Original Article

Impact of Proton-pump Inhibitors on the Pharmacodynamic Effect and Clinical Outcomes in Patients Receiving Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: A Propensity Score Analysis

Pei Zhu, Zhan Gao, Xiao-Fang Tang, Jing-Jing Xu, Yin Zhang, Li-Jian Gao, Jue Chen, Shu-Bin Qiao, Yue-Jin Yang, Run-Lin Gao, Bo Xu, Jin-Qing Yuan

Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100037, China

Abstract

Background: Prior studies have reported controversial conclusions regarding the risk of adverse cardiovascular events in patients using proton-pump inhibitors (PPIs) combined with clopidogrel therapy, causing much uncertainty in clinical practice. We sought to evaluate the safety of PPIs use among high-risk cardiovascular patients who underwent percutaneous coronary intervention (PCI) in a long-term follow-up study.

Methods: A total of 7868 consecutive patients who had undergone PCI and received dual antiplatelet therapy (DAPT) at a single center from January 2013 to December 2013 were enrolled. Adenosine diphosphate (ADP)-induced platelet aggregation inhibition was measured by modified thromboelastography (mTEG) in 5042 patients. Propensity score matching (PSM) was applied to control differing baseline factors. Cox proportional hazards regression was used to evaluate the 2-year major adverse cardiovascular and cerebrovascular events (MACCEs), as well as individual events, including all-cause death, myocardial infarction, unplanned target vessel revascularization, stent thrombosis, and stroke.

Results: Among the whole cohort, 27.2% were prescribed PPIs. The ADP-induced platelet aggregation inhibition by mTEG was significantly lower in PPI users than that in non-PPI users (42.0 ± 30.9% vs. 46.4 ± 31.4%, $t = 4.435$, $P < 0.001$). Concomitant PPI use was not associated with increased MACCE through 2-year follow-up (12.7% vs. 12.5%, $\chi^2 = 0.086$, $P = 0.769$). Other endpoints showed no significant differences after multivariate adjustment, regardless of PSM.

Conclusion: In this large cohort of real-world patients, the combination of PPIs with DAPT was not associated with increased risk of MACCE in patients who underwent PCI at up to 2 years of follow-up.

Key words: Clopidogrel; Drug Interactions; Percutaneous Coronary Intervention; Proton-pump Inhibitors

Introduction

Dual antiplatelet therapy (DAPT) mitigates the risk of stent thrombosis (ST) and ischemic events in patients who undergo percutaneous coronary intervention (PCI).[1] Nonetheless, antiplatelet therapy is also associated with increased bleeding risk, and gastrointestinal bleeding accounts for a notable proportion of the bleeding complications of DAPT and probably leads to DAPT cessation, which further increases adverse cardiovascular events.[2] Proton-pump inhibitors (PPIs) are often concomitantly prescribed to patients in combination with DAPT to help reduce the occurrence of gastrointestinal bleeding.[3] However, several pharmacokinetic studies and observational studies have demonstrated potential interaction of PPIs with

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.220304

Address for correspondence: Dr. Jin-Qing Yuan, Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 Beilishi Road, Xicheng District, Beijing 100037, China
E-Mail: dr_jinqingyuan@sina.com

Received: 14-08-2017 **Edited by:** Peng Lyu

How to cite this article: Zhu P, Gao Z, Tang XF, Xu JJ, Zhang Y, Gao LJ, Chen J, Qiao SB, Yang YJ, Gao RL, Xu B, Yuan JQ. Impact of Proton-pump Inhibitors on the Pharmacodynamic Effect and Clinical Outcomes in Patients Receiving Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: A Propensity Score Analysis. Chin Med J 2017;130:2899-905.

clopidogrel via competition with liver cytochrome P450 isoenzymes (especially CYP2C19), leading to reduced antiplatelet activity and increased ischemic events.[2,4-8] New evidences showed that the interaction may have no clinical significance.[9,10] Limited by the controversial conclusions, the 2016 American College of Cardiology/American Heart Association guideline on DAPT in patients with coronary artery disease suggested no routine PPI use in the setting of DAPT.[11] However, the 2017 European Society of Cardiology focused update on DAPT in coronary artery disease recommended PPI in combination with DAPT.[1] Therefore, we performed a large prospective observational study to evaluate the interaction between PPIs and DAPT among high-risk cardiovascular patients who underwent PCI from both pharmacodynamic and clinical aspects. Propensity score matching (PSM) was implemented to eliminate the covariate imbalance.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Fuwai Hospital Institutional Ethical Review Board. Informed written consent was obtained from all patients or their guardians, in the case of children, prior to their enrollment in this study.

