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The efficacy and safety of acid suppressants for gastrointestinal bleeding prophylaxis in cardiac care unit patients

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Abstract

Background and Aim: Concerns regarding adverse events associated with proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) for gastrointestinal bleeding (GIB) prophylaxis in the intensive care unit have increased in recent years. Few studies have focused on acid suppressant use in the cardiac care unit (CCU) setting exclusively. We performed a cohort study to determine the efficacy and safety of acid suppressants for GIB prophylaxis in CCU patients.

Methods: This retrospective cohort study included adults who were admitted directly to the CCU for more than 2 days from January 1, 2014, to April 30, 2019. The Crusade score was calculated to evaluate the risk of GIB. The primary outcomes were clinically important gastrointestinal bleeding (CIGIB), hospital-acquired pneumonia (HAP), and in-hospital mortality.

Results: Of the 3318 patients enrolled, 2284 (68.8%) patients received PPIs, 515 (15.5%) received H2RAs, and 519 (15.7%) received no acid suppressants. After adjusting for potential confounders, utilization of PPIs (2.69, 95% confidence interval [0.62–11.73]) and H2RAs (1.41, 95% confidence interval [0.19–10.36]) were not associated with a lower risk of CIGIB than the control. Sensitivity analyses revealed that PPI use was an independent risk factor for in-hospital mortality in patients over 75 years old, with an adjusted odds ratio of 4.08 (1.14–14.63). PPIs increased the risk of HAP in patients over 75 years old and in those with heart failure, with adjusted odds ratios of 2.38 (1.06–5.34) and 2.88 (1.34–7.28), respectively.

Conclusions: Proton pump inhibitors and H2RAs for GIB prophylaxis in CCU patients were not associated with a lower risk of CIGIB than the controls. PPI therapy is associated with increased risks of HAP and in-hospital mortality in patients over 75 years old. PPIs may increase the risk of HAP in patients with heart failure.

Introduction

Critically ill patients are at risk of developing clinically important gastrointestinal bleeding (CIGIB) due to stress ulcers, which is associated with an increased risk of death and length of intensive care unit (ICU) stay.[1] Acid suppressants, including proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), are widely used to prevent CIGIB, even though recommendations in international guidelines are conflicting.[2,3] A multicenter international survey indicated that more than 30% of ICUs did not have guidelines, and indications varied considerably; up to 80% of ICU patients received improper acid suppressant treatment.[4,5] Concerns regarding adverse effects associated with such drugs, including the risk of *Clostridium difficile* infection (CDI) and pneumonia, which may offset their potential benefits, have been increasing in recent years.[6] The latest network meta-analysis by Wang *et al*. indicated that PPIs and H2RAs reduced gastrointestinal bleeding (GIB) compared with no prophylaxis in high-risk critically ill patients, but among low-risk patients, the reduction in bleeding was irrelevant, and both PPI and H2RA use may result in an increase in the risk of pneumonia.[7] The results by Alhazzani *et al*. showed that PPIs were more effective in preventing CIGIB than H2RAs and a placebo but were associated with a higher risk of developing pneumonia than H2RAs.[8] Weighing the potential benefits and harms of acid suppressants for GIB prophylaxis in critically ill patients is important for clinicians.

Compared with ICU patients, patients in the cardiac care unit (CCU) are more likely to be prescribed anticoagulants and

antiplatelet drugs, meaning they have a high risk of GIB. Thus, CCU patients are more likely to receive PPIs for GIB prophylaxis than ICU patients. The guidelines recommend PPIs as the first-line drug for GIB prophylaxis in patients with acute coronary syndrome at high risk of bleeding.[9] Real-world data on guideline adherence and the associated effectiveness and adverse events associated with acid suppressant therapy are scarce. A nationwide study in Denmark demonstrated that only 35% of patients at high risk of GIB received recommended treatment with a PPI based on the guideline criteria, and PPIs were generally associated with reduced risk of GIB.[10,11] However, the overall low risk of bleeding (1.0–1.7%) suggests that focus should be placed on identifying those patients who would benefit the most from PPI therapy.[10] Several studies have suggested that prophylactic PPI treatment in patients receiving dual antiplatelet therapy (DAPT) does not reduce the incidence of GIB but improves compliance with antiplatelet treatment, as PPI treatment reduces dyspepsia related to low-dose aspirin treatment and is associated with a reduction in mortality with no apparent impact on cardiovascular events.[12,13] Nevertheless, other studies have indicated that PPI use is independently associated with high platelet reactivity and increased risk of major adverse cardiac events and all-cause mortality after discharge in cardiovascular patients.[14,15] Few studies have focused on the in-hospital use of acid suppressants in CCU patients and the associated adverse events, such as in-hospital mortality and hospital-acquired pneumonia (HAP). Data comparing the effects of and adverse events associated with PPI and H2RA use in CCU patients are scarce. Therefore, the present study sought to explore the efficacy and safety of acid suppressants for GIB prophylaxis in CCU patients. The primary aim was to determine whether acid suppressant therapy is associated with the incidence of CIGIB, HAP, and in-hospital mortality.

