MAYO CLINIC

Proton Pump Inhibitors and In-Hospital Gastrointestinal Bleeding in Patients With Acute Coronary Syndrome Receiving Dual Antiplatelet Therapy

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Abstract

Objective: To evaluate the association between proton pump inhibitor (PPI) use and in-hospital gastrointestinal (GI) bleeding in patients with acute coronary syndrome (ACS) taking dual antiplatelet therapy (DAPT).

Patients and Methods: This study is based on the Improving Care for Cardiovascular Disease in China-ACS project, an ongoing collaborative registry and quality improvement project of the American Heart Association and the Chinese Society of Cardiology. A total of 25,567 patients with ACS taking DAPT from 172 hospitals from July 1, 2017, through December 31, 2018, were included. Multivariable Cox regression and propensity score–matched analyses were used to evaluate the association between PPI use and in-hospital GI bleeding.

Results: Of these patients with ACS, 63.9% (n=16,332) were prescribed PPIs within 24 hours of admission. Patients using PPIs had a higher rate of GI bleeding compared with those not using PPIs (1.0% vs 0.5%; $P<.001$). In the multivariable Cox regression analysis, early PPI use was associated with a 58% higher risk of GI bleeding (hazard ratio, 1.58; 95% CI, 1.15 to 2.18; $P=.005$). Further propensity score matching attenuated the association but still showed that patients using PPIs had a higher rate of GI bleeding (0.8% vs 0.6%; $P=.04$).

Conclusion: In China, PPIs are widely used within 24 hours of admission in patients with ACS taking DAPT. An increased risk of GI bleeding is observed in inpatients with early PPI use. Randomized trials on early use of PPIs in patients with ACS receiving DAPT are warranted.

Trial Registration: clinicaltrials.gov Identifier: NCT02306616.

 ■ Mayo Clin Proc. 2022;97(4):682-692

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Dual antiplatelet therapy (DAPT) with aspirin plus $P2Y_{12}$ receptor inhibitors has become the cornerstone treatment for patients with acute coronary syndrome (ACS), but it also carries the safety hazard of bleeding.[1-6] Of all-type bleeding events, gastrointestinal (GI) bleeding is recognized as the most common[7] and preventable by using proton pump inhibitors (PPIs), a group of drugs with the main action of reducing the production of stomach acid.[8-10] To date, almost all guidelines for ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation (NSTE) ACS have recommended PPI use in patients at higher-than-average risk for GI bleeding.[2-6] However, evidence is lacking as to whether PPIs have a protective effect on GI bleeding for patients with ACS in the acute phase, when patients are at the highest risk of

bleeding. Some studies have suggested adverse effects of PPI use, including damage to the lower GI tract.[11-14] Therefore, evaluation of the association between PPI use and overall (including upper and lower) GI bleeding in patients with ACS in the acute phase, when patients are loaded with various medications, may be informative.

In this study, we report the status of PPI use in patients with ACS receiving DAPT during hospitalization and evaluate the association between PPI use and in-hospital GI bleeding in these patients based on the Improving Care for Cardiovascular Disease in China (CCC)-ACS project.

METHODS

Study Design

The CCC-ACS project is a large nationwide registry and quality improvement study with an ongoing database focusing on quality of ACS care launched in 2014 as a collaborative initiative of the American Heart Association and the Chinese Society of Cardiology. In brief, in phases I and II of this project, 150 tertiary hospitals were included across China. During phase III (from July 2017 onward) and phase IV (from November 2018 onward), a further 82 secondary hospitals and 8 new tertiary hospitals were enrolled. A standard web-based data collection platform (Oracle Clinical Remote Data Capture; Oracle Corp) was used in this study, with the most recent update in July 2017. Details of the design and methods of the CCC project have been published elsewhere.[15,16]

This study complied with the Declaration of Helsinki. Institutional review board approval was granted for this research by the ethics committee of Beijing Anzhen Hospital, Capital Medical University. No informed consent was required.