Study population

All 10,724 consecutive patients from a single center (Fu Wai Hospital, National Center for Cardiovascular Diseases, Beijing, China) who underwent PCI throughout 2013 were enrolled in the study. Of these, 21 patients were prescribed aspirin and ticagrelor, and two patients were prescribed oral anticoagulant after PCI. Ticagrelor is a P2Y12 inhibitor that does not need biotransformation and has no effect on the CYP2C19 isoenzyme. Thus, only patients treated with aspirin and clopidogrel were included (n = 10,701). Patients with missing values of PPI use and loss of follow-up were excluded [n = 2833, Figure 1].

Procedure and medications

The PCI strategy and stent type were determined by the physician's discretion. Before the procedure, all patients who had not taken long-term aspirin and P2Y12 inhibitors received oral 300 mg aspirin and 300 mg clopidogrel. After the procedure, patients were to take aspirin 100 mg/d indefinitely and clopidogrel 75 mg/d for at least 1 year after PCI. PPI use was determined at the physician's discretion and was recorded at the time of PCI. The specific PPI was not reported.

Data collection and study endpoints

Baseline clinical characteristics, past medical history, laboratory tests, PCI data, and discharge medications were collected. All patients were evaluated at a clinic visit or by phone at 1, 6, 12, and 24 months. The average follow-up was 875.3 days. The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE) during follow-up. MACCE were defined as a composite

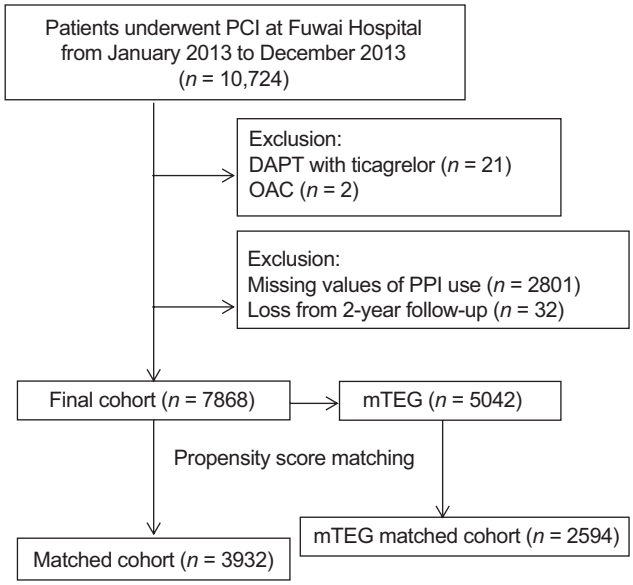

Figure 1: Patient flowchart for the study cohort. PCI: Percutaneous coronary intervention; DAPT: Dual antiplatelet therapy; OAC: Oral anticoagulants; PPI: Proton-pump inhibitors; mTEG: Modified thromboelastograph.

of all-cause death, myocardial infarction (MI), unplanned target vessel revascularization (TVR), ST, and stroke. MI was defined according to the clinical and laboratory parameters established in the third universal definition of MI.[12] Unplanned TVR was defined as any repeat PCI or surgical bypass of any segment of the target vessel for ischemic symptoms and events. ST was defined by the Academic Research Consortium, and definite and probable ST were included in the analysis.[13] Secondary endpoints included each component of the primary endpoint. Bleeding was quantified according to the Bleeding Academic Research Consortium Definition (BARC) criteria, and types 2, 3, and 5 were included in the analysis.[14] Major bleeding was defined as type 3 and 5 according to the BARC criteria. All endpoints were adjudicated centrally by two independent cardiologists, and disagreement was resolved by consensus.

Blood sampling

According to the physician's discretion, platelet aggregation inhibition tests were performed by modified thromboelastography (mTEG, Haemonetics Corp., Massachusetts, USA). Blood was collected at least 6 h after using clopidogrel in a Vacutainer tube containing 3.2% trisodium citrate. The Vacutainer tube was filled to capacity and inverted 3–5 times to ensure complete mixing of the anticoagulant. The mTEG instrument uses 4 channels to detect the effects of antiplatelet therapy acting via the arachidonic acid and adenosine diphosphate (ADP) pathways.[15] An mTEG hemostasis analyzer (Haemonetics Corp., Massachusetts, USA) and automated analytical software (Haemonetics Corp., Massachusetts, USA) were used to measure the physical properties. ADP inhibition % of <30% was considered a clopidogrel low response (CLR).[16]

Statistical analysis

Categorical variables are presented as numbers (percentages) and were compared using the Chi-squared test. Continuous variables are presented as the means ± standard deviation or median (interquartile range) and were compared using the *t*-test or Mann-Whitney *U*-test. Hazard ratios (*HR*s) are presented with the 95% confidence intervals (*CI*s). All statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA), and a two-tailed $P < 0.05$ was considered statistically significant. Kaplan-Meier analysis was applied to evaluate endpoints. The covariates for Cox proportional regression were those variables with significant differences at baseline or important clinical meaning.