Methods

Study population. We performed a retrospective analysis of patients aged 18 years and above who were admitted directly to the CCU of Peking University Third Hospital from January 1, 2014, to April 30, 2019, and remained there for more than 2 days. To compare the effects and safety of acid suppressants in CCU patients, we excluded patients with the following: (i) crossover use of PPIs and H2RAs. Of the patients who received a single type of acid suppressant, those with any of the following were subsequently excluded: (ii) a diagnosis of GIB within 2 days of CCU admission; (iii) prior use of a PPI or H2RA within 1 month of admission; (iv) a diagnosis of pancreatitis, gastroesophageal reflux disease, or other diseases that required treatment with acid suppressants; (v) pregnancy; and (vi) incomplete information. For those with multiple CCU admissions during the study period, only data from the first admission were analyzed.

Full ethical approval for this study was obtained from the Peking University Third Hospital Medical Science Research Ethics Committee (2019-485-03).

Outcomes and definitions. The primary outcomes in this study were CIGIB during the CCU stay, HAP, and in-hospital mortality. The secondary outcome measures were CDI, bloodstream infection, readmission within 90 days, and CCU and hospital lengths of stay. CIGIB was defined as overt bleeding and at the presence of at least one of the following features within 24 h of overt bleeding in the absence of other causes (clinical evaluation): (i) a blood pressure decrease of 20 mmHg or more; (ii) initiation of or a 20% or more increase in vasopressor use; (iii) a decrease in hemoglobin of at least 2 g/dL (1.24 mmol/L); and (iv) transfusion of two or more units of red blood cells during a bleeding episode. HAP was defined as pneumonia onset > 48 h after admission and chest radiograph or computed tomography scan showing new or progressive pulmonary infiltration shadows + $\geq 2/3$, along with (i) a fever > 38 °C with no other identifiable cause; (ii) a white blood cell count $< 4 \times 10^9$/L or $> 12 \times 10^9$/L; or (iii) new-onset purulent sputum or a change in the characteristics of sputum, cough/dyspnea/tachypnoea.[16] CDI was defined as (i) a positive enzyme immunoassays and nucleic acid amplification test or glutamate dehydrogenase test and (ii) a diagnosis of pseudomembranous colitis according to colonoscopy or colonic histopathology.[17] Bloodstream infection was defined as positive bacterial growth on blood culture drawn either peripherally or centrally at or after 48 h of hospitalization.[18]

Data collection and statistical analysis. Patient demographic and clinical data were collected retrospectively from the electronic medical records. We collected information about acid suppressants, comorbidities, complications, outcomes, and other clinical data. Descriptive analyses were performed to characterize the participants. Continuous variables are presented as medians (interquartile ranges), and categorical variables are presented as numbers (percentages). The Mann–Whitney *U*-test and chi-square test were applied to compare the differences between patients receiving and not receiving acid suppressants. The variables with a significant difference ($\alpha = 0.1$) and a standard mean difference larger than 10% were considered potential risk factors. Multiple logistic regression was used to estimate the crude and adjusted odds ratios (ORs) (95% confidence intervals [CIs]) for the associations between acid suppressants and primary and secondary outcomes.

Sensitivity analysis was used to identify the dose effect of PPIs and group differences by age and Crusade score. The PPIs used in the CCU included rabeprazole, esomeprazole, omeprazole, pantoprazole, and lansoprazole. The mixed PPI group received two or more kinds of PPIs successively, while H2RAs included famotidine and ranitidine. Statistical analyses were performed with SPSS version 26.0. A *P*-value of < 0.05 was considered statistically significant.

Results

Demographic and baseline characteristics. From January 1, 2014, to April 30, 2019, a total of 3757 patients were admitted directly to the CCU; 3318 patients were enrolled in our study, of which 2284 (68.8%) patients were prescribed PPIs (PPI group) and 515 (15.5%) patients were treated with H2RAs (H2RA group) for at least 2 days. In total, 519 (15.7%) patients received no acid suppressant treatment (control group) (Fig. 1). The annual use of acid suppressants from 2014 to 2019 and its trend over time was pictured in Figure S1.

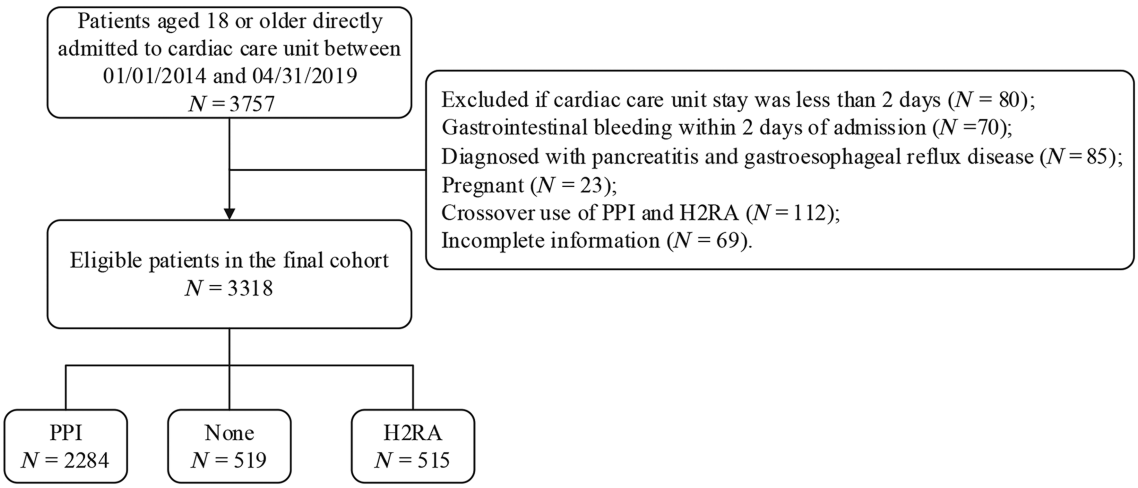

FIGURE 1 Flowchart showing how patients were selected for inclusion in the final cohort. H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