Study Population

We started collecting PPI information from phase III of the CCC-ACS project, so the population of this study was enrolled from July 2017 onward. From July 1, 2017, through December 31, 2018, a total of 25,567 patients from 172 hospitals across China with a definite principal diagnosis of ACS and receiving DAPT during hospitalization were included in this study. Acute coronary syndrome was defined according to the guidelines issued by the Chinese Society of Cardiology for the diagnosis and management of patients with STEMI and NSTE-ACS.[5,6]

Study Variables

PPI Use and PPI Type. Information about PPIs was obtained from patients' medical records, including whether patients used PPIs before hospitalization and within 24 hours of this hospitalization, and the type of PPI used within 24 hours of this hospitalization.

In-Hospital Outcomes. The primary outcome of this study was GI bleeding, defined as GI bleeding that occurred during hospitalization, was diagnosed by physicians, and was recorded in medical records with time of occurrence. Patients who had the GI bleeding before taking PPIs were excluded through the double check of medical records on all the cases with records of GI bleeding that occurred within 24 hours of hospitalization among patients using PPIs. The secondary outcome was all-type bleeding, defined as all documented bleeding in case records or a decline in hemoglobin levels of at least 4 g/dL (to convert to g/L, multiply by 10) during hospitalization.[17]

Definition of Bleeding-Related Variables. Because the CRUSADE bleeding score can be used as an objective means of stratifying the risk of GI bleeding and judging the need for GI-protective medications,[10] it was used as an indicator of GI and all-type bleeding risk in this study (Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org). CRUSADE bleeding risk scores were calculated based on corresponding scores of predictors.[18] Because of the high rate of missing data concerning weight of patients, we used estimated glomerular filtration rate, instead of creatinine clearance rate estimated using the Cockcroft-Gault formula, to represent patients' renal function. Patients were classified as very low risk, low risk, intermediate risk,

TABLE. Comparison of Characteristics and Treatment Between Patients With and Without PPI use

Characteristic	PPI use (n=16,332)	No PPI use (n=9235)	*P* value
Age (y), mean ± SD	63.7±12.4	62.7±12.2	<.001
Age >75 y (No. [%])	3266 (20.0)	1544 (16.7)	<.001
Female sex (No. [%])	4308 (26.4)	2474 (26.8)	.47
CHD history (No. [%])	1910 (11.7)	1278 (13.8)	<.001
Heart failure history (No. [%])	297 (1.8)	207 (2.2)	.02
Renal failure history (No. [%])	282 (1.7)	130 (1.4)	.05
Bleeding history/tendency (No. [%])	233 (1.4)	82 (0.9)	<.001
Baseline hemoglobin <9 g/dL (No. [%])	362 (2.2)	178 (1.9)	.12
Systolic blood pressure <90 mm Hg (No. [%])	376 (2.3)	156 (1.7)	.001
First Killip class (No. [%])			.003
I	13,051 (79.9)	7361 (79.7)	
II-III	2749 (16.8)	1635 (17.7)	
IV	532 (3.3)	239 (2.6)	
Cardiac arrest at admission (No. [%])	108 (0.7)	57 (0.6)	.67
Substantially elevated myocardial injury marker (No. [%])	14,496 (88.8)	7055 (76.4)	<.001
CRUSADE bleeding risk stratification (No. [%])			.09
Very low	6038 (37.0)	3525 (38.2)	
Low	4787 (29.3)	2637 (28.6)	
Moderate	2856 (17.5)	1652 (17.9)	
High	1613 (9.9)	891 (9.7)	
Very high	1038 (6.4)	530 (5.7)	
Prehospital treatment (No. [%])			
Antiplatelet therapy			<.001
DAPT	1758 (10.8)	1508 (16.3)	
Aspirin only	1172 (7.2)	786 (8.5)	
$P2Y_{12}$ receptor inhibitors only	449 (2.8)	233 (2.5)	
None	12,953 (79.3)	6708 (72.6)	
Warfarin	37 (0.2)	19 (0.2)	.73
PPI	1033 (6.3)	48 (0.5)	<.001
In-hospital treatment (No. [%])			
Loading status of DAPT			<.001
Dual loading	11,628 (71.2)	5458 (59.1)	
Aspirin loading only	343 (2.1)	318 (3.4)	
$P2Y_{12}$ inhibitors loading only	806 (4.9)	463 (5.0)	
Nonloading	3555 (21.7)	2996 (32.4)	
Glycoprotein IIb/IIIa receptor antagonist	4386 (26.9)	1861 (20.2)	<.001
Anticoagulants	11,936 (73.1)	5722 (62.0)	<.001
Warfarin	97 (0.6)	62 (0.7)	.45
Fibrinolytic therapy	753 (4.6)	456 (4.9)	.24
PCI	12,451 (76.2)	6285 (68.1)	<.001
Type of ACS (No. [%])			<.001
STEMI	10,107 (61.9)	4711 (51.0)	
NSTE-ACS	6225 (38.1)	4524 (49.0)	

