Prevalence and the Associated Factors of Proton Pump Inhibitor Co-Prescribed with Dual Antiplatelet Therapy among Adult Patients Diagnosed with Acute Coronary Syndrome upon Hospital Discharge

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Abstract

Introduction: There are conflicting evidence and expert opinion surrounding the co-prescription of proton pump inhibitor (PPI) and dual antiplatelet therapy (DAPT) among patients diagnosed with acute coronary syndrome (ACS).

Objective: This study aimed to determine the prevalence and factors associated with of PPI co-prescription with DAPT among patients diagnosed with ACS at hospital discharge.

Methods: A single-centre, cross-sectional study was conducted among adult ACS patients admitted to the general wards of Port Dickson Hospital between 1 January and 31 December 2021 who were discharged with DAPT (acetylsalicylic acid / glyprin and clopidogrel) with or without a PPI (pantoprazole). Simple and multiple logistic regression were used to determine the factors associated with PPI co-prescription with DAPT at discharge.

Results: Out of 322 included patients, the majority were male (68.3%), Malay (58.7%), and diagnosed with non-ST-elevation myocardial infarction (70.5%). A total of 234 (72.7%) patients were discharged with a co-prescription of PPI and DAPT. Patients who received PPI at admission were 26 times more likely to be co-prescribed with PPI and DAPT at discharge than those who did not (adjusted OR 26.00, 95% CI 11.52-58.70, p<0.001). Older patients and those with lower hemoglobin levels were more likely to receive a PPI co-prescription with DAPT (adjusted OR 1.04, 95% CI 1.01-1.06, p=0.006 and adjusted OR 0.82, 95% CI 0.72-0.95, p=0.007, respectively).

Conclusion: This study shown relatively high percentage of PPI prescription in ACS patients receiving DAPT. Further studies are warranted to determine the appropriateness of the PPI prescription.

Keywords: Proton pump inhibitor, dual antiplatelet therapy, acute coronary syndrome

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Introduction

The occurrence of acute coronary syndromes (ACS) involves a variety of life-threatening acute myocardial ischemic events caused by the rupture or erosion of an atherosclerotic plaque, as well as different levels of thrombosis and distal embolisation (1). The major cause of ACS is arterial thrombosis after the rupture or erosion of atherosclerotic plaque (2). ACS encompasses unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) (3). The basis treatment for patients with acute coronary syndrome was dual antiplatelet therapy (DAPT) (4). Antiplatelet therapy was crucial for treating ACS because platelet adhesion, activation, and aggregation are key in forming arterial thrombi (5). The combined effects of two antiplatelet agents, that involve blocking COX-1 with aspirin and inhibiting the P2Y12 receptor, have been the focus of numerous clinical trials over the past decade. These trials have been conducted in patients diagnosed with ACS, including unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction (2). Nevertheless, there was an unavoidable higher risk of bleeding as a side effect when dual antiplatelet medications are given. Bleeding from gastrointestinal peptic ulcers occurs 0.5% of the time, even among people using only low-dose aspirin

(6). Since DAPT increases the risk of gastrointestinal bleeding, many post-ACS patients were started on an H2 receptor antagonist or proton pump inhibitor (PPI).

PPIs are commonly used to lower the risk of gastrointestinal bleeding (7). PPI co-therapy has been shown to reduce the incidence of peptic ulcers and peptic ulcer complications in individuals receiving aspirin alone or in combination with clopidogrel, although it has the potential to affect the antiplatelet action of these drugs (8,9). The clinical use of PPIs along with clopidogrel is still under debates. In a statement released in November 2009, the U.S. Food and Drug Administration (FDA) advised against taking clopidogrel along with omeprazole and esomeprazole. The major reason for this was pharmacokinetic research which showed that concurrent omeprazole and clopidogrel may raise platelet reactivity levels in comparison to clopidogrel alone (10). When PPIs were used more widely and for longer periods, there was also greater concern about the potential negative effects such as developing clostridium difficile infections, osteoporosis and fractures (11). According to the 2016 American Heart Association targeted update, PPIs should only be given together with DAPT in patientswith a history of gastrointestinal bleeding (Class 1) and those at a higher risk of gastrointestinal bleeding, such as older patients, and those taking warfarin, steroids, or non-steroidal anti-inflammatory drugs (Class IIa). The regular use of PPIs was not recommended for patients at low risk of gastrointestinal bleeding (Class III: No Benefit) (12). In contrast, the European Society of Cardiology recommended using a PPI in conjunction with DAPT (13).