The clinical characteristics and therapeutic agents used in the PPI group, the H2RA group, and the control group are shown in Table 1. The mean age of the H2RA group was younger than those of the other groups. The Crusade score in the PPI group was significantly higher than those in the H2RA group and the control group, indicating that patients with an increased risk of GIB are more likely to be prescribed PPIs. The rates of comorbidities (hypertension, type 2 diabetes mellitus, peripheral vascular disease, cerebrovascular disease [CVD], peptic ulcer or GIB history, and shock) and treatment with cardiopulmonary resuscitation and mechanical ventilation were significantly higher in the PPI group than in the other groups. The rates of percutaneous coronary intervention and anticoagulant/antiplatelet therapy were significantly higher in both the PPI group and the H2RA group than in the control group.

Incidence and risk factors for clinically important gastrointestinal bleeding. Forty-three patients (1.3%) were diagnosed with CIGIB during their CCU stay. The incidence of CIGIB in the PPI group (1.7%, 39/2284) was significantly higher than those in the H2RA group (0.4%, 2/515) and the control group (0.4%, 2/519). The median time from CCU admission to bleeding was 6 (interquartile range 4–11) days. The clinical characteristics of the CIGIB group and the no CIGIB group are compared in Table S1. In the univariate analysis, acid suppressant

Table 1 Characteristics of the study population

Characteristic	Control (A) (*N* = 519)	PPI (B) (*N* = 2284)	H2RA (C) (*N* = 515)	*P*-value	Post hoc[a]
Age, median (IQR), years	68 (49–79)	68 (58–79)	61 (51–71)	< 0.001	A/B, A/C, B/C
Male, *n* (%)	301 (58.0)	1589 (69.5)	385 (74.8)	< 0.001	A/B, A/C
BMI, median (IQR), kg/m^2	23.9 (22.3–25.9)	24.2 (22.6–26.1)	24.3 (22.7–26.5)	0.021	A/C
Smoking, *n* (%)	170 (32.8)	1194 (52.3)	274 (53.2)	< 0.001	A/B, A/C
Alcohol consumption, *n* (%)	147 (28.3)	832 (36.4)	204 (39.6)	< 0.001	A/B, A/C
Comorbidities, *n* (%)					
Hypertension	372 (71.7)	1452 (63.6)	311 (60.4)	< 0.001	A/B, B/C
Type 2 diabetes mellitus	133 (25.6)	878 (38.4)	146 (28.3)	< 0.001	A/B, B/C
Previous CVD	82 (15.8)	440 (19.3)	65 (12.6)	0.001	B/C
Previous CABG	12 (2.3)	62 (2.7)	5 (1.0)	0.064	
Previous PVD	96 (18.5)	476 (20.8)	71 (13.8)	0.001	B/C
History of peptic ulcer or GIB	4 (0.8)	115 (5.0)	5 (1.0)	< 0.001	B/C
History of gastrointestinal surgery	10 (1.9)	39 (1.7)	2 (0.4)	0.066	
Chronic lung disease[b]	16 (3.1)	47 (2.1)	8 (1.6)	0.210	
Chronic renal failure[c]	60 (11.6)	272 (11.9)	26 (5.0)	< 0.001	A/C, B/C
Chronic/acute liver disease[d]	9 (1.7)	33 (1.4)	2 (0.4)	0.113	
Cancer[e]	33 (6.4)	107 (4.7)	12 (2.3)	0.008	A/C
Autoimmune disease	11 (2.1)	33 (1.4)	9 (1.7)	0.518	

(Continues)

Table 1 (Continued)

Characteristic	Control (A) (*N* = 519)	PPI (B) (*N* = 2284)	H2RA (C) (*N* = 515)	*P*-value	Post hoc[a]
Complications, *n* (%)					
Heart failure	199 (38.3)	942 (41.2)	187 (36.3)	0.083	
Shock/persistent hypotension	4 (0.8)	68 (3.0)	3 (0.6)	< 0.001	A/B, B/C
Coagulopathy[f]	30 (5.8)	88 (3.9)	16 (3.1)	0.067	
Crusade score[g], *n* (%)				< 0.001	A/C, B/C
Very low risk (1–20)	126 (24.3)	427 (18.7)	165 (32.0)		
Low risk (21–30)	103 (19.9)	484 (21.2)	130 (25.2)		
Medium risk (31–40)	99 (19.1)	437 (19.1)	93 (18.1)		
High risk (41–50)	90 (17.3)	398 (17.4)	84 (16.3)		
Very high risk (51–91)	101 (19.4)	538 (23.6)	43 (8.3)		
APACHE-II score[h], *n* (%)				< 0.001	A/C, B/C
≤ 5	180 (34.7)	843 (36.9)	271 (52.6)		
6–9	182 (35.1)	871 (38.1)	179 (34.8)		
≥ 10	157 (30.3)	570 (25)	65 (12.6)		
Main diagnosis				< 0.001	A/B, A/C, B/C
Acute coronary syndrome	108 (20.8)	2015 (88.2)	417 (81.0)		
Heart failure	138 (26.6)	156 (6.8)	38 (7.4)		
Others	273 (52.6)	113 (4.9)	60 (11.7)		
Treatment, *n* (%)					
Mechanical ventilation ≥ 48 h	20 (3.9)	175 (7.7)	10 (1.9)	< 0.001	A/B, B/C
Percutaneous coronary intervention	49 (9.4)	1170 (51.2)	272 (52.8)	< 0.001	A/B, A/C
Cardiopulmonary resuscitation	0 (0.0)	29 (1.3)	2 (0.4)	0.004	A/B
High-dose glucocorticoid[i]	2 (0.4)	20 (0.9)	1 (0.2)	0.213	
Anticoagulant/antiplatelet				< 0.001	A/B, A/C, B/C
Single antiplatelet/anticoagulant	170 (32.8)	131 (5.7)	50 (9.7)		
Dual antiplatelet	93 (17.9)	290 (12.7)	59 (11.5)		
Dual antiplatelet + anticoagulant	79 (15.2)	1822 (79.8)	392 (76.1)		
Admission year				< 0.001	A/C, B/C
2014	101 (19.5)	445 (19.5)	121 (23.5)		
2015	85 (16.4)	354 (15.5)	230 (44.6)		
2016	112 (21.6)	450 (19.7)	89 (17.3)		
2017	94 (18.1)	433 (19.0)	49 (9.5)		
2018	93 (17.9)	463 (20.3)	20 (3.9)		
2019 (4 months)	34 (6.5)	139 (6.0)	6 (1.2)		

