendation for PPI use in patients treated with DAPT who had a history of gastrointestinal bleeding; the routine use of PPIs was not recommended (Class III).[2] Similarly, the 2019 ESC guidelines on chronic coronary syndrome (CCS) only recommended PPI use in those with high risk of GI bleeding (Class I).[11] Despite these recommendations, vast numbers of practitioners are still routinely prescribing PPIs without taking into account the potential risks and benefits.[12,13]

In the present subgroup analysis of the GLOBAL LEADERS trial, we aimed to investigate the effect of PPIs on clinical outcomes under different antiplatelet regimens, including DAPT, aspirin monotherapy, and ticagrelor monotherapy following PCI in the largest contemporary PCI cohort of an all-comers randomized controlled trial.

2 | METHODS

2.1 | Study design and patient population

The present study is a post hoc subgroup analysis of the GLOBAL LEADERS study (NCT01813435).[14] The details of the trial have been previously reported elsewhere.[14,15] In brief, the GLOBAL LEADERS study was an investigator-initiated, prospective randomized, multicenter, multicontinental, open-label trial designed to evaluate two antiplatelet strategies after PCI using uniformly bivalirudin and a biolimus A9 eluting stent (BioMatrix; Biosensors) in an all-comers population with no restriction regarding clinical presentation (CCS or acute coronary syndrome [ACS][13]), complexity of the lesions, or number of stents used.[14] Patients who required oral anticoagulation therapy after PCI, had known overt major bleeding, were planned for surgery within 12 months of PCI, or had severe hepatic impairment were not eligible for the study. In the experimental antiplatelet strategy arm, patients received aspirin 75–100 mg once daily in combination with ticagrelor 90 mg twice daily for 1 month after the index PCI; followed by ticagrelor 90 mg twice daily monotherapy for 23 months (from 1 to 24 months, regardless of the clinical presentation). In the conventional antiplatelet strategy arm (the reference arm), patients received aspirin 75–100 mg daily in combination with either clopidogrel 75 mg once daily in patients with CCS or ticagrelor 90 mg twice daily in patients with ACS for 1 year after the index PCI; followed by aspirin 75–100 mg once daily monotherapy for the following 12 months (from 12 to 24 months).

The institutional review board at each participating institution approved the GLOBAL LEADERS study. All patients provided informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practice. An independent data and safety monitoring committee oversaw the safety of all patients.

2.2 | PPI use

Patients had an outpatient clinic visit at 1, 3, 6, 12, 18, and 24 months after the index procedure. The status of PPI use was collected at discharge and subsequent clinical visits. Individual PPI type was not collected. In 20 patients (0.13%) who were hospitalized longer than 1 month after the index procedure, the PPI status at discharge were regarded as same as the PPI status at 1 month. Forty-four patients (0.28%) who died during the index hospitalization were excluded from the present analysis.

2.3 | Study end points

The primary endpoint of the present study was the patient-oriented composite endpoint (POCE) within 2 years of randomization, which was defined as a composite of all-cause mortality, any myocardial infarction (MI) (periprocedural or spontaneous), any stroke (ischemic, hemorrhagic, or uncertain), and any revascularization (re-PCI or coronary artery bypass graft surgery [CABG] in target or nontarget vessel) according to the Academic Research Consortium (ARC) II definition.[16,17] The survival status of patients lost to follow-up was obtained through public civil registries. The composite endpoints were analyzed according to time-to-first event analysis. Other endpoints included individual component of POCE, definite stent thrombosis according to the ARC definition,[18] Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding,[19] BARC type 2 bleeding, and the net adverse clinical events (NACE: defined as POCE plus BARC type 3 or 5 bleeding).[23] All endpoints were investigator-reported without a clinical adjudication committee (CEC).

2.4 | Statistical analysis

Continuous variables are expressed as mean ± standard deviation and are compared using independent *t*-test. Categorical variables are presented as counts and percentages and are compared using χ^2 test or Fisher's exact test as appropriate. The event rates were calculated by using Kaplan–Meier method.

