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Original Research

Use of proton pump inhibitors in patients with acute coronary syndrome treated with dual antiplatelet therapy: a tertiary care observation

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Abstract

Background: Dual antiplatelet therapy (DAPT) reduces the incidence of ischemic events and increases the risk of gastrointestinal bleeding (GIB). Proton pump inhibitors (PPIs) can be utilized to mitigate and prevent this risk; however, they are commonly underutilized.

Objectives: This study evaluated PPI prescription practices and identified the factors influencing PPI use in patients with acute coronary syndrome (ACS) treated with DAPT in a regional tertiary care setting.

Methods: We conducted a retrospective chart review of 310 patients with ACS treated with DAPT between 2017 and 2020. Data regarding PPI use, GIB events, and patient demographics were collected. Logistic regression was used to identify the factors associated with PPI prescriptions.

Results: Among the 310 patients who met inclusion criteria, 83.3% of high-risk GIB patients received PPIs optimally, whereas 16.7% were overprescribed PPIs. In the non-PPI group, 72.7% of the high-risk patients did not receive PPIs. Significant factors influencing PPI prescribing included prior PPI use (OR 3.10, 95% CI 1.16–8.24), age ≥65 years (OR 2.55, 95% CI 1.49–4.38), and alcohol consumption (OR 2.24, 95% CI 1.04–4.81). Conclusion: The proportion of patients with ACS-DAPT with GIB risk who should receive PPI was high in Thailand. However, the optimal prescription rate was also high. A practice gap exists among patients with ACS DAPT without GIB risk because PPI are frequently overused. Age of at least 65 years, alcohol consumption, and current use of PPI significantly influenced optimal PPI prescription. Physicians should carefully consider these factors in all patients with ACS-DAPT to mitigate bleeding events.

Keywords: acute coronary syndrome, antiplatelet agents, proton pump inhibitors, gastrointestinal hemorrhage, retrospective study

INTRODUCTION

Acute coronary syndrome (ACS) requires dual antiplatelet therapy (DAPT) to reduce the risk of cardiovascular events, such as recurrent myocardial infarction, myocardial ischemia, or death from coronary artery disease.[1, 2] DAPT involves the administration of aspirin in combination with a P2Y12 inhibitor, such as clopidogrel, ticagrelor, or prasugrel. Current treatment guidelines recommend DAPT for all patients with ACS, except those with contraindications.[1]

Although DAPT reduces ischemic events, it also increases the risk of severe bleeding compared with aspirin alone.[3, 4] Gastrointestinal bleeding (GIB) is a major adverse event.[5] GIB reported from one-year observation among patients with DAPT ranges from 4.6% to 9.2%.[3, 6] Patients receiving antiplatelet combination had 2.08-fold GIB risk compared to those using aspirin alone (odds ratio [*OR*] = 2.08, 95% confidence interval [CI] 1.34–3.21).[7] The risk of GIB increases in patients with additional risk factors, such as aging or a previous history of GIB.[8]

Proton pump inhibitors (PPIs) also reduce GIB risk. A randomized controlled trial found that the combined use of omeprazole and DAPT significantly reduced the incidence of bleeding compared to the non-omeprazole group (hazard ratio [HR] = 0.13, 95% CI 0.03–0.56).[9] Similarly, an observational study reported that the risk of upper GIB was lower in patients receiving DAPT using PPIs than in those not using PPIs.[10] PPIs permanently inhibit the H+/K+ ATPase (proton pump) enzyme in the cytoplasmic membrane of parietal cells in the stomach, resulting in a prolonged acid-reducing effect.[11] However, the use of PPIs in patients receiving DAPT raises concerns about potential drug interactions, particularly with a pair of PPIs, such as omeprazole and clopidogrel. PPIs can reduce the efficacy

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of clopidogrel and increase the risk of major cardiovascular events.[12] Additionally, long-term PPIs use may increase the risk of adverse effects, such as *Clostridium difficile*-associated diarrhea, osteoporosis, and vitamin B deficiency.[13] Therefore, the American College of Cardiology Foundation (ACCF)/ the American College of Gastroenterology (ACG)/American Heart Association (AHA) treatment guidelines recommend the use of PPIs in DAPT-treated patients who are at a high risk of upper GIB, have a history of GIB or ulcers, are taking medications that increase bleeding risk (e.g., anticoagulants, non-steroidal anti-inflammatory drugs [NSAIDs], or corticosteroids), and age at least 65 years.[14-16]