There has been a notable increase in the prescribing of PPIs among ACS patients who were receiving antiplatelet therapy. In our setting, observations made during daily practice suggested that a substantial number of patients may not have clinical indications to use PPIs. Furthermore, we notice an inconsistent pattern of PPI prescribing in ACS patients on DAPT at the time of hospital discharge. There was a lack of local published data regarding the prevalence of PPI co-prescription with DAPT, and the predictors of PPI prescribing among ACS patients receiving DAPT (14). Therefore, this study aimed to determine the prevalence and explore the factors associated with PPI co-prescription with DAPT among patients diagnosed with ACS at hospital discharge. Our findings may be able to help in establishing local guidelines to improve prescribing practices and ensure rational drug use.

Method

Study design and study subjects

This study was a single-centre, cross-sectional study conducted among adult ACS patients admitted to the general wards of Port Dickson Hospital in Negeri Sembilan, Malaysia who were discharged with DAPT (acetylsalicylic acid / glyprin and clopidogrel) with or without a PPI (pantoprazole). The list of patients hospitalised for ACS between 1 January and 31 December 2021 was obtained from the hospital admission record and arranged chronologically in Microsoft Excel. Only the first admission episode of patients with multiple hospital admissions were selected. Subsequently, computer-generated random numbers were used to enroll potential study subjects. Subjects were eligible for inclusion in the study if they were adults (aged 18 years or older) diagnosed with ACS and had received DAPT. Patients who did not complete ACS treatment due to a change of diagnosis, concurrent use of anticoagulation, and non-Malaysians were excluded from the study.

The sample size of study subjects required was calculated based on a 5% margin of error, 95% confidence interval, 32% response distribution (based on a previous study in Qatar) (14), and 1,400 inpatient general ward admissions in 2021. A total of 269 study subjects were needed. This study was registered with the National Medical Research Registry, Ministry of Health Malaysia (NMRR 21-02303-JIJ) and approved by the Medical Research Ethics Committee, Ministry of Health Malaysia before the commencement of this study.

Data collection

A standardised data collection form was used. It consisted of four parts: (A) socio-demographic and clinical information, including age, gender, race, smoking status, alcohol intake, and hemoglobin level at admission; (B) past medical history, including diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease; (C) types of ACS (STEMI, NSTEMI and UA); (D) prescription of PPI at admission and the list of discharge medications. All required information were extracted from the Pharmacy Information System (PhIS) prescription database and Hospital Information System (HIS).

Data analysis

Data collected were tabulated in the International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 26 for further analysis. Normality test was performed for continuous variable (age and hemoglobin). Descriptive and inferential statistics were employed for the data analyses. Continuous data were presented as mean and standard deviation (SD), while categorical data were presented as numbers (n) and percentages (%). Simple logistic regression analysis was performed on all variables. Variables with *p*-value less than 0.25 in the simple logistic regression were subsequently included in a multiple logistic regression model to determine significant factors associated with PPI co-prescription with DAPT at discharge. The adjusted odds ratios (OR) with 95% confidence interval (CI) were presented, with a *p*-value of <0.05 considered statistically significant.

Results

A total of 404 subjects met the inclusion criteria. However, 82 subjects were not included in the study due to insufficient data. Therefore, only 322 patients were included. Table 1 presented the characteristics of included patients. The majority of the subjects were Malay, male, admitted for NSTEMI, and already on PPI use at admission. The mean age and hemoglobin level at admission were 57.35 years old and 12.8g/dL respectively. Common comorbidities were diabetes mellitus, hypertension, and chronic kidney disease. The prevalence of PPI co-prescription with DAPT at discharge was 72.7%. Elderly (65 years or older) comprised 35.4% of PPI users. (Table 2).