Active PPI treatment was examined as a time-dependent covariate, where if use of a PPI was documented at any time point (index hospital discharge, 1, 3, 6, 12, or 18 months) the patient was treated as continuing to take the PPI until the next timepoint. Clinical outcomes at 2 years were compared between patients taking and

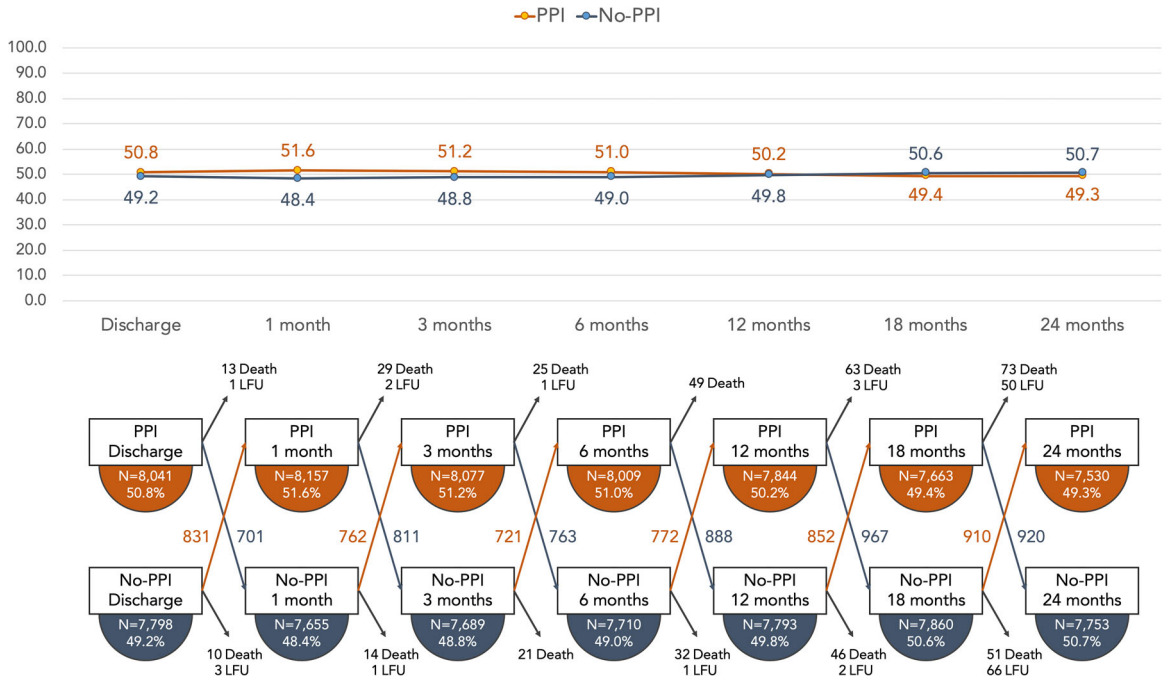

FIGURE 1 Changes of PPI use up to 2 years. PPI, proton pump inhibitor [Color figure can be viewed at wileyonlinelibrary.com]

not-taking PPI by using the time-dependent Cox regression hazards models (PPI vs. no-PPI) with or without multivariate adjustment. The covariates in the adjusted model included age, sex, body mass index (BMI), clinical presentation (CCS vs. ACS), diabetes, hypertension, hypercholesterolemia, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), current smoker, renal failure, previous stroke, previous MI, previous PCI, previous coronary artery bypass graft (CABG), previous bleeding, PCI for left main coronary artery disease (LMCAD), and multivessel disease (MVD), which had been selected based on prior knowledge of the association of these covariates with the outcomes.[20]

The effects of PPI versus no-PPI use on clinical outcomes were also assessed stratified according to the randomly assigned antiplatelet strategies (the experimental antiplatelet strategy arm and the conventional antiplatelet strategy arm). Unadjusted and inverse probability of treatment weighting (IPTW)-adjusted Kaplan–Meier curves were generated to estimate a cumulative incidence of the primary endpoint up to 2 years of follow-up.[21] In addition, landmark analyses with the prespecified timepoint of 1 year (at the time of the planned cessation of a $P2Y_{12}$ inhibitor in the conventional strategy) was performed to evaluate the effects of PPI use between ticagrelor monotherapy versus DAPT (up to 12 months), and ticagrelor monotherapy versus aspirin monotherapy (from 12 to 24 months). Since in the conventional antiplatelet strategy arm, the antiplatelet regimens differed between CCS (clopidogrel + aspirin) and ACS (ticagrelor + aspirin), we also assessed the impact of PPI on clinical outcomes in the two clinical presentation subgroups (CCS and ACS) of the reference arm.

As a sensitivity analysis, we also conducted a propensity-score-matched analysis to compare PPI with no-PPI in the two antiplatelet arms (Supporting Information: Appendix). We used a greedy algorithm to match 1:1 without replacement between PPI and no-PPI use at discharge by using a caliper width of 0.1 SD of the logit of the propensity score.