ACS, acute coronary syndrome; CHD, coronary heart disease; DAPT, dual antiplatelet therapy; NSTE, non–ST-segment elevation; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

SI conversion factors: To convert hemoglobin values to g/L, multiply by 10.

Mayo Clin Proc. ■ April 2022;97(4):682-692 ■ https://doi.org/10.1016/j.mayocp.2021.11.037
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high risk, and very high risk according to CRUSADE bleeding risk scores.

Prehospital and in-hospital treatment data of patients with ACS were also collected. Prehospital treatment was defined as in-use if the patient used the drug within 2 weeks before this hospitalization. Prehospital antiplatelet therapy was divided into 4 groups according to drug use status: none, aspirin only, $P2Y_{12}$ inhibitors only, and DAPT. According to the type and dose of DAPT administered within 24 hours of first medical contact, the loading status of DAPT was divided into 4 groups as follows: loading with neither aspirin nor $P2Y_{12}$ receptor inhibitor (nonloading); aspirin loading only; $P2Y_{12}$ receptor inhibitor loading only; and loading with aspirin and $P2Y_{12}$ receptor inhibitor (dual loading). The loading dose of aspirin was defined as 150 mg or more, and the loading dose of $P2Y_{12}$ receptor inhibitor was defined as 300 mg or more of clopidogrel or 180 mg or more of ticagrelor. Other in-hospital treatments were defined as used or not used according to the original medical records. Detailed definitions of other variables are provided in the Supplemental Methods, available online at http://www.mayoclinicproceedings.org.

Statistical Analyses

Continuous variables with normal distribution are shown as mean ± SD, and differences between groups were compared using *t* tests; categorical variables are presented as number (percentage) and were compared using the χ^2 test. Survival curves of GI bleeding are displayed using Kaplan-Meier curves and were compared using log-rank tests. Multivariable Cox proportional hazard modeling was performed to examine the association between PPI use and GI bleeding by controlling for potential confounding factors. All candidate adjustment variables are shown and compared between patients with and without PPI use in the Table. After stepwise selection with entry and exit criteria both set at the $P=.05$ level, the variables listed in Supplemental Table 1, available online at http://www.mayoclinicproceedings.org, were eventually included in the multivariable-adjusted Cox regression model. The observation period for the patients as the parameter of Kaplan-Meier analysis and the Cox regression model was defined as the time from the day of admission to the day of discharge or to day 15 of hospitalization when hospitalization exceeded 15 days. Hazard ratios (HRs) with 95% CIs are reported.

Multivariable logistic regression was applied to evaluate the association between PPI use and all-type bleeding that occurred during hospitalization. The same candidate adjustment variables presented in the Table were considered in the logistic regression model, and variables included in the final model are also presented in Supplemental Table 1. Odds ratios (ORs) with 95% CIs are reported.

Subgroup analyses of types of ACS (STEMI/NSTE-ACS) and CRUSADE bleeding risk stratifications (very low or low risk/moderate risk/high or very high risk) were also performed, with multivariable adjustment in Cox regression and logistic regression models. In addition, we excluded patients who had bleeding on the day of admission for sensitivity analysis.