Table 1: Baseline and treatment-related characteristics of study subjects (N=322)

Variables	n (%)	Mean (SD)
Age, year		57.35 (13.64)
≥ 65 years	98 (30.4)	
< 65 years	224 (69.6)	
Race		
Malay	189 (58.7)	
Chinese	39 (12.1)	
Indian	91 (28.3)	
Others	3 (0.9)	
Gender		
Male	220 (68.3)	
Female	102 (31.7)	
ACS		
STEMI	24 (7.5)	
NSTEMI	227 (70.5)	
UA	71 (22)	
Smoking status		
Yes	65 (20.2)	
No	200 (62.1)	
Unknown	57 (17.7)	
Alcohol status		
Yes	11 (3.4)	
No	239 (74.2)	
Unknown	72 (22.4)	
Diabetes Mellitus		
Yes	201 (62.42)	
No	121 (37.58)	
Dyslipidemia		
Yes	43 (13.4)	
No	279 (86.6)	
Hypertension		
Yes	224 (69.6)	
No	98 (30.4)	
Chronic kidney disease		
Yes	74 (22.9)	
No	248 (77)	

Hb at admission, g/dL		12.8 (2.54)
PPI at admission		
Yes	176 (54.7)	
No	146 (45.3)	

Abbreviations: SD = standard deviation; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; Hb = haemoglobin; PPI = proton pump inhibitor.

Table 2: PPI prescription at hospital discharge (N=322)

Characteristics	Received PPI (n=234), n (%)	No PPI (n=88), n (%)
Gender, n (%)		
Male	158 (71.8)	62 (28.2)
Female	76 (74.5)	26 (25.5)
Age, year ,mean (SD)	59.34 (13.23)	52.06 (13.38)
≥ 65 years	83 (84.7)	15 (15.3)
< 65 years	151 (67.4)	73 (32.6)
Race, n (%)		
Malay	136 (72.0)	53 (28.0)
Non–Malay	98 (73.7)	35 (26.3)
Smoking status, n (%)		
Yes	48 (73.8)	17 (26.2)
No / Unknown	186 (72.4)	71 (27.6)
Alcohol status, n (%)		
Yes	8 (80.0)	2 (20.0)
No / Unknown	226 (72.4)	86 (27.6)
Diabetes Mellitus, n (%)		
Yes	148 (73.6)	53 (26.4)
No	86 (71.1)	35 (28.9)
Dyslipidemia, n (%)		
Yes	30 (69.8)	13 (30.2)
No	204 (73.1)	75 (26.9)
Hypertension, n (%)		
Yes	163 (72.8)	61 (27.2)
No	71 (72.4)	27 (27.6)
Chronic kidney disease, n (%)		
Yes	61 (82.4)	13 (17.6)
No	173 (69.8)	75 (30.2)
ACS type, n (%)		
STEMI	20 (83.3)	4 (16.7)
NSTEMI / UA	214 (71.8)	84 (28.2)
Hb at admission, g/dL, mean (SD)	12.43 (2.60)	13.78 (2.10)
PPI at admission, n (%)		
Yes	168 (95.5)	8 (4.5)
No	66 (45.2)	80 (54.8)

Abbreviations: SD = standard deviation; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; Hb = haemoglobin; PPI = proton pump inhibitor.

The logistic regression analysis was presented in Table 3. Simple logistic regression showed statistically significant associations between age (p<0.001), hemoglobin level at admission (p<0.001), presence of chronic kidney disease (p=0.034), and use of PPI at admission (p<0.001) with PPI co-prescription with DAPT at hospital discharge. The multiple logistic regression model showed a statistically significant association between age, hemoglobin level at admission, and the use of PPI at admission with PPIs co-prescription with DAPT at hospital discharge. No interactions and multicollinearity were found among the independent variables in this study. Patients who received PPI at admission were twenty-six times more likely to be co-prescribed with PPI and DAPT at discharge than those who did not receive PPI on admission (adjusted OR 26.00, 95% CI 11.52-58.70, p<0.001). Older patients and patients with lower hemoglobin

levels were more likely to get PPI co-prescription with DAPT at discharge (adjusted OR 1.04, 95% CI 1.01-1.06, p=0.006 and adjusted OR 0.82, 95% CI 0.72-0.95, p=0.007, respectively).