A two-sided *p*-value of less than 0.05 was considered to indicate statistical significance. All analyses were performed in SPSS Statistics, version 26 (IBM Corp.) and R software version 3.5.1 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Study flowchart and status of PPI use

The GLOBAL LEADERS study enrolled 15,991 patients between July 2013 and November 2015. Twenty-three (0.14%) patients withdrew consent and requested that their data be deleted from the database, leaving a total of 15,968 patients in the main study. Among these, the 44 (0.28%) patients who died during the index hospitalization and the 85 (0.53%) patients where no information on PPI use was available, were excluded. Therefore, 15,839 (99.0%) patients were included in the present study (Supporting Information: Figure 1).

In both randomization arms, the overall usage of PPIs was nearly 50% and did not significantly change over time irrespective of the discontinuation of DAPT according to the assigned treatment (at 1 month in the experimental antiplatelet strategy arm and at 12 months in the conventional antiplatelet strategy arm) (Figure 1, Supporting Information: Figure 2, Supporting Information: Tables 1–3).

3.2 | Patient characteristics at discharge

The baseline patient characteristics between patients with PPI or no-PPI at discharge stratified by the two antiplatelet strategies are shown in Table 1. Regardless of antiplatelet strategies, patients taking PPI were older, were more frequently female, had greater frequency of ACS, had higher prevalence of hypercholesterolemia, PVD, and COPD, had a more frequent history of previous MI and previous PCI, more frequently underwent PCI for LMCAD and MVD, and had higher PRECISE-DAPT scores compared to those with no-PPI at discharge.

3.3 | Association of PPI with outcomes in the randomized antiplatelet arms

Figure 2 illustrates the unadjusted and IPTW-adjusted Kaplan–Meier curves between PPI and no-PPI use stratified by antiplatelet strategy. After adjusting for covariates, PPI use was independently associated with a significantly increased risk of POCE with the conventional antiplatelet strategy (adjusted hazard ratio [HR]: 1.27; 95% confidence interval [CI]: 1.12–1.44; $p < 0.001$) (Figures 2 and 3). In the conventional antiplatelet strategy arm, PPI use was also associated with a significantly higher risk in all the components of POCE, including all-cause mortality, any MI, any stroke, and any revascularization, as well as NACE at 2 years.

In the experimental ticagrelor monotherapy arm, PPI use was not associated with the risk of POCE at 2 years (adjusted HR: 1.04; 95% CI: 0.92–1.19; $p = 0.503$; $p_{interaction} = 0.035$) (Figures 2 and 3). In addition, there was no significant association between PPI use and any clinical endpoints at 2 years (Figure 3).

3.4 | Landmark analyses with timepoint of 12 months

Up to 12 months (the experimental arm: ticagrelor monotherapy following 1-month DAPT, the reference arm: aspirin + clopidogrel/ticagrelor), PPI use was not associated with the incidence of any endpoints including POCE irrespective of antiplatelet strategies (Table 2).

From 12 to 24 months (the experimental arm: ticagrelor monotherapy, the reference arm: aspirin monotherapy), in the reference arm, PPI use was independently associated with significant increased risks in the ischemic endpoints including POCE (adjusted HR: 1.57; 95% CI: 1.27–1.94; $p < 0.001$), all-cause mortality (adjusted HR: 1.58; 95% CI: 1.08–2.33; $p = 0.019$), any MI (adjusted HR: 1.80; 95% CI: 1.15–2.83; $p = 0.010$), any stroke (adjusted HR: 3.20; 95% CI: 1.36–7.53; $p = 0.008$), any revascularization (adjusted HR: 1.45; 95% CI: 1.11–1.89; $p = 0.006$), and definite stent thrombosis (adjusted HR: 2.98; 95% CI: 1.08–8.21; $p = 0.035$). In contrast, in the ticagrelor monotherapy arm, there was no significant difference in the risk of POCE (adjusted HR: 1.03; 95% CI: 0.83–1.28; $p = 0.809$; $p_{interaction} = 0.008$) as well as any other clinical endpoints between PPI and no-PPI use (Table 2).

Among ACS patients of the reference arm (ticagrelor + aspirin), PPI use was independently associated with increase in any MI or BARC type 3 or 5 bleeding, whereas among CCS patients of the reference arm (clopidogrel + aspirin), PPI use was not independently associated with increased risks of any clinical endpoints (Table 3). However, there were no evidence of significant treatment-by-subgroup interactions between PPI use and clinical presentation (CCS or ACS) on any clinical endpoints (all $p_{interaction} > 0.05$, Table 3).