We further conducted a propensity score–matched analysis to reevaluate the association between PPI use and in-hospital outcomes. First, a propensity score for using PPIs was calculated using a logistic regression model with the following variables: participating hospital, patient age, sex, systolic blood pressure, heart rate, hemoglobin level, estimated glomerular filtration rate, substantially elevated myocardial injury markers, first Killip class, cardiogenic shock at admission, diabetes mellitus, history coronary heart disease, cerebrovascular disease, heart failure, renal failure, prehospital treatment with antiplatelet drugs, warfarin, in-hospital loading status of DAPT, in-hospital treatment with glycoprotein IIb/IIIa receptor antagonist, warfarin, anticoagulants, fibrinolytic therapy, percutaneous coronary intervention, and type of ACS. Patients with and without PPI use were then matched at a 1:1 ratio by propensity score using nearest-neighbor matching without replacement, with a caliper of 0.02. The absolute standardized differences

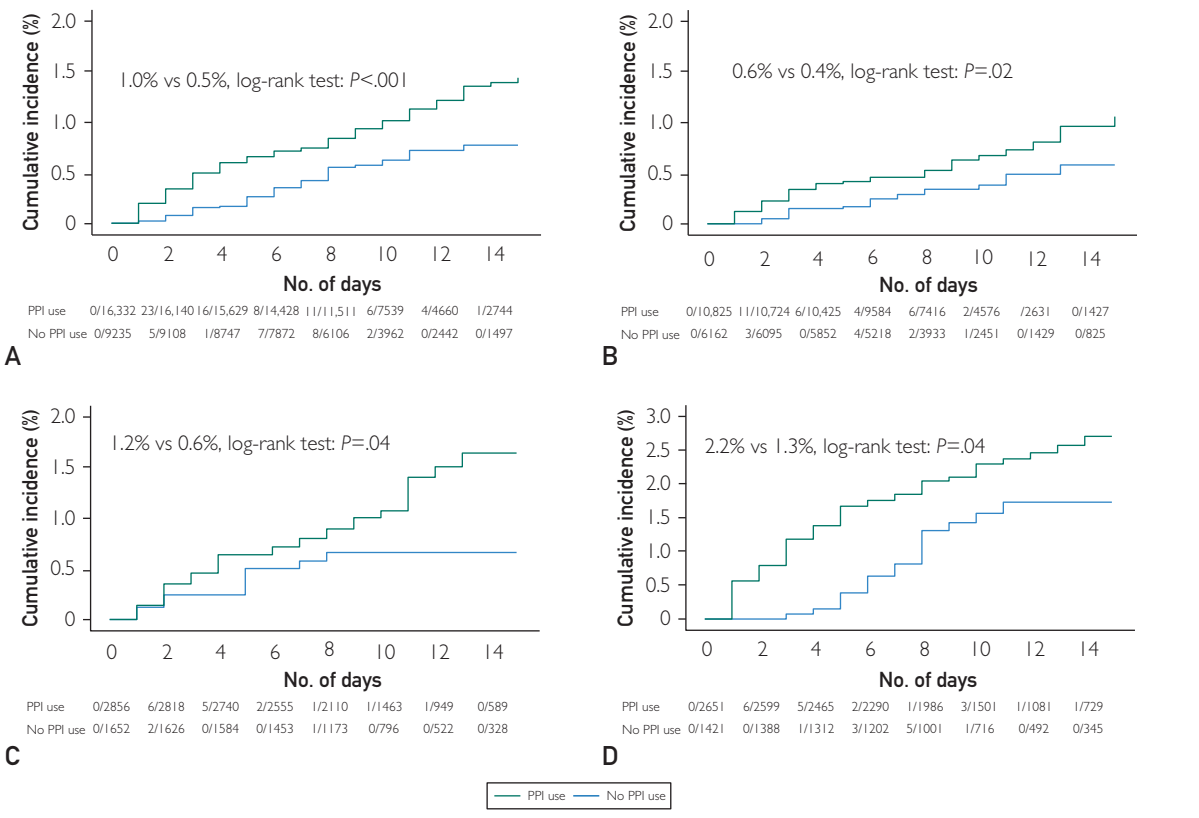


FIGURE 1. Incidence of in-hospital gastrointestinal bleeding in patients with acute coronary syndrome (ACS) with and without proton pump inhibitor (PPI) use. A, All patients. B, Patients with very low or low CRUSADE bleeding risk. C, Patients with moderate CRUSADE bleeding risk. D, Patients with high or very high CRUSADE bleeding risk.

of variables included for the calculation of propensity score were compared before and after propensity score matching. Standardized differences less than 10.0% for these included variables indicated a relatively small imbalance. In-hospital outcomes are presented as number (percentage) and are compared using a χ^2 test for paired data. Univariate Cox regression analysis was performed to calculate HRs and 95% CIs.