To minimize the effect of confounding factors caused by differences in baseline characteristics between patients with and without PPI use, PSM was performed for both the whole population and the mTEG population. A propensity score was estimated for each patient using a logistic regression model. Patients were matched on estimated propensity scores, with replacement, using a nearest neighbor approach. A caliper width of 0.02 was used. For the total population, the dependent variable was PPI use, and the covariates were age, gender, hypertension, dyslipidemia, diabetes mellitus, prior cerebrovascular disease, prior MI, prior PCI, prior coronary artery bypass grafting, acute MI, ejection fraction, Killip class, estimated glomerular filtration rate, hemoglobin, intra-aortic balloon pump, and warfarin use. For the mTEG population, the dependent variable was PPI use, and the covariates were age, gender, prior cerebrovascular disease, prior MI, prior PCI, acute MI, ejection fraction, estimated glomerular filtration rate, hemoglobin, and intra-aortic balloon pump.

Results

Study population and demographics

Among 7868 enrolled patients, 2142 (27.2%) patients were prescribed PPIs. PPI users were older and were more likely to be female with a higher rate of cerebrovascular disease and a lower rate of prior MI. These individuals presented more frequently with acute MI and needed more intra-aortic balloon pump support. With respect to laboratory tests, PPI-treated patients had worse heart and renal function, lower hemoglobin levels, and a faster erythrocyte sedimentation rate. PPI users received warfarin more often than non-PPI users. There were significant differences in the baseline levels between the two groups. After PSM, 1966 patients had an estimated propensity score that matched within the 0.02 caliper to 1966 patients without PPI use [Table 1].

Adenosine diphosphate-induced platelet aggregation inhibition test

ADP-induced platelet aggregation inhibition was measured by mTEG in 5042 patients per the physician's discretion. The baseline characteristics of patients were compared according to PPI use in the mTEG population, and the two groups were better matched after PSM with 1297 patients selected from each group [Table 2].

Before PSM, the ADP-induced platelet aggregation inhibition was lower in PPI users than in non-PPI users (42.0 ± 30.9% vs. 46.4 ± 31.4%, $t = 4.435$, $P < 0.001$). A greater proportion of patients had CLR in the group that received PPIs (41.3% vs. 36.1%, $\chi^2 = 11.420$, $P = 0.001$). After PSM, the differences were even larger, and 30 (2.3%) non-PPI users were identified as having a CLR, whereas 528 (40.7%) PPI users were identified as having a CLR (2.3% vs. 40.7%, $\chi^2 = 566.262$, $P < 0.001$) [Table 3].

Clinical outcomes

Before PSM, the occurrence of MACCE between PPI users and non-PPI users in the total population showed no significant difference (12.7% vs. 12.5%, $\chi^2 = 0.086$, $P = 0.769$), and no differences were observed in the incidence of all-cause death (1.4% vs. 1.3%, $\chi^2 = 0.097$, $P = 0.755$), MI (2.4% vs. 2.0%, $\chi^2 = 0.950$, $P = 0.330$), unplanned TVR (9.1% vs. 8.8%, $\chi^2 = 0.199$, $P = 0.655$), ST (1.2% vs. 0.9%, $\chi^2 = 1.095$, $P = 0.295$), stroke (1.4% vs. 1.4%, $\chi^2 = 0.084$, $P = 0.772$), bleeding (6.6% vs. 6.5%, $\chi^2 = 0.060$, $P = 0.806$), BARC 3 or 5 bleeding (0.5% vs. 0.5%, $\chi^2 = 0.095$, $P = 0.758$), and gastrointestinal bleeding events (1.7% vs. 1.2%, $\chi^2 = 2.272$, $P = 0.132$). After PSM, the occurrence of MACCE (12.4% vs. 12.7%, $\chi^2 = 0.048$, $P = 0.827$), all-cause death (1.3% vs. 1.4%, $\chi^2 = 0.080$, $P = 0.777$), MI (2.4% vs. 2.4%, $\chi^2 = 0.000$, $P = 0.998$), unplanned TVR (8.9% vs. 9.0%, $\chi^2 = 0.006$, $P = 0.937$), ST (1.1% vs. 0.9%, $\chi^2 = 0.425$ $P = 0.515$), stroke (1.4% vs. 1.1%, $\chi^2 = 0.721$, $P = 0.396$), bleeding (7.0% vs. 5.9%, $\chi^2 = 1.860$, $P = 0.173$), and BARC 3 or 5 bleeding events (0.5% vs. 0.2%, $\chi^2 = 2.623$, $P = 0.105$) did not significantly differ between the two groups, and there was only a trend for an increase in gastrointestinal bleeding events in PPI users (1.8% vs. 1.2%, $\chi^2 = 2.960$, $P = 0.085$) [Table 4a].

After multivariate Cox proportional hazards regression analysis, there was only a trend for an increase in BARC 3 or 5 bleeding and gastrointestinal bleeding in PPI users after PSM (*HR*: 0.586, 95% *CI*: 0.341–1.009, $P = 0.054$), and the other endpoints showed no significant differences after multivariate adjustment, regardless of PSM, between two groups [Table 4b].