3.5 | Sensitivity analysis

In the propensity score matched cohort ($N = 9724$), the results were consistent; there was a significant treatment-by-subgroup interaction between PPIs and antiplatelet regimens in terms of POCE at 2 years ($p_{interaction} = 0.021$), which was mainly driven by the second-year results (Supporting Information: Table 4).

4 | DISCUSSION

Previous studies proposed different potential mechanisms of how PPIs reduced the antiplatelet efficacy of aspirin or clopidogrel. The pH partition hypothesis has been suggested to explain the drug interaction between aspirin and PPIs.[4,22] PPIs increase intragastric pH by inhibiting the H + /K + -exchanging ATPase of the gastric parietal cells, potentially resulting in a reduced lipophilicity of aspirin, and lowering its gastric absorption.[23] PPIs may inhibit the activity of CYP2C19, which may cause insufficient bioactivation of clopidogrel and an impaired platelet inhibitory effect.[5] However, the COGENT trial,[8] which is the only large randomized trial evaluating the association of PPI use on clinical outcomes among CAD patients treated with clopidogrel on top of aspirin, demonstrated that using omeprazole yielded a significant reduction in the incidence of upper gastrointestinal bleeding without increasing cardiovascular events.

Unlike clopidogrel, ticagrelor is a noncompetitive, direct-acting $P2Y_{12}$-receptor antagonist, and does not require hepatic bioactivation. Theoretically therefore, the efficacy of ticagrelor should not be affected by any PPIs. In fact, in the PLATO PLATELET substudy, PPI use was associated with higher platelet reactivity with clopidogrel but not ticagrelor.[24]

Another possible mechanism for the adverse effect of PPIs was proposed by Ghebremariam et al.[25] The authors found that PPIs can interfere with the clearance of asymmetric dimethylarginine, which can reduce nitric oxide synthesis and impair endothelium-dependent vasodilatation, possibly resulting in increased cardiovascular events. According to this hypothesis, the risk of ischemic events would be increased regardless of the antiplatelet regimen. However, in a substudy of the randomized COMPASS study, where patients were randomly assigned to pantoprazole or placebo, there was no significant difference on cardiovascular death, MI, or stroke at

TABLE 1 Patient characteristics by PPI use at discharge.