An American retrospective observation of percutaneous coronary intervention found that 86.7% of patients with indications for PPI to prevent GIB did not receive it at discharge; however, it was prescribed to 6.6% of patients without such indications.[17] Similarly, a study in Denmark reported that only 35% of high-risk patients with GIB receiving DAPT received PPI.[10]

The underutilization of PPI is globally diverse owing to the routine practices of each country. Evidence regarding this issue remains limited in Thailand, but it is important for enhancing pharmacotherapy practice. This study aimed to: (1) examine the use of PPI in patients with ACS receiving DAPT (patients with ACS-DAPT) and GIB events among those patients; and (2) identify GIB risk factors potentially influencing PPI prescription. These findings serve as a foundation for developing guidelines for the use of acid-suppressing drugs in hospitalized patients receiving DAPT.

METHODS

A retrospective chart review was conducted at two units of a general hospital (580-bed tertiary care) in northeast Thailand: the internal medicine ward and the coronary critical unit. Sample size was calculated using a proportion estimation formula with key parameters from a previous study [18], resulted in a target sample size of 350 patients. The information and technology staff compiled a list of patients admitted to both units based on the inclusion criteria. Patients admitted between January 1, 2017, and December 31, 2020, were recruited.

Inclusion and exclusion

The inclusion criteria were: (1) hospitalized patients aged at least 18 years old; (2) newly diagnosed with ACS; and (3) received DAPT. Researchers reviewed all identified patient records to match the inclusion criteria and subsequently excluded patients if they were allergic to PPIs, died during hospitalization, were referred to higher-level care, or were under terminal care. Patients with incomplete data were excluded.

Outcomes

The primary outcome was the PPIs prescribed to patients with ACS-DAPT at risk of GIB at discharge. GIB risk was identified according to the ACCF/ACG)/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines.[14] Patients were considered to have GIB risk if they had at least one of the following: 1) a history of GIB/ulcers/peptic ulcer/gastroesophageal reflux disease within the previous 6–12 months; 2) current use of anticoagulants; 3) ongoing use of NSAIDs for at least three months; 4) current use of aspirin; 5) a history of *Helicobacter pylori* infection; and 6) age of at least 65 years.

The 2010 guidelines were chosen because they correspond with the data recruitment timeframe; the newer guidelines (2016) have not yet been launched. The secondary outcome was patients who experienced GIB incidence during hospitalization. Observations of these outcomes were collected as recorded by physicians in the medical records. Other patient information concurrently collected included demographic information, medical history, and laboratory test results, such as *H. pylori* testing via breath tests, endoscopic examinations, and stool occult blood tests. Factors that increased the risk of upper GIB were also recorded (described per the assessment criteria).

The date when patients were diagnosed with ACS and began DAPT was considered the index date, and patient details were observed from 6-12 months prior to diagnosis to discharge. The use of PPI was observed from the index date until discharge.

Statistics

The researchers verified the accuracy and completeness of the data before beginning the data analysis using the statistical software STATA version 15. The frequency and percentage of patients with ACS-DAPT receiving PPI according to the recommended criteria and the proportion of patients who experienced GIB were analyzed. Multiple logistic regression was used to identify GIB risk factors associated with PPI prescription, using ten GIB risk factors as covariates. An entry approach was used to determine the best model for predicting the dependent variable. The OR and 95% CI were reported. A $p < 0.05$ was the cutoff point for identifying GIB risk significantly associated with PPI prescription. A multiple logistic regression analysis was performed using two dependent variables. *Analysis I*: PPI prescription refers to all patients with ACS-DAPT who were prescribed PPIs. *Analysis II:* optimal PPI prescription, refers to all patients with ACS-DAPT with GIB risk who were prescribed PPI and those without GIB risk who were not prescribed PPI.[19]

Ethics approval

This study approved by two institutional review boards (approval code: 63-02-052 date October 20, 2020, and 316/2020 date December 25, 2020).