Discussion

In this prospective observational study, we investigated the impact of concomitant administration of PPIs with DAPT therapy among patients who underwent PCI. The major strength of this study was the use of a large sample size from a single-center database with a long follow-up duration of 2 years, and we evaluated the interaction between DAPT and PPIs in both pharmacodynamic and clinical aspects. To overcome this selection bias for PPI use, PSM was implemented so that the 2 cohorts could be meaningfully compared. The study has the following notable findings.

Table 1: Baseline characteristics among all patients according to PPI use before and after PSM

Parameters	Before PSM				After PSM			
	PPI (n = 2142)	No PPI (n = 5726)	Statistics	P	PPI (n = 1966)	No PPI (n = 1966)	Statistics	P
Demographics								
Gender (female)	527 (24.6)	1145 (20.0)	19.768*	<0.001	485 (24.7)	447 (22.7)	2.031*	0.154
Age (years)	60.2 ± 10.6	57.7 ± 10.3	−9.402†	<0.001	60.2 ± 10.5	60.8 ± 9.9	1.908†	0.057
Past medical history								
Hypertension	1362 (63.6)	3653 (63.8)	0.030*	0.862	1259 (64.0)	1286 (65.4)	0.812*	0.368
Dyslipidemia	1417 (66.2)	3870 (67.6)	1.453*	0.228	1316 (66.9)	1409 (71.7)	10.340*	0.001
Diabetes mellitus	615 (28.7)	1773 (31.0)	3.742*	0.053	571 (29.0)	595 (30.3)	0.702*	0.402
PAD	66 (3.1)	137 (2.4)	2.941*	0.086	63 (3.2)	71 (3.6)	0.494*	0.482
Prior CVD	289 (13.5)	570 (10.0)	20.057*	<0.001	261 (13.3)	260 (13.2)	0.002*	0.962
Prior MI	430 (20.1)	1586 (27.7)	47.539*	<0.001	404 (20.5)	666 (33.9)	88.138*	<0.001
Prior PCI	591 (27.6)	1653 (28.9)	1.248*	0.264	500 (25.4)	960 (48.8)	230.530*	<0.001
Prior CABG	85 (3.9)	276 (4.8)	2.883*	0.090	81 (4.1)	152 (7.7)	22.998*	<0.001
Admission features								
Acute MI	598 (27.9)	1224 (21.4)	37.488*	<0.001	486 (24.7)	432 (22.0)	4.144*	0.042
LVEF, %	61.5 ± 7.9	62.2 ± 7.6	3.360†	0.001	62.0 ± 7.7	61.6 ± 7.9	−1.623†	0.105
Killip class ≥2	45 (2.1)	72 (1.3)	7.570*	0.006	30 (1.5)	37 (1.9)	0.744*	0.388
SAP (mmHg)	126.1 ± 17.5	126.3 ± 16.8	0.346†	0.729	126.3 ± 17.4	126.9 ± 16.5	1.133†	0.257
Current smoking	1247 (58.2)	3384 (59.1)	0.501*	0.479	1134 (57.7)	1109 (56.4)	0.649*	0.421
Laboratory test								
BNP (pg/ml)	649.8 (480.3–912.7)	616.6 (474.9–847.3)	−2.879‡	0.004	649.3 (479.9–649.3)	640.2 (490.6–895.6)	−0.124‡	0.901
eGFR (ml/min)	88.9 ± 15.9	91.8 ± 15.1	7.209†	<0.001	89.2 ± 15.5	88.6 ± 15.6	−1.203†	0.229
ESR (mm/h)	7 (3–16)	7 (3–14)	−2.780‡	0.005	7 (3–16)	7 (3–14)	−0.383‡	0.702
Hemoglobin (g/L)	141.4 ± 16.0	144.2 ± 15.1	6.970†	<0.001	141.4 ± 16.0	141.4 ± 15.3	0.070†	0.944
Procedural characteristics								
Thrombolysis	85 (4.0)	194 (3.4)	1.534*	0.215	79 (4.0)	63 (3.2)	1.870*	0.171
Syntax score								
0–22	1871 (87.3)	5078 (88.7)	2.773*	0.250	1726 (87.9)	1800 (91.6)	13.953*	0.001
23–32	234 (10.9)	555 (9.7)			206 (10.5)	145 (7.4)		
≥33	37 (1.7)	93 (1.6)			31 (1.6)	21 (1.1)		
Number of Stents								
0	137 (6.4)	318 (5.6)	2.082*	0.353	117 (6.0)	121 (6.2)	6.534*	0.038
1	875 (40.8)	2344 (40.9)			784 (39.9)	859 (43.7)		
≥2	1130 (52.8)	3064 (53.5)			1065 (54.2)	986 (50.2)		
IABP	49 (2.3)	74 (1.3)	10.034*	0.002	32 (1.6)	29 (1.5)	0.150*	0.699
Medication								
Warfarin	9 (0.4)	8 (0.1)	5.687*	0.017	4 (0.2)	6 (0.3)	0.401*	0.527
GPI	360 (16.8)	936 (16.3)	0.240*	0.624	322 (16.4)	336 (17.1)	0.358*	0.550