	Experimental antiplatelet strategy			Conventional antiplatelet strategy		
	PPI at discharge N = 4036	No-PPI at discharge N = 3883	p Value	PPI at discharge N = 4005	No-PPI at discharge N = 3915	p Value
Age (years)	64.9 ± 10.3	64.0 ± 10.3	<0.001	64.8 ± 10.3	64.3 ± 10.3	0.015
Female	24.7 (996/4036)	21.9 (852/3883)	0.004	24.6 (987/4005)	21.5 (843/3915)	0.001
BMI (kg/m^2)	28.1 ± 4.5	28.3 ± 4.7	0.071	28.1 ± 4.7	28.3 ± 4.6	0.027
Clinical presentation			<0.001			<0.001
Chronic coronary syndrome	45.3 (1829/4036)	61.2 (2376/3883)		44.9 (1797/4005)	61.9 (2425/3915)	
Acute coronary syndrome	54.7 (2207/4036)	38.8 (1507/3883)		55.1 (2208/4005)	38.1 (1490/3915)	
Unstable angina	13.5 (543/4036)	11.7 (455/3883)		13.9 (558/4005)	11.6 (453/3915)	
NSTEMI	24.4 (985/4036)	17.7 (689/3883)		24.3 (974/4005)	17.8 (697/3915)	
STEMI	16.8 (679/4036)	9.3 (363/3883)		16.9 (676/4005)	8.7 (340/3915)	
Comorbidities						
Diabetes mellitus	27.4 (1104/4032)	23.8 (923/3881)	<0.001	24.9 (997/4002)	24.7 (967/3914)	0.835
Insulin-treated	7.8 (312/4015)	7.4 (288/3879)	0.581	7.8 (312/3988)	7.7 (301/3911)	0.834
Hypertension	74.4 (2993/4021)	73.6 (2849/3873)	0.383	73.0 (2911/3987)	73.5 (2871/3905)	0.611
Hypercholesterolemia	67.7 (2645/3908)	71.0 (2662/3750)	0.002	67.8 (2644/3898)	72.3 (2733/3782)	<0.001
Current smoker	27.1 (1094/4036)	24.6 (956/3883)	0.012	27.0 (1081/4005)	25.7 (1005/3915)	0.185
PVD	6.7 (269/3988)	5.2 (202/3856)	0.005	7.2 (287/3962)	6.1 (236/3890)	0.037
COPD	5.9 (236/4013)	4.1 (160/3874)	<0.001	5.8 (231/3986)	4.6 (180/3895)	0.020
Renal impairment[a]	14.8 (593/4014)	12.9 (497/3861)	0.016	14.1 (562/3995)	12.8 (497/3887)	0.099
Medical history						
Previous bleeding	0.7 (30/4029)	0.4 (16/3879)	0.055	0.9 (34/4000)	0.5 (18/3911)	0.036
Previous stroke	2.6 (106/4031)	2.6 (100/3876)	0.944	2.9 (116/4002)	2.4 (93/3908)	0.161
Previous MI	24.9 (1001/4028)	21.2 (821/3869)	<0.001	25.6 (1024/3999)	21.5 (838/3901)	<0.001
Previous PCI	34.0 (1373/4034)	31.5 (1223/3880)	0.018	34.3 (1375/4003)	31.1 (1216/3910)	0.002
Previous CABG	5.6 (226/4035)	5.6 (218/3879)	1.000	6.0 (242/4004)	6.4 (250/3910)	0.545
Procedure						
Number of lesion treated						
One lesion	68.1 (2729/4007)	67.5 (2604/3858)	0.224	68.2 (2705/3968)	68.8 (2675/3888)	0.510
Two lesions	23.7 (948/4007)	23.2 (894/3858)		23.0 (912/3968)	22.0 (854/3888)	
Three or more	8.2 (330/4007)	9.3 (360/3858)		8.8 (351/3968)	9.2 (359/3888)	
Average number	1.43 ± 0.73	1.45 ± 0.75	0.299	1.43 ± 0.74	1.43 ± 0.75	0.998
Left main PCI	3.4 (135/4007)	2.2 (84/3858)	0.002	3.1 (123/3968)	2.1 (83/3888)	0.009
LAD PCI	48.9 (1961/4007)	51.3 (1978/3858)	0.040	51.3 (2035/3968)	51.7 (2011/3888)	0.701
LCX PCI	32.2 (1292/4007)	31.1 (1201/3858)	0.297	32.5 (1288/3968)	30.6 (1191/3888)	0.085
RCA PCI	39.3 (1576/4007)	37.2 (1437/3858)	0.060	36.7 (1455/3968)	37.1 (1444/3888)	0.674
Bypass graft PCI	1.3 (52/4007)	1.5 (58/3858)	0.444	1.5 (58/3968)	1.2 (48/3888)	0.434

(Continues)

TABLE 1 (Continued)

	Experimental antiplatelet strategy			Conventional antiplatelet strategy		
	PPI at discharge N = 4036	No-PPI at discharge N = 3883	p Value	PPI at discharge N = 4005	No-PPI at discharge N = 3915	p Value
Multivessel PCI	23.8 (955/4007)	21.6 (835/3858)	0.021	23.5 (934/3968)	21.2 (824/3888)	0.013
PRECISE-DAPT score	17.1 ± 9.2	15.9 ± 8.5	<0.001	16.9 ± 8.9	15.9 ± 8.4	<0.001

Note: Data are presented as mean ± standard deviation or percentage (number).

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; NSTEMI, non-ST segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PVD, peripheral vascular disease; RCA, right coronary artery; STEMI, ST segment elevation 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.