[a]Post hoc significant differences between the groups after Bonferroni adjustment.
[b]Chronic lung disease was defined as any history of chronic obstructive pulmonary disease, asthma, or other chronic lung disease or treatment with any relevant drug indication at hospital admission.
[c]Chronic renal failure was defined as a creatinine clearance rate ≤ 30 mL/min for more than 3 months before admission.
[d]Chronic/acute liver disease was defined as liver cirrhosis or alanine aminotransferase elevated to at least five times the upper limit of normal for 72 h before admission.
[e]Cancer included solid tumors and hematological malignancies confirmed by imaging, histopathology, or other methods.
[f]Coagulopathy was defined as platelets $< 50 \times 10^9$/L or an international normalized ratio > 1.5 or an activated partial thromboplastin time > 2 times the upper limit of normal at CCU admission.
[g]In the 24 h before admission, Crusade scores were calculated for each patient to evaluate the risk of gastrointestinal bleeding based on the red blood cell-specific volume, creatinine clearance rate, heart rate, systolic blood pressure, diabetes mellitus, previous vascular disease, sex, and congestive heart failure.
[h]In the 24 h before admission, APACHE-II scores were calculated for each patient to evaluate the severity of illness on admission based on vital signs, laboratory results, and the Glasgow coma scale.
[i]High-dose glucocorticoid was defined as a ≥ 1 mg/kg/day methylprednisolone equivalent.
APACHE-II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CABG, coronary artery bypass grafting; CVD, cerebrovascular disease; GIB, gastrointestinal bleeding; H2RA, histamine-2 receptor antagonist; IQR, interquartile range; PPI, proton pump inhibitor; PVD, peripheral vascular disease.

use, age, sex, alcohol consumption, Crusade score, Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, chronic renal failure (CRF), shock, heart failure (HF), coagulopathy, mechanical ventilation ≥ 48 h, and high-dose glucocorticoid use were significantly associated with the development of CIGIB. In the multivariate analysis, Crusade score,

high-dose glucocorticoid use, and mechanical ventilation ≥ 48 h were independent risk factors for CIGIB (Tables S2A and S2B). The crude ORs for PPI and H2RA treatment for CIGIB were 4.49 (1.08–18.66) and 1.01 (0.14–7.18), respectively. After adjustment in different models, there was no significant difference between PPI use (2.69, 95% CI [0.62–11.73]) and H2RA use (1.41, 95% CI [0.19–10.36]) in preventing CIGIB (Table 2). The categories of acid suppressants also had no significant impact on CIGIB among the three groups after additional adjustment for acid suppressant dosage and drug administration route based on Model 1 (Table S2C).

To verify the effect of acid suppressant use for GIB prophylaxis on patients with different risks of bleeding, we performed a sensitivity analysis. Patients were stratified by the Crusade score into two groups: the low-risk to medium-risk group (≤ 40 points) and the high-risk group (> 40 points). Acid suppressant treatment and type had no significant impact on CIGIB in patients with different bleeding risks after adjusting for multiple variables (Table 3).

Table 2 Associations between acid suppressant use and primary outcomes after adjustment