Data are presented as n (%), mean ± SD or median (interquartile range). *χ^2 values; †t values; ‡z value. PPI: Proton-pump inhibitors; PSM: Propensity score matching; PAD: Peripheral artery disease; CVD: Cerebrovascular disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; LVEF: Left ventricular ejection fraction; SAP: Systolic blood pressure; BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; ESR: Erythrocyte sedimentation rate; IABP: Intra-aortic balloon pump; GPI: Glycoprotein IIb/IIIa inhibitors; SD: Standard deviation.

First, approximately 27.2% of the patients were prescribed PPIs; these patients were likely to be older and female and to have increased comorbid illness, such as diabetes mellitus or cerebral vascular disease, and they were more likely to present with lower hemoglobin, lower creatinine clearance, and higher BNP. The PPI use pattern suggests that physicians were prescribing PPIs to those who were at higher baseline bleeding risk in accordance with new recommendations.[11] Interestingly, patients with prior MI were less likely to be prescribed PPIs, possibly due to concerns regarding the interaction between PPI and clopidogrel.

Second, the inhibition of platelet aggregation assessed by mTEG was significantly lower in patents with concomitant PPI use than in those without. In addition, a significant association between CLR and treatment with PPIs was observed. In 2006, Gilard *et al*.[4,17] first reported the competitive effect of PPIs on CYP2C19 by means of a platelet phosphorylated vasodilator-stimulated phosphoprotein test, which might diminish the antiplatelet action of clopidogrel. While vasodilator-stimulated phosphoprotein phosphorylation evaluates the platelet activation from the P2Y12 ADP receptor, mTEG uses whole

Table 2: Baseline characteristics among patients receiving mTEG according to PPI use before and after PSM

Parameters	Before PSM				After PSM			
	PPI (n = 1368)	No PPI (n = 3674)	Statistics	P	PPI (n = 1297)	No PPI (n = 1297)	Statistics	P
Demographics								
Gender (female)	341 (24.9)	721 (19.6)	16.857*	<0.001	324 (25.0)	260 (20.0)	9.052*	0.003
Age (years)	59.9 ± 10.5	57.6 ± 10.3	−7.145†	<0.001	59.9 ± 10.6	59.1 ± 10.5	−2.0368†	0.042
Past medical history								
Hypertension	890 (65.1)	2343 (63.8)	0.746*	0.388	849 (65.5)	854 (65.8)	0.043*	0.839
Dyslipidemia	916 (67.0)	2507 (68.2)	1.453*	0.228	869 (67.0)	879 (67.8)	0.175*	0.675
Diabetes mellitus	409 (29.9)	1124 (30.6)	0.228*	0.633	394 (30.4)	388 (29.9)	0.066*	0.797
PAD	48 (3.5)	94 (2.6)	3.289*	0.070	46 (3.5)	37 (2.9)	1.008*	0.315
Prior CVD	187 (13.7)	342 (9.3)	20.187*	<0.001	175 (13.5)	179 (138)	0.052*	0.819
Prior MI	279 (20.4)	1035 (28.2)	31.282*	<0.001	263 (20.3)	277 (21.4)	0.458*	0.498
Prior PCI	352 (25.7)	1062 (28.9)	4.979*	0.026	317 (24.4)	335 (25.8)	0.664*	0.415
Prior CABG	63 (4.6)	171 (4.7)	0.005*	0.941	61 (4.7)	62 (4.8)	0.009*	0.926
Admission features								
Acute MI	300 (21.9)	698 (19.0)	5.396*	0.020	267 (20.6)	228 (17.6)	3.797*	0.051
LVEF (%)	62.0 ± 7.8	62.4 ± 7.5	1.607†	0.108	62.2 ± 7.6	62.4 ± 7.5	0.587†	0.557
Killip class ≥2	19 (1.4)	30 (0.8)	3.393*	0.065	15 (1.2)	14 (1.1)	0.035*	0.852
SAP (mmHg)	126.2 ± 17.3	126.5 ± 16.7	0.641†	0.522	126.3 ± 17.3	127.3 ± 16.9	1.564†	0.118
Current smoking	783 (57.2)	2151 (58.5)	0.703*	0.402	738 (56.9)	749 (57.7)	0.191*	0.662
Laboratory test								
BNP (pg/ml)	648.8 (474.6–909.2)	615.7 (480.5–843.6)	−2.030‡	0.042	646.4 (474.1–911.6)	610.6 (480.6–842.5)	−1.832‡	0.067
eGFR (ml/min)	89.6 ± 15.4	92.2 ± 14.7	5.408†	<0.001	89.6 ± 15.4	90.4 ± 15.1	1.354†	0.176
ESR (mm/h)	7 (4–16)	7 (3–14)	−2.983‡	0.003	7 (4–16)	7 (3–13)	−3.795‡	<0.001
Hemoglobin (g/L)	140.9 ± 15.9	144.2 ± 14.8	6.553†	<0.001	140.9 ± 15.9	144.3 ± 16.0	5.472†	<0.001
Procedural characteristics								
Thrombolysis	50 (3.7)	134 (3.6)	<0.001*	0.990	49 (3.8)	50 (3.9)	0.011*	0.918
Syntax score								
0–22	1188 (86.8)	3233 (88.0)	1.615*	0.446	1129 (87.0)	1143 (88.1)	0.796*	0.672
23–32	153 (11.2)	383 (10.4)			143 (11.0)	133 (10.3)		
≥33	27 (2.0)	58 (1.6)			25 (1.9)	21 (1.6)		
Number of stents								
0	80 (5.8)	207 (5.6)	1.055*	0.590	72 (5.6)	66 (5.1)	0.279*	0.870
1	512 (37.48)	1433 (39.0)			485 (37.4)	486 (37.5)		
≥2	776 (56.7)	2034 (55.4)			740 (57.1)	745 (57.4)		
IABP	29 (2.1)	36 (1.0)	10.181*	0.001	21 (1.6)	19 (1.5)	0.102*	0.750
Medication								
Warfarin	2 (0.1)	6 (0.2)	0.018*	0.892	2 (0.1)	4 (0.3)	0.668*	0.414
GPI	222 (16.2)	604 (16.4)	0.033*	0.857	202 (15.6)	233 (18.0)	2.654*	0.103