Table 3: Factors associated with the co-prescription of PPI and DAPT at discharge

Variables	Simple Logistic Regression			Multiple Logistic Regression		
	(b)	Crude OR (95% CIs)	p-value	(b)	Adjusted OR (95% CI)	p-value[d]
Gender						
Male	0	1.00				
Female	0.14	1.15 (0.67-1.96)	0.614			
Age, year (mean)	0.04	1.04 (1.02-1.06)	**<0.001**	0.04	1.04 (1.01 – 1.06)	**0.006**
Race						
Malay	0	1.00				
Non–Malay	0.09	1.09 (0.66– 1.80)	0.732			
Smoking status						
Yes	0	1.00				
No/Unknown	-0.08	0.93 (0.50–1.72)	0.812			
Alcohol Status						
Yes	0	1.00				
No/Unknown	-0.42	0.66 (0.14–3.16)	0.600			
Diabetes Mellitus						
Yes	0	1.00				
No	-0.13	0.88 (0.53– 1.46)	0.618			
Dyslipidemia						
Yes	0	1.00				
No	0.16	1.18 (0.58- 2.38)	0.647			
Hypertension						
Yes	0	1.00				
No	-0.02	0.98 (0.58–1.68)	0.953			
Chronic Kidney Disease						
Yes	0	1.00		0	1.00	
No	-0.71	0.49 (0.26–0.95)	**0.034**	-0.36	0.70 (0.30-1.60)	0.397
ACS type						
STEMI	0	1.00		0	1.00	
NSTEMI/UA	-0.67	0.51 (0.17-1.54)	**0.231**	-0.32	0.73 (0.18-2.93)	0.656
Hb at admission, g/dL (mean)	-0.23	0.80 (0.72-0.89)	**<0.001**	-0.19	0.82 (0.72-0.95)	**0.007**
PPI on admission						
No	0	1.00		0	1.00	
Yes	3.24	25.46 (11.66–55.56)	**<0.001**	3.26	26.00 (11.52-58.70)	**<0.001**

[d] Backward Multiple Logistic Regression model was applied

Constant 0.393

Multicollinearity and interaction term were checked and not found

Hosmer and Lemeshow Test, p=0.216; Classification table 82.0%; Area under ROC curve 0.883

Abbreviations: OR = odds ratio; CI = confidence interval; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; Hb = haemoglobin; PPI = proton pump inhibitor.

Discussion

This study was carried out to assess the prevalence and associated factors of PPI co-prescription with DAPT at the time of hospital discharge among patients diagnosed with ACS. In this single-centre study, the percentage PPI and DAPT co-prescription at discharge was 72.2%. According to Ho et al. (2009), the prevalence of PPI co-prescriptions with clopidogrel among ACS patients at discharge in 127 Veteran Affair Hospital was 63.7%. The study reported that compared to clopidogrel use alone, concurrent use of PPI and clopidogrel for ACS was linked to a greater risk of unfavorable outcomes (9). Different findings were reported by a study in Qatar in 2016 whereby only 32% of the patients who were on DAPT were discharged with PPI (14). Other studies reported that 31 to 33% of ACS patients were co-prescribed with DAPT and PPIs (15, 16).

In our study, ACS patients who were older, had chronic kidney disease, lower hemoglobin levels, and on PPI at admission were significantly associated with PPI use in addition to DAPT at discharge. According to a previous study by Queen et al. in 2018, the severity, fatality, and functional outcome of bleeding in patients on long-term antiplatelet therapy worsen as patients age. The study results indicated that over 80% of elderly patients above 65 years old were prescribed with PPI upon discharge, suggesting the commonality of PPI prescriptions among the elderly (17). Deshpande, Admane, and Mardikar (2018) from the Spandan Heart Institute and Research Center mentioned that recognided factors contributing to an increased risk of bleeding include advanced age (over 75 years), history of prior bleeding, and a previous stroke (18). Nonetheless, because elderly people were more likely to be unwell and need to be hospitalised, age was not generally regarded as an independent determinant in PPI prescription. Research indicated that the elderly may be overprescribed PPIs, which could result in osteoporosis and fractures if the medication was taken for longer than eight weeks. Elderly patients were also at a higher risk of contracting Clostridium *difficile* infections (CDI) (19). The 2015 AGS Bears Criteria have included PPI as a potentially inappropriate medication for older adults, as a measure taken by the American Geriatrics Society (AGS) to reduce unnecessary prescribing of PPIs in this population (19).