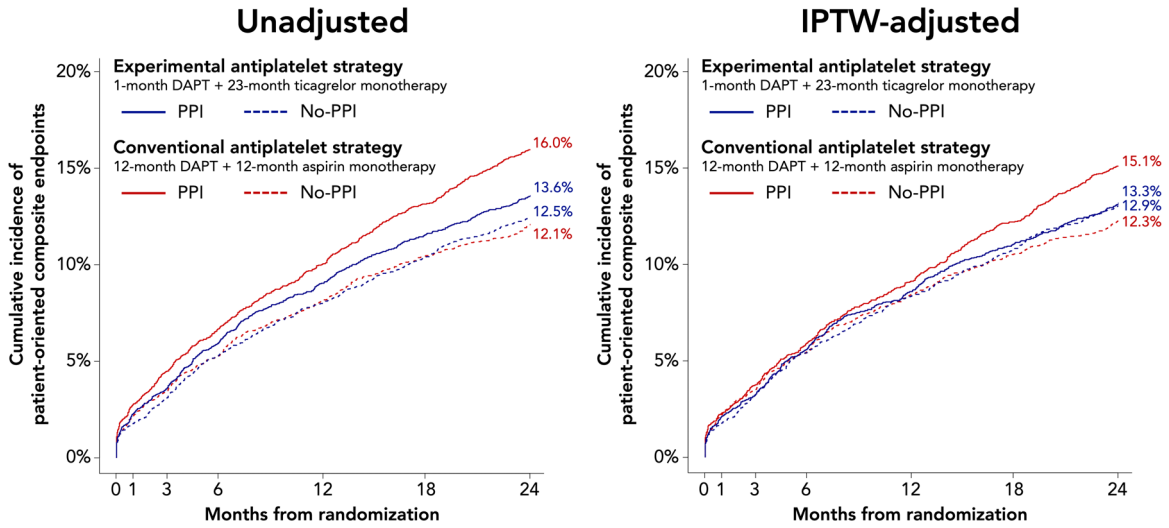

FIGURE 2 Unadjusted and IPTW-adjusted time-dependent Kaplan–Meier curves for POCE up to 2 years. Kaplan–Meier curves in patients with or without PPI use in the experimental or conventional antiplatelet strategies. Patients who took PPI on top of conventional antiplatelet strategy had the highest risk of POCE at 2 years in unadjusted and IPTW-adjusted model. The adjusted covariates are listed in Table 2. IPTW, inverse probability of treatment weighting; POCE, patient-oriented composite endpoint; PPI, proton pump inhibitor [Color figure can be viewed at wileyonlinelibrary.com]

	Experimental Antiplatelet strategy (N = 7,919)			Conventional Antiplatelet strategy (N = 7,920)			P for interaction
	Adjusted HR (95%CI)	P value	PPI better ← → no-PPI better	Adjusted HR (95%CI)	P value	PPI better ← → no-PPI better	
POCE	1.04 (0.92-1.19)	0.503		1.27 (1.12-1.44)	<0.001		0.035
All-cause mortality	0.94 (0.70-1.26)	0.693		1.53 (1.15-2.03)	0.003		0.018
Any MI	1.10 (0.84-1.44)	0.468		1.46 (1.11-1.91)	0.007		0.170
Any Stroke	1.41 (0.88-2.28)	0.158		1.92 (1.18-3.14)	0.009		0.377
Any revascularization	1.03 (0.89-1.20)	0.693		1.22 (1.05-1.42)	0.008		0.121
Definite stent thrombosis	1.31 (0.77-2.22)	0.321		1.32 (0.78-2.24)	0.295		0.975
BARC type 3 or 5 bleeding	1.16 (0.83-1.62)	0.393		1.34 (0.96-1.86)	0.087		0.788
BARC type 2 bleeding	1.17 (0.95-1.44)	0.140		1.10 (0.89-1.36)	0.376		0.678
NACE	1.05 (0.93-1.19)	0.411		1.26 (1.12-1.42)	<0.001		0.033

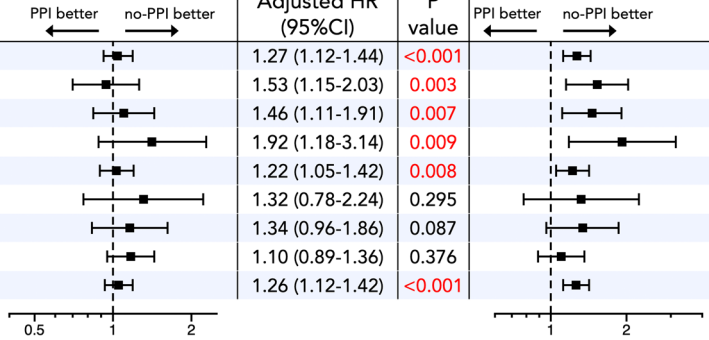

FIGURE 3 Effect of time-dependent PPI use on clinical outcomes at 2 years in patients treated with experimental antiplatelet strategy or conventional antiplatelet strategy. In the conventional antiplatelet strategy arm, PPI was associated with a significantly higher risks of POCE and the components, including all-cause mortality, any MI, any stroke, and any revascularization at 2 years, whereas in the experimental strategy arm there were no significant association between PPI and any endpoints at 2 years. The event rates were calculated by using Kaplan–Meier method. The PPI use was treated as a time-dependent covariate. The adjusted covariates are listed in Table 2. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NACE, net adverse clinical events; POCE, patient-oriented composite endpoint; PPI, proton pump inhibitor [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Landmark analysis with prespecified timepoints of 12 months for PPI use in the experimental antiplatelet strategy or the conventional antiplatelet strategy.