Data are presented as n (%), mean ± SD or median (interquartile range). *χ^2 values; †t values; ‡z value. PPI: Proton-pump inhibitors; mTEG: Modified thromboelastograph; PSM: Propensity score matching; PAD: Peripheral artery disease; CVD: Cerebrovascular disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; LVEF: Left ventricular ejection fraction; SAP: Systolic blood pressure; BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; ESR: Erythrocyte sedimentation rate; IABP: Intra-aortic balloon pump; GPI: Glycoprotein IIb/IIIa inhibitors; SD: Standard deviation; 1 mmHg=0.133 kPa.

blood to evaluate the clot strength and ensures a quantitative analysis of platelet function, which is more likely to mirror the platelet behavior in human blood vessels and is capable of identifying patients undergoing PCI who are at risk for ischemic events.[18,19]

Third, the combination of PPIs with DAPT might not increase the risk of MACCE at up to 2 years of follow-up. This finding is consistent with those of randomized controlled trials, which suggested no association of PPI use with increased risk of ischemic events.[20-22] Some retrospective analyses suggested higher incidence rates of cardiovascular events in patients taking both DAPT and PPIs.[5-7] The reason might be a lack of adjustment for confounding factors. A meta-analysis that included a total of 23 studies and 222,311 patients showing increased cardiovascular risks with PPIs in the absence of clopidogrel also suggested that confounding and bias were strong possibilities.[21] The PLATO trial studied 9291 patients with concomitant clopidogrel use and found that the risk of 1-year cardiovascular events was higher (*HR* 1.20, 95% *CI* 1.04–1.38) in patients treated with PPIs than in patients who were not treated with PPI. Similarly, this increased

Table 3: Platelet function results among patients receiving mTEG according to PPI use before and after PSM

Variables	Before PSM				After PSM			
	PPI (n = 1368)	No PPI (n = 3674)	Statistics	P	PPI (n = 1297)	No PPI (n = 1297)	Statistics	P
ADP-inhibition (%)	37.6 (15.9–64.2)	42.2 (20.4–73.2)	−4.402†	<0.001	37.7 (16.1–64.9)	43.0 (23.0–75.0)	−4.750†	<0.001
ADP-inhibition <30%	565 (41.3)	1327 (36.1)	11.420*	0.001	528 (40.7)	30 (2.3)	566.261*	<0.001

Data are presented as n (%) or median (interquartile range). *χ^2 values; †z values. mTEG: Modified thromboelastograph; PSM: Propensity score matching; PPI: Proton-pump inhibitors; ADP: Adenosine diphosphate.