Outcomes	Drug	No.	Case (%)	OR (95% CI)			
				Crude	Model 1	Model 2	Model 3
CIGIB[†]	Control	519	2 (0.39)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Acid suppressant	2799	41 (1.46)	3.84 (0.93–15.94)	2.52 (0.58–10.96)	2.32 (0.52–10.34)	2.23 (0.50–9.93)
	PPI	2284	39 (1.71)	4.49 (1.08–18.66)	2.69 (0.62–11.73)	2.48 (0.55–11.10)	2.35 (0.52–10.53)
	H2RA	515	2 (0.39)	1.01 (0.14–7.18)	1.41 (0.19–10.36)	1.30 (0.17–9.72)	1.36 (0.18–10.29)
In-hospital mortality[‡]	Control	519	8 (1.54)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Acid suppressant	2799	88 (3.14)	2.07 (0.99–4.30)	2.16 (0.93–5.00)	2.11 (0.91–4.93)	1.73 (0.74–4.04)
	PPI	2284	81 (3.55)	2.35 (1.13–4.89)	2.13 (0.91–4.97)	2.08 (0.88–4.90)	1.78 (0.76–4.17)
	H2RA	515	7 (1.36)	0.88 (0.32–2.45)	2.39 (0.75–7.60)	2.34 (0.73–7.49)	1.50 (0.47–4.79)
HAP[§]	Control	519	18 (3.47)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Acid suppressant	2799	125 (4.47)	1.82 (1.02–3.25)	1.80 (1.00–3.25)	1.78 (0.98–3.23)	1.80 (0.99–3.25)
	PPI	2284	110 (4.82)	1.97 (1.10–3.53)	1.85 (1.02–3.35)	1.84 (1.01–3.34)	1.83 (1.01–3.33)
	H2RA	515	15 (2.91)	1.17 (0.55–2.48)	1.52 (0.71–3.27)	1.48 (0.69–3.20)	1.58 (0.72–3.45)

[†]Model 1, adjusted for coagulopathy, peptic ulcer or gastrointestinal bleeding history, mechanical ventilation ≥ 48 h, antiplatelet/anticoagulant use, high-dose glucocorticoid use, Crusade score, and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score; Model 2, based on Model 1, with additional adjustment for alcohol consumption, liver disease, percutaneous coronary intervention, and cardiopulmonary resuscitation (CPR); and Model 3, based on Model 2, with additional adjustment for admission year.

[‡]Model 1, adjusted for shock, coagulopathy, percutaneous coronary intervention, CPR, mechanical ventilation ≥ 48 h, Charlson Comorbidity Index, and APACHE-II score; Model 2, based on Model 1, with additional adjustment for high-dose glucocorticoid use, hypertension, and cancer; and Model 3, based on Model 2, with additional adjustment for admission year.

[§]Model 1, adjusted for male sex, mechanical ventilation ≥ 48 h, high-dose glucocorticoid use, cerebrovascular disease, chronic renal failure, chronic lung disease, and APACHE-II score; Model 2, based on Model 1, with additional adjustment for heart failure, shock, CPR, coagulopathy, alcohol consumption, and autoimmune disease; and Model 3, based on Model 2, with additional adjustment for admission year.

CI, confidence interval; CIGIB, clinically important gastrointestinal bleeding; H2RA, histamine-2 receptor antagonist; HAP, hospital-acquired pneumonia; OR, odds ratio; PPI, proton pump inhibitor.

Table 3 Associations between acid suppressant use and clinically important gastrointestinal bleeding, stratified by risk of gastrointestinal bleeding (low–middle risk: Crusade score ≤ 40; high risk and above: Crusade score > 40)

Drug	Bleeding risk	No.	CIGIB	(%)	Adjusted OR[†] (95% CI)
Control	Low–middle risk	328	1	0.30	1.00 (reference)
	High risk and above	191	1	0.52	1.00 (reference)
Acid suppressant	Low–middle risk	1736	9	0.52	1.33 (0.14–12.68)
	High risk and above	1063	32	3.01	4.50 (0.59–35.11)
PPI	Low–middle risk	1348	7	0.52	1.16 (0.11–11.71)
	High risk and above	936	32	3.42	5.10 (0.66–39.30)
H2RA	Low–middle risk	388	2	0.52	2.93 (0.20–42.55)
	High risk and above	127	0	0.00	0.00

[†]Adjusted for coagulopathy, peptic ulcer or gastrointestinal bleeding history, mechanical ventilation ≥ 48 h, antiplatelet/anticoagulant use, high-dose glucocorticoid use, Crusade score, and Acute Physiology and Chronic Health Evaluation II score.

CI, confidence interval; CIGIB, clinically important gastrointestinal bleeding; H2RA, histamine-2 receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor.

Incidence and risk factors for in-hospital mortality. The overall in-hospital mortality rate was 2.9% (96/3318). In the univariate analysis, acid suppressant use, age, mean arterial pressure (MAP), Charlson Comorbidity Index, APACHE-II score, hypertension, type 2 diabetes mellitus, peripheral vascular disease, CVD, CRF, chronic/acute liver disease, shock, coagulopathy, cardiopulmonary resuscitation, mechanical ventilation ≥ 48 h, and high-dose glucocorticoid use were significantly associated with in-hospital mortality (Table S3). In the multivariate analysis, the APACHE-II score, shock, and mechanical ventilation ≥ 48 h independently increased the risk of death, while percutaneous coronary intervention decreased the risk of death in CCU patients (Tables S4A and S4B). The crude and adjusted ORs for the association between PPI use and mortality were 2.35 (1.13–4.89) and 2.13 (0.91–4.97), respectively, and the crude and adjusted ORs for the association between H2RA use and mortality were 0.88 (0.32–2.45) and 2.39 (0.75–7.60), respectively (Table 2). After stratification by age, the use of PPIs increased the risk of in-hospital mortality in patients over 75 years old independently; the adjusted OR was 4.08 (1.14–14.63) (Table 4). We further analyzed causes of death, and 65.6% (63/96) of the CCU patients died due to cardiac events, including HF deterioration, recurrent myocardial infarction, arrhythmia, and heart rupture. However, prophylactic PPI and H2RA therapy had no apparent impacts on cardiac-related death in our study, and the same was true in patients over 75 years old.