For variables with a missing rate of less than 15%, we imputed missing values using the sequential regression multiple imputation method implemented by IVEware software, Version 0.2 (Survey Research Center, University of Michigan). Detailed information on missing rates of each variable and strategies for the management of missing data are presented in Supplemental Table 2, available online at http://www.mayoclinicproceedings.org.

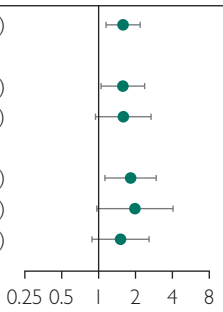
Statistical analyses were performed using SAS Software, Version 9.4 (SAS Institute Inc) and Stata Statistical Software: Release 14.0 (StataCorp LP). Two-tailed $P<.05$ was considered statistically significant.

RESULTS

PPI Use Among Patients With ACS

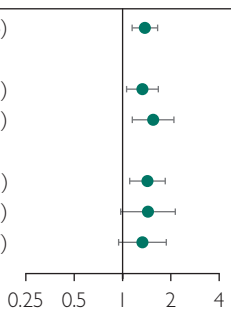
Of 25,567 patients with ACS, 63.9% (n=16,332) used PPIs within 24 hours of admission, varying from 0.7% to 100% among participating hospitals, with more than 68.3% of hospitals' PPI use rates at 50% or higher. Patients in different CRUSADE bleeding risk stratifications had similar rates of PPI use, with 63.1% in patients with very low risk and 66.2% in those with very high risk (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org).

	PPI use	No PPI use	HR (95% CI)[a]	*P* value
	Events (No./total No.)	Events (No./total No.)		
All ACS	161/16,332	50/9235	1.58 (1.15-2.18)	.005
Type of ACS				
STEMI	106/10,107	30/4711	1.58 (1.05-2.37)	.03
NSTE-ACS	55/6225	20/4524	1.59 (0.94-2.68)	.07
CRUSADE bleeding risk stratifications				
Very low or low risk	69/10,825	22/6162	1.82 (1.12-2.95)	.02
Moderate risk	33/2856	10/1652	1.98 (0.97-4.05)	.06
High or very high risk	59/2651	18/1421	1.51 (0.88-2.58)	.13



A

	PPI use	No PPI use	OR (95% CI)[a]	*P* value
	Events (No./total No.)	Events (No./total No.)		
All ACS	467/16,332	169/9235	1.38 (1.15-1.66)	<.001
Type of ACS				
STEMI	307/10,107	105/4711	1.30 (1.04-1.63)	.01
NSTE-ACS	160/6225	64/4524	1.55 (1.15-2.09)	.004
CRUSADE bleeding risk stratifications				
Very low or low risk	237/10,825	85/6162	1.43 (1.11-1.85)	.006
Moderate risk	98/2856	36/1652	1.44 (0.97-2.13)	.07
High or very high risk	132/2651	48/1421	1.33 (0.94-1.87)	.10



B

FIGURE 2. Associations between proton pump inhibitor (PPI) use and in-hospital gastrointestinal bleeding (A) and all-type bleeding (B). [a]No PPI use was the reference group. ACS = acute coronary syndrome; HR = hazard ratio; NSTE = non–ST-segment elevation; OR = odds ratio; STEMI = ST-segment elevation myocardial infarction.

Of the different types of PPIs used, pantoprazole accounted for the highest proportion (50.6%), followed by rabeprazole (27.2%), lansoprazole (12.2%), and others (10%).