Table 4a: Clinical outcomes among all patients according to PPI use before and after PSM

Clinical endpoint	Before PSM				After PSM			
	PPI (n = 2142)	No PPI (n = 5726)	χ^2	P	PPI (n = 1966)	No PPI (n = 1966)	χ^2	P
Primary endpoint								
MACCE	273 (12.7)	716 (12.5)	0.086	0.769	244 (12.4)	249 (12.7)	0.048	0.827
Secondary endpoint								
All cause death	30 (1.4)	75 (1.3)	0.097	0.755	25 (1.3)	27 (1.4)	0.080	0.777
MI	51 (2.4)	116 (2.0)	0.950	0.330	48 (2.4)	48 (2.4)	<0.001	0.998
Unplanned TVR	195 (9.1)	504 (8.8)	0.199	0.655	174 (8.9)	176 (9.0)	0.006	0.937
Stent thrombosis	25 (1.2)	52 (0.9)	1.095	0.295	21 (1.1)	17 (0.9)	0.425	0.515
Stroke	31 (1.4)	78 (1.4)	0.084	0.772	28 (1.4)	22 (1.1)	0.721	0.396
Safety endpoint								
Bleeding	142 (6.6)	372 (6.5)	0.060	0.806	137 (7.0)	116 (5.9)	1.860	0.173
BARC 3 or 5	10 (0.5)	10 (0.5)	0.095	0.758	10 (0.5)	4 (0.2)	2.623	0.105
GI bleeding	36 (1.7)	71 (1.2)	2.272	0.132	36 (1.8)	23 (1.2)	2.960	0.085

Data are presented as n (%). PPI: Proton-pump inhibitors; PSM: Propensity score matching; MACCE: Major adverse cardiovascular and cerebrovascular events; MI: Myocardial infarction; TVR: Target vessel revascularization; BARC: Bleeding Academic Research Consortium; GI: Gastrointestinal.

Table 4b: Multivariate Cox proportional regression analysis among all patients according to PPI use before and after PSM

Clinical endpoint	Before PSM		After PSM	
	HR (95% *CI*)	P	*HR* (95% *CI*)	P
Primary endpoint				
MACCE	1.049 (0.854–1.289)	0.651	0.970 (0.808–1.165)	0.745
Secondary endpoint				
All cause death	0.775 (0.410–1.465)	0.433	0.935 (0.534–1.634)	0.812
MI	0.838 (0.508–1.383)	0.490	0.904 (0.597–1.368)	0.634
Unplanned TVR	1.042 (0.822–1.322)	0.733	0.992 (0.798–1.233)	0.942
Stent thrombosis	0.964 (0.451–2.064)	0.925	0.736 (0.380–1.425)	0.363
Stroke	2.171 (0.896–5.258)	0.086	0.730 (0.409–1.302)	0.286
Safety endpoint				
Bleeding	1.094 (0.821–1.458)	0.539	0.841 (0.651–1.086)	0.184
BARC 3 or 5	0.572 (0.218–1.502)	0.257	0.341 (0.103–1.132)	0.079
GI bleeding	0.800 (0.455–1.409)	0.440	0.586 (0.341–1.009)	0.054

PPI: Proton-pump inhibitors; PSM: Propensity score matching; *HR*s: Hazard ratios; *CI*s: Confidence intervals; MACCE: Major adverse cardiovascular and cerebrovascular events; MI: Myocardial infarction; TVR: Target vessel revascularization; BARC: Bleeding Academic Research Consortium; GI: Gastrointestinal.

risk in the PPI group was also reported with the use of ticagrelor, which is a P2Y12 inhibitor that does not need biotransformation and has no effect on the CYP2C19 isoenzyme. That study also indicated that PPI use is more of a marker for higher rates of cardiovascular events.[22]

There are several limitations of this study. The use of PPIs was not selected in a randomized fashion and was determined at the discretion of the physician. The indication for PPI treatment was not captured. Although PSM was performed, potential unmeasured confounding factors remain. Different PPI types might have variable interactions with the cytochrome P450 system, which is not specified in this study. In this observational study, we did not conduct a before and after analysis, which could provide more powerful evidence on the pharmacodynamic effect of PPIs on platelet

aggregation inhibition by clopidogrel. In addition, PPI use might be discontinued during the 2-year follow-up.

In conclusion, the combination of PPIs with DAPT was not associated with increased risk of MACCE in patients who underwent PCI at up to 2 years of follow-up.

Financial support and sponsorship

This study was supported by grants from the National Natural Science Foundation of China (No. 81470486), and the National Key Research and Development Program of China during the 13th 5-Year Plan Period (No. 2016YFC1301301).

Conflicts of interest

There are no conflicts of interest.