RESULTS

A total of 743 patients were identified from the Information and Technology Center; 510 were excluded because they were referred for a higher level of care (n=308) and other reasons (n=125). Finally, 310 patients were eligible for inclusion (Figure 1).

Characteristics of patients with ACS-DAPT

The study found that among the 310 patients with ACS-DAPT,

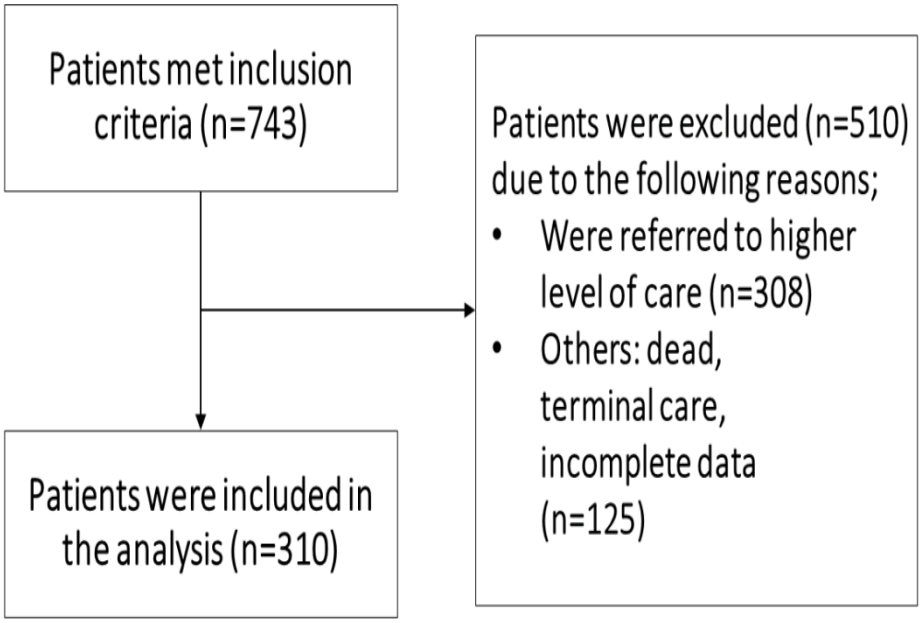

Figure 1. Patient selection flow

the average age was 67.3 years (SD = 11.9), with 50.3% males. The three most frequent comorbidities were hypertension (61%), diabetes (52.3%), and kidney disease (29.0%). Most patients had at least one comorbidity (87.1%). Patients were mainly diagnosed with non-ST-elevation myocardial infarction (73.9%) and received aspirin 81 mg as an antiplatelet (Table 1). Regarding the DAPT regimen, the most common combination was aspirin (81 mg) with clopidogrel (99.4%).

GIB risk in patients with ACS-DAPT

Two hundred and fifty patients (80.6%) were at risk of GIB and should have received PPI. The most common GIB risk was an age of at least 65 years (66.1%), followed by other risks, as shown in Table 2. Sixty patients had no GIB risk. Most patients had fewer than two risks at admission (73.6%).

Use of proton pump inhibitors

Among patients with GIB risk, the majority (77.6%) received PPI for GIB prevention, accounting for the optimal PPI prescription. However, 22.4% of the patients in this group did not receive PPIs, indicating that PPIs were underutilized. Among patients without GIB risk, 65% of this group still received PPI, which was unnecessary. Only 35% of patients without GIB risk did not receive PPI, indicating low optimization in this group. In the entire study sample, 69.4% used PPIs optimally, whereas 30.6% used PPIs sub-optimally Table 3. Notably, four GIB events were observed only in patients at risk of GIB who received PPIs (optimal PPI prescription).