	Experimental arm (*N* = 7919)		Conventional strategy (*N* = 7920)		
	HR (95% CI) PPI/no-PPI	*p* Value	HR (95% CI) PPI/no-PPI	*p* Value	$p_{interaction}$
Up to 12 months					
POCE	1.05 (0.90–1.23)	0.528	1.13 (0.97–1.32)	0.130	0.516
All-cause mortality	0.96 (0.61–1.52)	0.875	1.51 (0.99–2.30)	0.053	0.158
Any MI	1.03 (0.75–1.42)	0.835	1.29 (0.92–1.82)	0.143	0.380
Any stroke	1.31 (0.72–2.40)	0.378	1.42 (0.77–2.61)	0.264	0.811
Any revascularization	1.03 (0.86–1.24)	0.747	1.12 (0.94–1.34)	0.197	0.465
Definite stent thrombosis	1.51 (0.83–2.75)	0.175	0.90 (0.47–1.72)	0.749	0.271
BARC type 3 or 5 bleeding	1.38 (0.91–2.08)	0.127	1.39 (0.95–2.01)	0.086	0.734
BARC type 2 bleeding	1.15 (0.90–1.46)	0.253	1.06 (0.84–1.33)	0.646	0.526
NACE	1.08 (0.93–1.25)	0.336	1.13 (0.98–1.31)	0.098	0.523
From 12 to 24 months					
POCE	1.03 (0.83–1.28)	0.809	1.57 (1.27–1.94)	<0.001	0.008
All-cause mortality	0.91 (0.62–1.34)	0.635	1.58 (1.08–2.33)	0.019	0.050
Any MI	1.30 (0.78–2.15)	0.315	1.80 (1.15–2.83)	0.010	0.312
Any stroke	1.54 (0.70–3.39)	0.288	3.20 (1.36–7.53)	0.008	0.244
Any revascularization	1.03 (0.78–1.36)	0.821	1.45 (1.11–1.89)	0.006	0.091
Definite stent thrombosis	0.74 (0.22–2.50)	0.632	2.98 (1.08–8.21)	0.035	0.110
BARC type 3 or 5 bleeding	0.76 (0.42–1.39)	0.377	1.12 (0.54–2.32)	0.765	0.402
BARC type 2 bleeding	1.22 (0.80–1.85)	0.352	1.32 (0.81–2.15)	0.273	0.716
NACE	1.00 (0.81–1.24)	0.984	1.55 (1.25–1.91)	<0.001	0.005

Note: Adjusted for age, sex, BMI, clinical presentation (CCS vs. ACS), diabetes, hypertension, hypercholesterolemia, PVD, COPD, current smoker, renal failure, previous stroke, previous MI, previous PCI, CABG, previous bleeding, PCI for left main coronary artery disease, and multivessel disease.

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NACE, net adverse clinical events; POCE, patient-oriented composite endpoint; PPI, proton pump inhibitor.

3 years between pantoprazole and placebo in the overall population,[9] suggesting that the adverse effect of PPIs was not evident even treated with antiplatelet therapy with aspirin at least when using pantoprazole.

In the current post hoc analysis of the GLOBAL LEADERS trial, continued use of a PPI in the second-year after PCI was associated with a significant increase in cardiovascular events in patients on aspirin monotherapy, which might be affected by unadjusted confounders in line with previous observational studies. In fact, PPI group had numerically higher bleeding risks than non-PPI group both in the experimental and reference arms, albeit there were no statistical significances. In contrast, however, the PPI use was not associated with adverse events during the first year after PCI in the reference arm, in which DAPT was continued for 12 months (CCS: aspirin and clopidogrel; ACS: aspirin and ticagrelor). We also assessed the impacts of PPI use on clinical outcomes up to 12 months between the two antiplatelet regimens of the reference arm (CCS and ACS), however, there were no evidence suggesting that the effects of PPI use differed depending on the different DAPT regimens (Table 3). In addition, among those treated with ticagrelor monotherapy, there were no significant differences in clinical outcomes between PPI-user and non-PPI-user. Our study therefore could support the safety of PPI use in patients with ticagrelor monotherapy up to 2 years or DAPT up to 1 year after PCI.[10]

Our analyses highlight that in the contemporary PCI cohort, the prescription rate of PPIs is nearly 50% despite patient's having a relatively low bleeding risk (e.g., mean PRECISE-DAPT score was 16.4 ± 8.8,[26] and <1.0% of patients had a history of previous severe bleeding). In addition, the prescription rates were almost consistent throughout the follow-up regardless of cessation of DAPT. These facts would suggest frequent, yet unnecessary use of PPIs.