Table 4 Associations between acid suppressant use and in-hospital mortality, stratified by age

Drug	Age	No.	Death	(%)	Adjusted OR† (95% CI)
Control	≤ 60	204	1	0.49	1.00 (reference)
	61–74	130	3	2.31	1.00 (reference)
	≥ 75	185	4	2.16	1.00 (reference)
Acid suppressant	≤ 60	928	9	0.97	7.35 (0.23–237.05)
	61–74	955	15	1.57	0.78 (0.19–3.20)
	≥ 75	916	63	6.88	3.99 (1.12–14.31)
PPI	≤ 60	686	7	1.02	4.88 (0.13–177.53)
	61–74	783	14	1.79	0.76 (0.18–3.25)
	≥ 75	815	60	7.36	4.08 (1.14–14.63)
H2RA	≤ 60	242	2	0.83	27.34 (0.44–1705.85)
	61–74	172	2	1.16	0.83 (0.12–5.56)
	≥ 75	101	3	2.97	3.11 (0.51–19.04)

†Adjusted for shock, coagulopathy, percutaneous coronary intervention, cardiopulmonary resuscitation, mechanical ventilation ≥ 48 h, Charlson Comorbidity Index, and Acute Physiology and Chronic Health Evaluation II score.

CI, confidence interval; H2RA, histamine-2 receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor.

Incidence and risk factors for hospital-acquired pneumonia. Of the 3318 CCU patients, 138 (4.2%) developed HAP during their hospital stay. HAP occurred more often in older patients and females. The APACHE-II score was significantly higher in those who developed HAP than in those who did not. Patients with comorbidities including CVD, CRF, shock, cardiopulmonary resuscitation (CPR), HF, and coagulopathy had increased risks for HAP. Risk factors during CCU treatment including mechanical ventilation and prescription of acid suppressants were associated with HAP in CCU patients (Table S5). The crude and adjusted ORs of the association between PPI use and HAP were 1.97 (1.10–3.53) and 1.85 (1.02–3.35), and the crude and adjusted ORs of the association between H2RA use and HAP were 1.17 (0.55–2.48) and 1.52 (0.71–3.27) (Table 2). In addition, mechanical ventilation, CVD, and HF were independent risk factors for HAP (Tables S6A and S6B). In the sensitivity analysis, PPIs increased the risk of HAP in patients over 75 years old and in those with HF after stratification by age and HF status; the adjusted ORs were 2.38 (1.06–5.34) and 2.88 (1.34–7.28), respectively (Table 5).

We did not observe any relationship between acid suppressant use and bloodstream infection, CDI, or readmission within 90 days (Table S7). The numbers of CCU and hospital days in the PPI group were higher than those in the other two groups. The hospital stay in the H2RA group was longer than that in the control group, while the CCU stays in the H2RA and control groups were not different.

Discussion

In this retrospective cohort study, we found that CIGIB and all-cause in-hospital mortality were not different among CCU patients treated with PPIs, H2RAs, or no prophylaxis. However, PPIs may increase the risk of in-hospital mortality in patients over 75 years old according to the sensitivity analysis. In addition, the prescription of PPIs was significantly associated with the development of HAP, especially in patients over 75 years old and in those

Table 5 Associations between acid suppressant use and hospital-acquired pneumonia, stratified by age and heart failure

		Control		PPI		H2RA	
HAP		*N* (%)	Adjusted OR† (95% CI)	*N* (%)	Adjusted OR† (95% CI)	*N* (%)	Adjusted OR† (95% CI)
Age	≤ 60	1 (0.49)	1.00 (reference)	14 (2.04)	3.31 (0.42–26.01)	6 (2.48)	5.74 (0.67–49.10)
	61–74	5 (3.85)	1.00 (reference)	24 (3.07)	0.77 (0.28–2.13)	2 (1.16)	0.36 (0.07–1.94)
	≥ 75	7 (3.78)	1.00 (reference)	72 (8.83)	2.38 (1.06–5.34)	7 (6.93)	2.08 (0.70–6.21)
Heart failure	No	8 (2.50)	1.00 (reference)	38 (2.83)	1.24 (0.56–2.76)	5 (1.52)	0.89 (0.28–2.81)
	Yes	5 (2.51)	1.00 (reference)	72 (7.64)	2.88 (1.34–7.28)	10 (5.35)	2.61 (0.86–7.88)

†Adjusted for sex, mechanical ventilation ≥ 48 h, high-dose glucocorticoid use, cerebrovascular disease, chronic renal failure, chronic lung disease, and Acute Physiology and Chronic Health Evaluation II score.

CI, confidence interval; H2RA, histamine-2 receptor antagonist; HAP, hospital-acquired pneumonia; OR, odds ratio; PPI, proton pump inhibitor.

with HF. The numbers of CCU and hospital days in the PPI group were both higher than those in the other two groups.