High-risk GIB that influenced PPI prescription for patients with ACS-DAPT

In Analysis Ia, prior use of a PPI is significantly associated with PPI prescription (OR 3.10, 95%CI 1.16:8.24). In Analysis IIa, age was a significant factor influencing the optimal PPI prescription (OR 2.55, 95%CI 1.49:4.38). Alcohol drinking (OR 2.24, 95%CI 1.04:4.81) and use of PPI (OR 4.25, 95%CI 1.59:11.40) were also significant for optimal prescribing. The Ib and IIb Analyses show that having at least two high-risk GIB factors

Table 1. Patient characteristic (*N*=310)

	N (%)	%
Age (mean, yrs)	67.3 (SD=11.9)	
Male	156	50.3
Underlying disease[a]		
Hypertension	189	61.0
Diabetes	162	52.3
Chronic kidney disease/End-stage renal failure	90	29.0
Other heart disease: heart failure, valvular heart disease	77	24.9
Pulmonary and respiratory disease	31	10.0
Other such as cancer, immune-deficiency, cirrhosis	46	14.8
Type of acute coronary syndrome		
Non-ST elevation Myocardial Infarction	229	73.9
ST elevation Myocardial Infarction	15	4.8
Unstable angina	65	21.0
Prescribed antiplatelet		
Aspirin 81 mg	308	99.4
Aspirin 300 mg	2	0.6
Clopidogrel	310	100.0
Length of stay (mean, days)	5.1 (SD = 6.7)	

Note: [a]Some patients had more than one underlying disease.

Table 2. Acute coronary syndrome patients with high risk gastrointestinal bleeding (*N* = 310)

High risk gastrointestinal bleeding	**N**	**%**
None	60	19.4
Age at least 65 years old	205	66.1
Use of a PPI	52	16.8
Alcohol drinking	49	15.8
Prior GIB	15	4.8
Prior history of dyspepsia	15	4.8
Prior history of GERD	10	3.2
Concurrent use of anticoagulants	6	1.9
Concurrent use of NSAIDs	3	1.0
Concurrent use of steroids	3	1.0
Prior history of *Helicobacter pylori* infection	0	0.0
Number of GIB risks that patients had		
0	60	19.4
1	168	54.2
2	59	19.0
3	20	6.5
4	3	1.0
< 2	228	73.6
≥ 2	82	26.5

Note: [a]Some patients had more than one risk factors. GIB, gastrointestinal bleeding; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; GERD, gastroesophageal reflux

Table 3. Use of proton pump inhibitors in patients with ACS-DAPT with high-risk-GIB

Patients with ACS-DAPT	**N**	**%**	**GIB events**
With GIB risk (n=250)			
Received PPI (optimal PPI prescriptions)	194	77.6	4
Not received PPI (under use – Suboptimal)	56	22.4	0
Without GIB risk (n=60)			
Received PPI (overuse – suboptimal)	39	65.0	0
Not received PPI (optimal PPI prescriptions)	21	35.0	0
Overall PPI prescriptions (n=310)			
Optimal use	215	69.4	
Suboptimal use	95	30.6	

Note: ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; GIB, gastrointestinal bleeding; PPI, proton pump inhibitor

significantly influences PPI and optimal PPI prescriptions (OR 2.33, 95%CI 1.18:4.58 and OR 3.34, 95%CI 1.71:6.52 respectively) Table 4. Several factors, such as prior GIB, concurrent use of anticoagulants, prior history of dyspepsia, and gastroesophageal reflux disease (GERD), showed higher ORs, but did not reach statistical significance.

DISCUSSION

This retrospective chart review found that 80.6% of patients with ACS-DAPT with GIB risk should have received PPI. However, 77.6% of the participants received it appropriately. Patients with ACS-DAPT without GIB risk (n=60) were possibly treated sub-optimally, and 65% received PPI, although it was unnecessary. Age of at least 65 years, alcohol consumption, and current use of PPI significantly influenced optimal PPI prescription. The increase in the number of GIB risk (≥ 2) potentially induced optimal PPI prescriptions.