References

1. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The task force for dual antiplatelet therapy in coronary artery disease of the European society of cardiology (ESC) and of the European association for cardio-thoracic surgery (EACTS). Eur Heart J 2017;[Epub ahead of print]. doi: 10.1093/eurheartj/ehx419.
2. Chandrasekhar J, Bansilal S, Baber U, Sartori S, Aquino M, Farhan S, *et al.* Impact of proton pump inhibitors and dual antiplatelet therapy cessation on outcomes following percutaneous coronary intervention: Results from the PARIS registry. Catheter Cardiovasc Interv 2017;89:E217-25. doi: 10.1002/ccd.26716.
3. Juurlink DN, Gomes T, Paterson JM, Hellings C, Mamdani MM. Trends in the coprescription of proton pump inhibitors with clopidogrel: An ecological analysis. CMAJ Open 2015;3:E428-31. doi: 10.9778/cmajo.20140078.
4. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, *et al.* Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: The randomized, double-blind OCLA (Omeprazole CLopidogrel aspirin) study. J Am Coll Cardiol 2008;51:256-60. doi: 10.1016/j.jacc.2007.06.064.
5. Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, *et al.* A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713-8. doi: 10.1503/cmaj.082001.
6. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, *et al.* Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937-44. doi: 10.1001/jama.2009.261.
7. Stockl KM, Le L, Zakharyan A, Harada AS, Solow BK, Addiego JE, *et al.* Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. Arch Intern Med 2010;170:704-10. doi: 10.1001/archinternmed.2010.34.
8. Weisz G, Smilowitz NR, Kirtane AJ, Rinaldi MJ, Parvataneni R, Xu K, *et al.* Proton pump inhibitors, platelet reactivity, and cardiovascular outcomes after drug-eluting stents in clopidogrel-treated patients: The ADAPT-DES study. Circ Cardiovasc Interv 2015;8. pii: e001952. doi: 10.1161/CIRCINTERVENTIONS.114.001952.
9. Ayub A, Parkash O, Naeem B, Murtaza D, Khan AH, Jafri W, *et al.* Proton pump inhibitors and other disease-based factors in the recurrence of adverse cardiovascular events following percutaneous coronary angiography: A long-term cohort. Indian J Gastroenterol 2016;35:117-22. doi: 10.1007/s12664-016-0645-0.
10. Gargiulo G, Costa F, Ariotti S, Biscaglia S, Campo G, Esposito G, *et al.* Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6- or 24-month dual-antiplatelet therapy duration: Insights from the prolonging dual-antiplatelet treatment after grading stent-induced intimal hyperplasia Study trial. Am Heart J 2016;174:95-102. doi: 10.1016/j.ahj.2016.01.015.
11. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, *et al.* 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A Report of the American college of cardiology/American heart association task force on clinical practice guidelines: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016;134:e123-55. doi: 10.1161/CIR.0000000000000404.
12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Circulation 2007;116:2634-53. doi: 10.1161/CIRCULATIONAHA.107.187397.
13. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, *et al.* Clinical end points in coronary stent trials: A case for standardized definitions. Circulation 2007;115:2344-51. doi: 10.1161/CIRCULATIONAHA.106.685313.
14. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, *et al.* Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. Circulation 2011;123:2736-47. doi: 10.1161/CIRCULATIONAHA.110.009449.
15. Hobson AR, Petley GW, Dawkins KD, Curzen N. A novel fifteen minute test for assessment of individual time-dependent clotting responses to aspirin and clopidogrel using modified thrombelastography. Platelets 2007;18:497-505. doi: 10.1080/09537100701329162.
16. Madsen EH, Saw J, Kristensen SR, Schmidt EB, Pittendreigh C, Maurer-Spurej E, *et al.* Long-term aspirin and clopidogrel response evaluated by light transmission aggregometry, verifyNow, and thrombelastography in patients undergoing percutaneous coronary intervention. Clin Chem 2010;56:839-47. doi: 10.1373/clinchem.2009.137471.
17. Gilard M, Arnaud B, Le Gal G, Abgrall JF, Boschat J. Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin. J Thromb Haemost 2006;4:2508-9. doi: 10.1111/j.1538-7836.2006.02162.x.
18. Lee JK, Wu CK, Juang JM, Tsai CT, Hwang JJ, Lin JL, *et al.* Non-carriers of reduced-function CYP2C19 alleles are most susceptible to impairment of the anti-platelet effect of clopidogrel by proton-pump inhibitors: A pilot study. Acta Cardiol Sin 2016;32:215-22. doi: 10.6515/ACS20160201A.
19. Tang XF, Han YL, Zhang JH, Wang J, Zhang Y, Xu B, *et al.* Comparing of light transmittance aggregometry and modified thrombelastograph in predicting clinical outcomes in Chinese patients undergoing coronary stenting with clopidogrel. Chin Med J 2015;128:774-9. doi: 10.4103/0366-6999.152611.
20. Vaduganathan M, Cannon CP, Cryer BL, Liu Y, Hsieh WH, Doros G, *et al.* Efficacy and safety of proton-pump inhibitors in high-risk cardiovascular subsets of the COGENT trial. Am J Med 2016;129:1002-5. doi: 10.1016/j.amjmed.2016.03.042.
21. Kwok CS, Jeevanantham V, Dawn B, Loke YK. No consistent evidence of differential cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: Meta-analysis. Int J Cardiol 2013;167:965-74. doi: 10.1016/j.ijcard.2012.03.085.
22. Goodman SG, Clare R, Pieper KS, Nicolau JC, Storey RF, Cantor WJ, *et al.* Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: Insights from the platelet inhibition and patient outcomes trial. Circulation 2012;125:978-86. doi: 10.1161/CIRCULATIONAHA.111.032912.