The second factor associated with the co-prescription of DAPT and PPI was chronic kidney disease. The presence of chronic kidney disease was statistically significant in simple logistic regression, but not in multiple logistic regression. Exposure to PPIs was linked to an increased risk of acute kidney injury, chronic kidney disease progression, and end-stage renal disease (ESRD). Due to the high prevalence of PPI use and long-term negative consequences, PPI deprescribing must be prioritised to lessen the harm and burden (20). PPI use has also been linked to an increased incidence of chronic kidney disease according to Xie et al. (21). However, given that most of the patients in this study were white men, the results of this study might not be generally applicable. According to a survey by Carrero et al., a greater percentage of patients received noninvasive treatment as renal function deteriorated. The study found that proton pump inhibitors and calcium channel blockers were more frequently used in patients with worsening kidney function (22). When age, diabetes, hypertension, hyperlipidemia, angiotensin-converting enzyme (ACE) inhibitor, diuretic, and H2-receptor blocker use were taken into account, PPI use was linked to a 1.2-fold increased risk of chronic kidney disease compared to non-users. The study also found that patients who were exposed to PPIs had a noticeably greater incidence rate of chronic kidney disease than patients who did not take PPIs (20).

The third factor associated with the co-prescription of DAPT and PPI was low hemoglobin at admission. The results of our study were in line with another Asian study, where the primary cause of inappropriate PPI prescription was anemia (23). Fah et al. stated in their study that stress ulcer prophylaxis was the most common indication, while anemia with no evidence of gastrointestinal bleeding was the main non-indication for starting PPIs (12). Several clinical studies suggested that starting PPIs regularly for anemia patients was not advisable because this could cause hyposecretion of gastric acid and impair the absorption of iron (24). Meanwhile, the low reading of hemoglobin did not necessarily indicate gastrointestinal blood loss (18). Still, studies indicated that anemia may play a significant role in inappropriate PPI prescribing (25).

The final factor associated with the co-prescription of DAPT and PPI was PPI prescribed at admission. Patients who were already on PPI during admission were more likely to be discharged with PPI. In a study conducted in Qatar by Awaitsu et al. (2016), it was found that patients who were prescribed with PPIs upon admission were at least 16 times more likely to be prescribed PPIs at discharge compared to those who did not receive PPIs at admission (14). In our study, patients who received PPI at admission were 28 times more likely to be co-prescribed with DAPT than those patients who did not receive PPI at

admission. According to a study by Gamelas et al. (2019), almost half of the patients (46.5% at admission and 55% at discharge) were receiving PPI, even though more than half of them did not need it. The primary cause of the overprescription of PPI was ulcer prevention in individuals at low risk (25). These findings were consistent with another study which stated that gastrointestinal bleeding prophylaxis was the most common inappropriate indication, even though the medical records did not specify clinical evidence for such indication (26).

There were several limitations for this study. Firstly, it was a single-centre study, limiting the generalisability of the study results. Secondly, there was a chance that significant historical and clinical data were overlooked when collecting retrospective data from the patient medical records. Several crucial pieces of information or factors related to the use of PPIs should be considered, including a history of prior gastrointestinal bleeding and concurrent use of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs), a history of pelvic ulcer disease, Helicobacter pylori infection, gastroesophageal reflux disease (GERD), and the use of PPIs at the time of admission, may have been completely missing from the medical records. Thirdly, we did not capture the patient outcomes of taking concurrent PPI and DAPT. Lastly, the results could have been influenced by additional unidentified confounders. Despite these drawbacks, the study has added valuable information about the prevalence of PPI use in the Malaysian setting and can be used as a reference for future research. A future study may be conducted to explore the reason behind the prescribing of PPI among patients treated for ACS in Malaysia and assess the long term outcomes of taking PPI together with DAPT.

Conclusion

The study's findings demonstrated that PPI use was prevalent among ACSpatients receiving DAPT in this district hospital. The associated factors of co-prescribing PPI with DAPT at hospital discharge were older age, lower hemoglobin levels, and the use of PPI at admission. However, given the constraints in the study design, these predictors were not definitive. More research is needed to identify the cardiovascular outcomes of this treatment combination and look into the appropriateness of PPI co-prescription with DAPT in ACS patients.

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Conflict of interest

No funding was received for this study. The authors have no conflict of interest to disclose.

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