The compliance rate of the guidelines in this study was high. This is in agreement with previous studies that reported 67.39% compliance with the AHA 2010 guidelines for patients receiving

Table 4. GIB risk influencing PPI prescribing in patients with ACS-DAPT

	Adjusted OR	95% CI	
		Lower	Upper
Analysis Ia: dependent variable = Prescribing PPI (Reference = no risk)			
Prior GIB	2.10	0.45	9.76
Concurrent use of anticoagulants	2.18	0.25	19.07
Age at least 65 years old	1.03	0.59	1.81
Prior history of dyspepsia	3.40	0.42	27.47
Prior history of GERD	2.35	0.28	19.77
Alcohol drinking	1.24	0.59	2.63
Use of a PPI	3.10	1.16	8.24
Analysis Ib: dependent variable = Prescribing PPI (reference = high-risk-GIB < 2)			
At least two high-risk-GIB	2.33	1.18	4.58
Analysis IIa: dependent variable = Prescribing PPI optimally (reference = no risk)			
Prior GIB	2.42	0.51	11.50
Concurrent use of anticoagulants	4.06	0.45	36.81
Age at least 65 years old	2.55	1.49	4.38
Prior history of dyspepsia	4.44	0.53	37.31
Prior history of GERD	4.21	0.48	36.63
Alcohol drinking	2.24	1.04	4.81
Use of a PPI	4.25	1.59	11.40
Analysis IIb: dependent variable = Prescribing PPI optimally (Reference = high-risk-GIB < 2)			
at least two high-risk-GIB	3.34	1.71	6.52

Note: ACS, acute coronary syndrome; CI, confidence interval; DAPT, dual antiplatelet therapy; GIB, gastrointestinal bleeding; OR< odds ratio; PPI, proton pump inhibitor; GERD, gastroesophageal reflux

aspirin and clopidogrel in Thailand[18], 50.5% in Korea[20] and 48% compliance in the United States.[19] Prescribing PPI to patients with ACS-DAPT without GIB risk seems problematic because PPI overuse is prevalent (65.0%). Other countries found a lower rate: 53.3% in China and 43.5 in the United States.[19, 21]

These varying compliance rates may be due to differences in national guidelines. For example, the European Society of Cardiology (ESC) 2017 guidelines recommend PPI use for all patients on DAPT [2] to reduce the risk of GI bleeding complications and bleeding-related deaths. However, the 2023 ESC guideline for management of ACS[22], the Thai[23] and the AHA guidelines[14-16] only recommend PPI for high-risk groups with the concern of drug-drug interactions and the need for more evidence (Table 5). These inconsistent recommendations may lead to high rates of PPI overuse. For example, an action research study in the United Kingdom encouraged multidisciplinary education programs and posters to raise awareness regarding gastrointestinal prophylaxis in patients with ACS-DAPT.[24] The study aimed to identify 100% of these patients receiving PPI.[24] A physician would prescribe PPI to all patients with ACS-DAPT if they had been exposed to such activities or followed the ESC recommendations[2]. It is difficult to judge the overuse of PPI in each setting because it depends on the selected guideline.

The most commonly prescribed P2Y12 inhibitor in our study was clopidogrel, a prodrug that requires CYP450 enzymes, including CYP2C19. This study found that omeprazole, a strong CYP2C19 inhibitor, was the most commonly used PPI. Therefore, drug-drug interactions between PPI and clopidogrel remain a significant concern because the reaction might increase the risk of myocardial infarction in patients with reduced-function CYP2C19 alleles who receive clopidogrel. Recently, the ESC of Cardiology 2023 guidelines for the management of cardiovascular disease in patients with diabetes did not recommend omeprazole if clopidogrel was used.[25] Therefore, patient-related variables must be considered while providing care.

Advanced age (≥ 65 years) was a major risk of patients with ACS-DAPT (66.1%). Previous studies reported a similar proportion for age risk (54.0%)[19, 26]. This study has added to the literature by identifying potential factors influencing PPI prescriptions. As mentioned previously, an age of at least 65 years, alcohol consumption, and current use of PPI significantly influence optimal PPI prescriptions. This may reflect the current practice of the study site, in that physicians may decide to prescribe PPI based on these three factors, and other factors might be unknown.