Comparison of Characteristics and Treatment Between Patients With and Without PPI Use

Users and nonusers of PPIs had similar CRUSADE bleeding risk stratifications, but PPI users received more active antithrombotic therapy during hospitalization, including higher frequencies of dual-loading DAPT (71.2% vs 59.1%; *P*<.001), glycoprotein IIb/IIIa receptor antagonist (26.9% vs 20.2%; *P*<.001) and anticoagulant (73.1% vs 62.0%; *P*<.001) use, and percutaneous coronary intervention (76.2% vs 68.1%; *P*<.001) (Table).

Association Between PPI Use and In-Hospital GI Bleeding

Gastrointestinal bleeding occurred in 217 patients with ACS (0.9%) during hospitalization, with 211 occurring within 15 days of hospitalization. In Kaplan-Meier analysis, patients using PPIs displayed a higher incidence of GI bleeding compared with patients not using PPIs (1.0% vs 0.5%; log-rank *P*<.001) (Figure 1A). In patients with low, moderate, or high risk of GI bleeding, those using PPIs still had higher bleeding rates (Figure 1B–D). After multivariable adjustment, PPI use was associated with a 58% higher risk of in-hospital GI bleeding among all patients with ACS (HR, 1.58; 95% CI, 1.15 to 2.18; *P*=.005) (Figure 2A).

After excluding patients with bleeding and death on the day of admission from the sensitivity analysis, it also showed that PPI use was associated with a higher risk of in-hospital GI bleeding (HR, 1.39; 95% CI, 1.00 to 1.94; P=.05).

In further subgroup analysis by ACS types and CRUSADE bleeding risk stratifications using multivariate Cox regression, PPI use was still associated with increased risks of GI bleeding, especially among those with very low or low risk (HR, 1.82; 95% CI, 1.12 to 2.95; P=.02) (Figure 2A).

Association Between PPI Use and In-Hospital All-Type Bleeding

All-type bleeding occurred in 636 patients with ACS during hospitalization. Patients using PPIs had a higher rate of all-type bleeding compared with patients not using PPIs (2.9% vs 1.8%; P<.001). And the higher rates of all-type bleeding in PPI users could also be observed in patients in different CRUSADE bleeding risk stratifications (Supplemental Figure 3, available online at http://www.mayoclinicproceedings.org). After multivariable adjustment, PPI use was associated with a 38% increased risk of all-type bleeding in all patients with ACS (OR, 1.38; 95% CI, 1.15 to 1.66; P<.001) (Figure 2B). In further subgroup analysis by ACS types and CRUSADE bleeding risk stratifications using multivariable logistic regression, PPI use was still associated with increased risks of all-type bleeding (Figure 2B).

Propensity Score–Matched Analysis

In propensity score matching, 8329 patients with PPI use were matched with 8329 patients without PPI use. After matching, the absolute standardized differences were less than 10.0% for all variables included for the calculation of propensity score, indicating that patients with ACS with and without PPI use were well matched (Supplemental Figure 4, available online at http://www.mayoclinicproceedings.org). The rates of GI bleeding as well as all-type bleeding remained higher in patients with PPI use compared with those without PPI use (GI bleeding: 0.8% vs 0.6%; P=.04; all-type bleeding: 2.6% vs 1.9%; P=.002). Patients with PPI use had a 1.4-fold risk of GI bleeding (HR, 1.38; 95% CI, 0.98 to 2.06; P=.07) and a 1.4-fold risk of all-type bleeding (OR, 1.39; 95% CI, 1.12 to 1.71; P<.001).

To further verify the results, hospitals were divided into 3 groups by the tertiles of PPI use rate of different hospitals. The results showed that the rates of GI bleeding increased with the increasing use rates of PPI in the hospital (first tertile: 0.6%, second tertile: 0.7%, last tertile: 0.8%; $P_{\text{for trend}}$=.116).

DISCUSSION

In this study, we found that the early use rate of PPIs in patients with ACS is high. Furthermore, there is an association between PPI use and increased risk of in-hospital GI bleeding in patients with ACS taking DAPT in the acute phase, even after adjustment for other factors, based on a nationally representative registry study.