Of the 3318 patients in the CCU, 43 patients (1.3%) were diagnosed with CIGIB during hospitalization, which was higher than reported in previous studies. The ARRIVE study by Gaziano *et al*. showed that GIB events in patients with a moderate estimated risk of a first cardiovascular event (mostly mild) occurred in 0.97% of the patients in the aspirin group and 0.46% of the patients in the placebo group (hazard ratio 2.11, 95% CI [1.36–3.28]; $P = 0.0007$).[19] It is worth pointing out that the ARRIVE study excluded patients at high risk of GIB, other bleeding, or diabetes, and aspirin was used as a monotherapy for the primary prevention of cardiovascular events. The subjects in our cohort were patients with acute cardiovascular events and with different risks of GIB. In addition, most of the patients received a second antiplatelet drug or anticoagulant therapy combined with aspirin during hospitalization, which may explain the higher rate of CIGIB in our study. Meanwhile, in the ASCEND study, which included patients with diabetes with different risks of GIB, serious GIB events occurred in 1.77% (137/7740) of the patients in the aspirin group and 1.30% (101/7740) of the patients in the placebo group (risk ratio 1.36, 95% CI [1.05–1.75]),[20] which is consistent with our results. Additionally, a previous meta-analysis showed that while aspirin increases the risk of GIB, the overall risk of fatal bleeding is not significantly elevated, and the fatality rate in patients with GIB is reduced.[21] In our study, six of the 43 patients with CIGIB died of cardiogenic shock or septic shock. Fatal bleeding did not occur in our study population, which may be attributed to close monitoring and timely medical intervention during hospitalization in the CCU.

There are important issues to consider in this population, such as the severity of GIB and the severity of coronary artery disease status, which includes the risk of stent thrombosis. The recent guidelines suggested that if treatment is stopped within the first month after the procedure, stent thrombosis in coronary artery disease cases increases with more time off treatment, particularly when the duration is longer than 5 days.[22] In our study, 14 patients received percutaneous intracoronary arterial stenting and experienced CIGIB, although all of them had received oral PPIs to prevent GIB before the bleeding occurred. After GIB occurred, four patients discontinued all antithrombotic drugs and resumed Plavix or ticagrelor 3–7 days after the GIB stopped. Seven patients discontinued aspirin and anticoagulants after bleeding and received antiplatelet therapy with Plavix alone, four of them resumed DAPT 3–7 days after the bleeding stopped and three of them did not resume the second antiplatelet drug. The other three patients continued antithrombotic drugs, and the bleeding stopped after active medical intervention (Fig. S2). No stent thrombosis events occurred in those 14 patients in our study. It is important to adjust antithrombotic therapy individually, strengthen monitoring after bleeding, and resume antiplatelet drugs as soon as possible after bleeding is stopped to avoid stent thrombosis events.

Recent studies have shown that acid suppressants, in particular PPIs, are very commonly used to prevent GIB. Several observational studies indicated that approximately 55.6–70.7% of the patients in the ICU received PPIs, and 5.8–38.1% of them received H2RAs for GIB prophylaxis.[23–25] Real-world data on acid suppressant therapy in CCU patients are scarce and may vary among countries, regions, or even health policies. In our study, only 15.7% (519/3318) of the patients did not receive acid suppressant treatment, and the utilization rate of acid suppressants was 84.3% (2799/3318); 15.5% (515/3318) of the patients received H2RAs, and PPIs were the most commonly prescribed acid suppressants for GIB prophylaxis (68.8%, 2284/3318), especially rabeprazole (58.0%, 1926/3318). This might be due to the possible inhibitory effect of PPIs on cytochrome P450 enzymes, which are responsible for the conversion of antiplatelets into their active metabolites and the metabolism of PPIs, as the inhibitory effect of rabeprazole is lower than those of the other PPIs.[26] Early studies reported that PPIs significantly reduced the CIGIB rate in critically ill patients compared with H2RAs.[27,28] Despite the decrease in the CIGIB rate in recent years, an increasing number of original studies are reporting contrary results. Lilly found that prophylaxis with a PPI for at least 2 to 3 days was associated with higher CIGIB risk (hazard ratio 1.97, 95% CI [1.48–2.63]) than prophylaxis with an H2RA, which is consistent with the MacLaren *et al*. findings.[29] Propensity score matching and instrumental variable analyses were used to control for selection bias and confounding by unmeasured factors, and the results were highly internally consistent and robust. H2RAs may limit reperfusion injury in animal models, possibly reducing oxidative stress after mucosal injury. And the role of PPI associated thrombocytopenia, the effects of medications on PPI or H2RA pharmacokinetics, and other interactions may contribute to these findings.[23,24] However, a multicenter prospective randomized controlled trial (RCT) by Krag *et al*. that included patients who were admitted to the ICU and had at least one risk factor for CIGIB found that the numbers of clinically important events, including GIB, mortality, and HAP, were similar between those administered pantoprazole and those administered the control treatment at 90 days after randomization.[6] Data comparing the efficacy of PPIs and H2RAs for CIGIB prophylaxis in CCU patients are limited. A systemic review of RCTs indicated that PPIs were superior to H2RAs for gastrointestinal protection in patients on DAPT; however, the end-points of the studies were not CIGIB.[30] Our sensitivity analyses failed to detect any plausible scenario in which PPIs were superior to H2RAs or the control for the prevention of CIGIB in CCU patients, and we did not find significant differences in the efficacy of different acid suppressant types or drug administration routes for GIB prophylaxis among the three groups; this supports the result that prophylactic PPI use does not reduce the incidence of GIB in patients receiving DAPT.[13]