Previous studies reported that in high-risk patients who did not receive PPI therapy, the rate of GIB was only 1.9%.[10] This data might indicate that patients with a low risk of GIB might have even lower risks, suggesting that some treatment guidelines

Table 5. Differences between the ACC/AHA and ESC guidelines on PPIs use in patients on DAPT

Guidelines	Level of recommendation	Evidence	Recommendations
2010 ACC/AHA	Not reported	Not reported	PPIs are recommended for patients on DAPT with a history of GIB or those at increased risk of GIB (e.g., advanced age, concomitant use of warfarin, steroids, or NSAIDs, H. pylori infection).
2016 ACC/AHA	Class I	Not reported	PPIs are recommended for patients on DAPT with a history of GIB.
	Class IIa	Not reported	PPIs are recommended for patients with increased risk of GIB (e.g., advanced age, concomitant use of warfarin, steroids, or NSAIDs, H. pylori infection).
	Class III:	Not reported	Routine use of PPIs is not recommended for patients at low risk of GIB.
2017 ESC	Class I	B	PPIs are recommended for all patients on DAPT
2023 ESC	Class I	A	- PPIs are recommended for patients on DAPT at high risk of GIB (i.e., history of GIB/ hemorrhage, anticoagulant therapy, chronic NSAIDs/corticosteroid use).
			- Other patients with two of three of the following risk factors: age ≥ 65 years, dyspepsia, GERD, H. pylori infection, chronic alcohol use.

Class I: strong recommendation; Class IIa: moderate recommendation; Class III: no benefit; Evidence A: high-quality evidence; Evidence B: moderate-quality evidence

recommending PPIs for all patients on DAPT, regardless of other risk factors, may lead to the overuse of medication, especially in the elderly or those with comorbid conditions. As a result, the overuse of PPI may increase the risk of adverse effects and drive up medical costs.[27]

Four GIB cases were found when patients with ACS-DAPT were observed until discharge; however, this event occurred only with an optimal PPI prescription. Therefore, the GIB incidence equates to 2.1% (4/194) of patients with ACS-DAPT with GIB risk who received PPI. All patients who experienced GIB had a history of bleeding and received PPI therapy according to established guidelines. The incidence was similar to that reported in previous studies, which reported a one-year incidence rate ranging from 0.8% to 4.5%.[3, 10, 28]

Implication to clinical practice and future research

Patients with ACS-DAPT with GIB risk are prevalent, indicating the need for gastrointestinal prophylaxis. Inconsistencies among international guidelines exist; it is unclear whether all patients with ACS-DAPT should receive PPI. Nevertheless, this confusion could be resolved at the practice level by obtaining consensus on this issue among the coronary care team. Physicians should carefully evaluate GIB risk in all patients with ACS-DAPT to mitigate bleeding events. Implementing regular training sessions on proper prescribing practices for new and trainee doctors, as well as involving pharmacists in reviewing medication orders, can help ensure that medications are prescribed appropriately. Our findings suggest that training should raise awareness of all GIB risk factors. A qualitative study is needed to explore further why physicians do or do not prescribe PPI to understand clinical practice more deeply better training design.

Limitations

The sample size included in the study did not reach the target of 350 patients. This is primarily because a significant number of patients with ACS being transferred to other hospitals. Additionally, some data, such as clear indications for PPI use and reasons for prescribing various medications, may have been incomplete or not recorded. Furthermore, the study did not find gastrointestinal ulcers through endoscopic examination, possibly because endoscopy was not performed, and the patients' observation of symptoms, such as black stools might have led to incomplete data or underreported GIB. As this study was conducted in a single general hospital, the findings may differ from those of other hospitals where endoscopic examinations may be conducted if the patient exhibits symptoms or consent to the procedure. Other hospitals may also have more precise systems for recording prescriptions and indications for medication use.

CONCLUSION

The proportion of patients with ACS-DAPT with GIB risk who should receive PPI is high in Thailand. However, the optimal prescription rate was also high. A practice gap exists among patients with ACS-DAPT without GIB risk because PPI are frequently overused. Age of at least 65 years, alcohol consumption, and current use of PPI significantly influenced optimal PPI prescriptions. Training sessions on proper prescription practices should be provided to all new and trainee doctors and pharmacists to ensure that medications are appropriately prescribed. A prospective research is warranted to further clarify the benefits and risks of PPI therapy, thereby guiding more informed clinical decision-making.

AUTHOR CONTRIBUTIONS

Conceptualization: All authors

Methodology: All authors

Formal Analysis: AL, KS

Investigation: AL, KW, CP, CR

Data Curation: AL, KS

Writing - Original Draft: AL, PS, KS

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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