We acknowledge some limitations. First, it is a post hoc subgroup analysis of an open-label randomized trial, where the PPI use was not randomized. Although we adjusted multiple confounding factors and confirmed the consistency of the results in the propensity score matched cohort as a sensitivity analysis, the possibility of

TABLE 3 The adjusted hazard ratios of PPI use on clinical outcomes up to 12 months among patients presenting with CCS (aspirin + clopidogrel) or ACS (aspirin + ticagrelor) of the conventional antiplatelet strategy arm.

	Conventional strategy				
	DAPT with clopidogrel (CCS) (*N* = 4222)		DAPT with ticagrelor (ACS) (*N* = 3698)		
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	$p_{interaction}$
Up to 12 months					
POCE	1.12 (0.91–1.38)	0.287	1.15 (0.91–1.46)	0.230	0.828
All-cause mortality	1.50 (0.85–2.68)	0.165	1.59 (0.86–2.95)	0.140	0.891
Any MI	0.91 (0.55–1.52)	0.725	1.84 (1.12–3.05)	0.017	0.054
Any stroke	1.45 (0.62–3.37)	0.395	1.42 (0.58–3.45)	0.444	0.938
Any revascularization	1.10 (0.87–1.40)	0.428	1.16 (0.88–1.52)	0.286	0.755
Definite stent thrombosis	0.46 (0.15–1.45)	0.185	1.46 (0.59–3.61)	0.410	0.097
BARC type 3 or 5 bleeding	1.03 (0.56–1.88)	0.922	1.69 (1.03–2.79)	0.039	0.161
BARC type 2 bleeding	1.30 (0.92–1.83)	0.131	0.86 (0.63–1.18)	0.360	0.079
NACE	1.09 (0.89–1.33)	0.415	1.20 (0.96–1.48)	0.103	0.448

Note: Adjusted covariates are listed in Table 2 (clinical presentation is removed).

Abbreviations: ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CCS, chronic coronary syndrome; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NACE, net adverse clinical events; POCE, patient-oriented composite endpoint.

unmeasured confounders that significantly affected both the use of PPIs and the outcomes cannot be excluded. Therefore, all the findings should be strictly considered as hypothesis generating. Second, we do not have detailed drug data such as enteric-coating of aspirin or specific PPI types. Therefore, we cannot provide insights into the mechanism of the interaction between PPIs and antiplatelet regimens. Third, we do not have data about the reason or basis for each PPI prescription. Although the usage rate of PPIs was relatively high in our study, we could not evaluate whether each PPI use was indicated or not. In addition, data on incidence of upper gastrointestinal bleeding is lacking, therefore, we could not assess the incremental benefit of a PPI prescription. However, since there was no significant difference in the risk of BARC type 2 or type 3 or 5 bleeding between PPI use and no-PPI, our results may suggest that the clinical benefit of PPI use was strictly limited to the prevention of severe bleeding events including fatal gastrointestinal bleeding. Finally, in this trial all endpoints were site-reported without CEC adjudication for serious adverse events. However, the GLASSY study,[27] which is a prespecified ancillary study of the GLOBAL LEADERS trial with event adjudication by an independent CEC, has reported results consistent with those of site-reported.[15]

5 | CONCLUSIONS

In the present post hoc study of the GLOBAL LEADERS trial, among patients treated with the conventional post-PCI antiplatelet strategy of 12-month DAPT followed by aspirin monotherapy, the use of PPIs was associated with an increased risk of cardiovascular events. In contrast, among those with the experimental antiplatelet strategy of 1-month DAPT followed by 23-month ticagrelor monotherapy, there were no evidence suggesting that PPIs could increase cardiovascular events. PPI use may be safe in patients with ticagrelor monotherapy, which should be confirmed in further studies.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

GLOBAL LEADERS trial is an investigator-initiated trial. Internal investigators, who actively participated in the study, and who provide a methodologically sound study proposal will be granted priority access to the study data for 60 months. After 60 months, this option might be extended to external investigators not affiliated to the trial, whose proposed use of the data has been approved by an independent review committee identified by the steering committee for this purpose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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