The results regarding adverse effects of acid suppressants for prophylaxis of GIB, including mortality, HAP, and CDI, are still unclear. In the PEPTIC RCT study by Young *et al*., GIB prophylaxis with the use of PPIs and H2RAs in ICU patients requiring mechanical ventilation resulted in in-hospital mortality rates of 18.3% and 17.5%, respectively, which did not reach the significance threshold.[31] Ninety-day mortality in ICU patients administered PPIs or H2RAs *versus* a placebo for GIB prophylaxis was not significantly different.[7,32] However, in a post hoc analysis of the placebo-controlled Stress Ulcer Prophylaxis-ICU trial by Marker *et al*., pantoprazole was associated with higher 90-day mortality and fewer days alive without life support than the placebo in patients with high disease severity,[33] while there was no significant difference in 1-year mortality among the same population.[34] The effects of acid suppressants on mortality in

patients with cardiovascular diseases are still unclear. Several studies have reported that the interaction between PPIs and antiplatelet drugs may increase the risks of cardiovascular events and potential infections, such as pneumonia and CDI, which may result in an increased risk of mortality.[35] A large cohort study involving US veterans suggested an excess risk of mortality among PPI users due to cardiovascular diseases,[14] while another large placebo-controlled randomized trial among patients receiving rivaroxaban or aspirin found that pantoprazole was not associated with all-cause mortality when used for 3 years.[36] However, the study by Hoedemaker *et al*. indicated that PPI prescription in patients with acute coronary syndrome was associated with reductions in mortality and myocardial infarction risk at 30 days after discharge.[12] The in-hospital mortality rate in our study was 2.9%, which was lower than those in previous studies, probably because we included only CCU patients, and most of them had relatively mild disease severity, as indicated by APACHE-II scores. We observed that PPIs were associated with relatively increased adjusted in-hospital mortality in CCU patients over 75 years old, but prophylactic PPI and H2RA therapy had no apparent impact on cardiac death.

In our study, we found that the PPI group was more likely to develop HAP than the other two groups, especially patients aged 75 years or older. HAP was associated with increased adjusted in-hospital mortality (OR 4.11, 95% CI [1.73–9.75]) in patients over 75 years old, which may explain their higher in-hospital mortality. Relationships between PPIs and the risks of community-acquired pneumonia and HAP, including ventilator-acquired pneumonia, have been found in previous studies.[29,37,38] The possible explanation for these associations is that the increased gastric pH generated by acid suppressants may facilitate gastric microbial growth, leading to pulmonary infection when reflux or aspiration occurs. In addition, PPIs may increase the permeability of the gastrointestinal mucosa, leading to the translocation of intestinal flora and subsequent infection.[39–41] Another acid suppressant-related infectious adverse event is CDI. Numerous studies have reported that PPI therapy is associated with a higher risk of CDI than H2RA therapy or control therapy in critically ill patients.[28,42,43] A large, multicenter retrospective cohort study by Faleck *et al*. indicated that PPIs do not affect the risk of CDI in ICU patients.[44] We did not find any relationship between PPIs and CDI in our study, probably because the sample size was limited and the combined use of antibiotics was relatively rare in CCU patients. Previous studies have shown that there may be an interaction between PPIs and antibiotics affecting the development of CDI.

To the best of our knowledge, this is the first study to evaluate the efficacy of and adverse events associated with acid suppressants for CIGIB prophylaxis in CCU patients. We found that the PPI group was more likely to develop HAP and had higher adjusted in-hospital mortality in patients aged 75 years or more than the other two groups. Our study has several limitations. First, as in any observational study, the validity of our results relies on the assumption of no unmeasured confounding. Although we adjusted for many baseline confounders, including steroid use and immunosuppression, we cannot exclude the possibility that unmeasured factors affected the effects of acid suppressants or the occurrence of adverse events. Second, real-world data on acid suppressant therapy in CCU patients are scarce and may vary among countries, regions, or even health policies. This cohort was recruited from a single hospital, which may limit the generalizability of our results, but our large cohort of 3318 CCU patients was homogeneous and likely adequately represents the population of critical patients with acute cardiovascular events. To validate our results, further prospective RCTs with larger sample sizes are warranted.

In conclusion, acid suppressants for GIB prophylaxis in CCU patients are not associated with a lower risk of CIGIB than control treatments. PPI therapy is associated with increased risks of HAP and in-hospital mortality in patients over 75 years old. PPIs may increase the risk of HAP in patients with HF. Further research on improving risk assessment schemes to potentially assist in identifying those patients who would benefit the most from acid suppressant therapy is warranted.

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Supporting information

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

Table S1. Relationship between risk factors and CIGIB.
Table S2A: Adjusted Model 1 for the association between acid suppressant use and CIGIB.
Table S2B: Adjusted Model 2 for the association between acid suppressant use and CIGIB.
Table S2C: Adjusted Model for the association between acid suppressant use and CIGIB, plus a dosage of acid suppressant, drug administration route, types of acid suppressant.
Table S3. Relationship between risk factors and in-hospital mortality.
Table S4A: Adjusted Model 1 for the association between acid suppressant use and in-hospital mortality.
Table S4B: Adjusted Model 2 for the association between acid suppressant use and in-hospital mortality.
Table S5. Relationship between risk factors and HAP.
Table S6A: Adjusted Model 1 for the association between acid suppressant use and HAP.
Table S6B: Adjusted Model 2 for the association between acid suppressant use and HAP.
Table S7. Association between acid suppressant and the secondary outcomes.
Figure S1. Trend of utilization rate of acid suppressants during 2014–2019.
Figure S2. The antithrombotic drugs adjustment of 14 patients with coronary stents after the bleeding and stent thrombosis events.