High Use Rate of PPIs Among Patients With ACS

We found that PPIs were widely used among inpatients with ACS taking DAPT in China. Despite gaps observed among different hospitals, most hospitals had PPI use rates greater than 50%, regardless of the risk of GI bleeding. A study from the United States reported that 41% of inpatients with ACS taking clopidogrel used PPIs in 2016.[19] A recently published study based on Danish nationwide registries reported that even among patients identified as being at high risk for GI bleeding by the guidelines, the use rate of PPIs within 7 days after discharge was only approximately 40% in 2014.[20] However, a single-center Dutch registry displayed that PPI treatment at discharge increased from 34.7% in 2010 to 88.7% in 2014,[21] indicating that the use of PPIs has increased in clinical practice in recent years.

The high use rate of PPIs in China might reflect clinicians' concerns about bleeding caused by active antithrombotic treatment; meanwhile, the similar use rates of PPIs among patients with different bleeding risk might reflect clinicians' uncertainty about bleeding risk.

PPIs and Increased GI Bleeding

In this study, we observed that early use of PPIs was associated with an increased risk of in-hospital GI bleeding in multivariable Cox regression analysis and propensity score matching. This result was contrary to clinicians' expectation that use of PPIs could reduce risk of GI bleeding. This result suggested that PPIs could not effectively prevent all GI bleeding in the acute phase. The mechanism of PPIs involves inhibition of the H-K-adenosine triphosphatase enzyme in the parietal cells of the gastric mucosa.[22] Therefore, it is effective for alleviating acid peptic symptoms, facilitating healing of inflamed or ulcerated mucosa, and reducing nonsteroidal anti-inflammatory drug (NSAID)—associated gastric injury, but its effect on preventing acute bleeding may be limited, although it can act quickly to inhibit gastric acid secretion. In addition, it could not protect the small intestine by its mechanism of action.[22,23] A study from Spain reported that lower GI bleeding was more common than upper GI bleeding (74% vs 26%) in patients on DAPT and PPI co-therapy.[24] Increasing studies have pointed out that PPIs might cause damage to the lower GI tract when combined with NSAIDs.[13,14,25,26] One population-based, retrospective cohort study from Canada in 2008 reported that the crude rates of hospitalization for complications in the lower GI tract were higher among users of NSAIDs with PPIs (1.4 cases per 1000 patient-years) compared with those using NSAIDs but without PPIs (0.7 cases per 1000 patient-years).[27] An animal study with rats published in 2011 reported that PPIs could alter the gut microbiota and significantly exacerbate naproxen- and celecoxib-induced intestinal ulceration and bleeding.[25] Consistent with this animal study, a randomized, placebo-controlled trial found that participants taking the cyclooxygenase 2 inhibitor celecoxib plus PPIs for 2 weeks had a significantly higher incidence of small-bowel injury than patients taking celecoxib plus placebo (44.4% vs 16.7%; P=.04); and the number of erosions in each member of the celecoxib plus PPI group was greater than that in each member of the celecoxib plus placebo group (P=.02).[26] A multicenter capsule endoscopy registry study published in 2014 also found that PPI use was associated with increased risk of the presence of mucosal breaks (OR, 2.04; 95% CI, 1.05 to 3.97).[28] This study supposed that acid suppression might exacerbate NSAID- and/or aspirin-induced small-bowel injuries.[28] A recent study based on Danish nationwide registries evaluated the effect of PPIs on 1-year all, upper, and non—upper GI bleeding in discharged patients treated with DAPT.[20] It found that PPI use was significantly associated with reduced risk of upper GI bleeding (risk ratio, 0.62; 95% CI, 0.48 to 0.77) but not with all bleeding (risk ratio, 0.88; 95% CI, 0.74 to 1.05) or non—upper GI bleeding (risk ratio, 1.06; 95% CI, 0.82 to 1.33).[20] Of those with European Society of Cardiology—defined low risk of GI bleeding,[3] patients with PPI use even had a potentially higher risk of non—upper GI bleeding (risk ratio, 1.22; 95% CI, 0.86 to 1.56).[20] However, direct evidence for the effect of combined use of PPIs and DAPT on lower GI bleeding, especially for patients with ACS in the acute phase, is still insufficient, and more studies are needed.[29]

Guidelines and expert consensus have recommended the use of PPIs in patients with ACS with a higher risk of bleeding, and some have even recommended the routine use of PPIs for patients in need of DAPT, although the evidence was insufficient.[3-6,9,10,30,31] One study widely cited in the guidelines evaluated the effect of PPI use on long-term overt upper GI bleeding,[32] rather than early PPI use on in-hospital GI bleeding. To date, we have not found direct evidence to support the prophylactic use of PPIs in the acute phase for patients with ACS to prevent bleeding. In addition, evidence supporting that PPIs have a protective effect against GI bleeding was mainly based on its effect on the upper GI tract instead of the entire GI tract.[32,33] Given the potential harm of PPIs to the lower GI tract, we believe that it is very necessary to assess

the risk of overall GI bleeding. Because total GI bleeding during hospitalization was less than 1%, even if PPIs have a protective effect against GI bleeding, the absolute benefit of using PPIs is very low. Considering that the current definition of high risk of GI bleeding is based on consensus rather than on models of risk prediction,[3,4,20] and a large number of patients could be classified as high-risk population based on the current definition (eg, meeting the criteria of age ≥65 years and infected with *Helicobacter pylori*), accurate identification of patients who really need PPI treatment in the acute phase is very important and needs more research in the future. In summary, we think that the current recommendations for the use of PPIs in patients with ACS taking DAPT should be more specific and need further evidence for support. Physicians should be more cautious in prescribing PPIs for patients with ACS taking DAPT in the acute phase, especially for these patients without high bleeding risk.

Limitations

There were several limitations to this study. First, these finding are observational, and selection bias along with residual measured or unmeasured confounding may account for these findings. Second, we could not distinguish the detailed locations of GI bleeding in this study and evaluate the effect of PPIs on lower GI bleeding. Considering the protective effect of PPIs on the upper GI tract and their potential harm to the lower GI tract, we believed that it is more reasonable to assess the risk of overall GI bleeding. Third, some risk factors for GI bleeding were not collected in this study, such as *H pylori* infection, history of GI ulcers, etc. However, the CRUSADE bleeding risk stratification, to some extent, represents the baseline risk of GI bleeding and all-type bleeding and should be used for patients with ACS in China to quantify bleeding risk,[5,6] before more precise and convenient risk assessment tools are developed. Nevertheless, further studies examining the association between PPI use and GI bleeding should take these limitations into consideration.

CONCLUSION

In China, PPIs are widely used within 24 hours of admission among patients with ACS taking DAPT during hospitalization. An increased risk of GI bleeding is observed among inpatients with early use of PPIs. Given the present findings and the lack of previous evidence, randomized clinical trials are needed to evaluate early use of PPIs in patients with ACS, and studies on accurately identifying patients with ACS who may benefit from PPI treatment in the acute phase are also needed.

ACKNOWLEDGMENTS

We acknowledge all the participating hospitals for their contributions to the project (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org).

Drs Zhou and Zhang contributed equally to this work.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACS**, acute coronary syndrome; **CCC**, Improving Care for Cardiovascular Disease in China; **DAPT**, dual antiplatelet therapy; **GI**, gastrointestinal; **HR**, hazard ratio; **NSAID**, nonsteroidal anti-inflammatory drug; **NSTE**, non–ST-segment elevation; **OR**, odds ratio; **PCI**, percutaneous coronary intervention; **PPI**, proton pump inhibitor; **SD**, standard deviation; **STEMI**, ST-segment elevation myocardial infarction

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Grant Support: This work was supported by a collaborative program of the American Heart Association and the Chinese Society of Cardiology. The American Heart Association was funded by Pfizer for the quality improvement initiative through an independent grant for learning and change. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Potential Competing Interests: Dr Ma has received honoraria for giving lectures from Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer-Ingelheim, Bayer, and AstraZeneca. Dr Fonarow has served as a consultant to Abbott, Amgen, AstraZeneca, Bayer, CHF Solutions, Janssen, Medtronic, Merck, and Novartis. The other authors report no competing interests.

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