International Journal of Clinical Pharmacy (2020) 42:174–183
https://doi.org/10.1007/s11096-019-00955-8

RESEARCH ARTICLE

The inappropriate use of proton pump inhibitors during admission and after discharge: a prospective cross-sectional study

Onuma Sattayalertyanyong[1] · Premrutai Thitilertdecha[2,3] · Chonticha Auesomwang[4]

Received: 13 May 2019 / Accepted: 13 December 2019 / Published online: 21 December 2019

Abstract

Background Proton pump inhibitors are often inappropriately prescribed during hospital admission and after discharge. The inappropriate prescription may be associated with increased and unnecessary healthcare costs. *Objective* To determine the prevalence of inappropriate prescription of proton pump inhibitors during hospital admission and after discharge at Thailand's largest national tertiary referral center. *Setting* Medicine wards at Siriraj Hospital (Bangkok, Thailand) during September 2016 to September 2017. *Method* This prospective observational cross-sectional study in hospitalized patients who were prescribed, or who were already taking proton pump inhibitors. Medical records were reviewed to determine whether proton pump inhibitors were prescribed at discharge and at the 1-month follow-up. *Main outcome measure* Prevalence of inappropriate prescription of proton pump inhibitors during hospital admission and after discharge, indication of inappropriate prescription. *Results* Two hundred and sixty-five patients (mean age: 65.8 ± 18.3 years, 50.9% men) were included. Approximately half of patients had proton pump inhibitor treatment initiated in the hospital, and the other 50.6% started treatment earlier. Among all patients, 50.6% were inappropriately prescribed proton pump inhibitors, in which 79.1% resulted from invalid indications. Fifty-two percent and 47.3% of patients who were prescribed proton pump inhibitors at discharge and at the 1-month follow-up had no indications for them. Gastrointestinal ulcer prophylaxis in low-risk patients was the most commonly observed incorrect indication. Aspirin ($p = 0.030$) and corticosteroids ($p = 0.038$) were both found to be significantly associated with the inappropriate prescription of proton pump inhibitors. The estimated cost of inappropriate use among inpatients and outpatients was $118,659 and $214,663 per year, respectively. *Conclusion* Proton pump inhibitors are excessively and inappropriately prescribed during hospital admission and after discharge in Thailand. The cost of this overprescribing is excessive and needs to be controlled.

Keywords Discharge · Hospital admission · Inappropriate prescription · Proton pump inhibitors · Thailand

Impacts on practice

- The rational prescription of proton pump inhibitors (PPIs) should be stricter in order to avoid inappropriate use in particular of low risk patients receiving PPIs for gastrointestinal ulcer prophylaxis.
- The standard guideline of proton pum inhibitor prescribing should be easily accessible at the working area for physicians so that the prescription can be standardized throughout the hospital to prevent inappropriate use and excessive expenses.
- Complete medical records together with discharge information om PPI use including indications, recommendations for duration of treatment, and optimal doses should be required for self-reminder or

✉ Chonticha Auesomwang
chonticha_nui@yahoo.com; chonticha.aue@mahidol.ac.th

[1] Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2] Research Group in Immunobiology and Therapeutic Sciences, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[3] Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[4] Division of Ambulatory Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand

for double check by other physicians, as well as for further decisions about continuing PPI prescription.
- Clinical pharmacists can assist the physicians to ensure the proper usages of PPI by encouraging them to use clinical guidelines, monitoring or auditing the prescription, and providing the supporting data of drug use during the clinical rounds.

Introduction

Proton pump inhibitors (PPIs) are the most potent medications currently available for reduction in gastric acid secretion. Indications for PPI therapy include peptic ulcer disease, functional dyspepsia [1, 2], gastrointestinal bleeding (GIB) [3], gastroesophageal reflux disease (GERD) [4], prophylaxis of stress-related mucosal disease (SRMD) [5], and ulcer prophylaxis when using nonsteroidal anti-inflammatory drugs (NSAIDs) [3], aspirin, and warfarin [6]. Although certain evidences have been reported on efficacy and safety of PPIs leading to their overuses, the prescription of PPIs without explicit indications has still frequently occurred and observed in many studies. High prevalence of PPI overprescription with 50–86% was reported in hospital settings [7–18] and this inadequate PPI often continued after discharge [19, 20].

Recent literatures showed several risks associated with PPIs including increased risks for hospital- and community-acquired pneumonia [21–23], an increased incidence of *Clostridium difficile* infection [24, 25] and an increased risk of hip fracture [26–28]. Additionally, PPI use was reported to be associated with vitamin and mineral deficiencies [29]. With respect to the financial value of PPIs in pharmaceutical market, a significant proportion of the global drug expenditure has been spent on PPIs. The estimated costs of inappropriate uses of PPIs in both inpatient and outpatient settings were $12,272 and $59,272 per year, respectively [30]. An observational retrospective study conducted at a military hospital in Thailand alone also reported the massive cost of inappropriate use of PPIs with $210,000 per year [17].

Although the appropriateness of PPI use has been extensively studied in the Western countries, data from Thailand about this important topic is limited and scarce. The aforementioned retrospective study conducted at the military hospital in Thailand only suggested the high prevalence of PPI overprescription in hospitalized patients; however, there is a lack of data about the inappropriateness of PPI use after patients are discharged to outpatient setting. This may unnecessarily increase the healthcare expenditure in the long term [17].

Aim of the study

The aim of this study was to determine the prevalence of inappropriate prescription of PPIs during hospital admission at Thailand's largest national tertiary referral center. The secondary objectives were to identify factors significantly associated with inappropriate PPI prescriptions, the number of inappropriate continuous PPI prescriptions at discharge and during outpatient care, and to estimate the cost of PPI prescriptions ordered for patients without definite indication for PPI.

Ethics approval

- The study protocol was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University. Reseach was conducted in accordance with the ethical standards of the institutional and/or national reseach committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
- Informed consent was obtained from all individual participants included in the study.

Methods

Study design and population

This study is prospective, observational and cross-sectional. A study population was recruited from hospitalized patients who were either initially prescribed for PPIs at the hospital or prescribed for PPIs prior to admission. The study was conducted in the internal medicine wards at Siriraj Hospital during September 2016 to September 2017. The hospital occupies 2300 beds and is located in Bangkok, Thailand. The enrollment schedule for participants was once a week selected randomly throughout a 1-year study period in order to reduce any possible bias from rotation of physicians and patients with specific diseases that are usually appointed on particular days. The patients were followed up from admission to discharge. Any patients who received PPIs at admission or during admission were analyzed and followed up at 1 month after hospital discharge. Patients receiving palliative or critical care were excluded.

Study procedures and data collection

Data from patient medical records or patient interviews were collected at 3 timepoints during the hospital visit including

days on admission, during hospitalization, and at discharge. The final timepoint for data collection was 1 month after discharge through reviewing the medical records. All patients with PPI treatment were prospectively registered and enrolled into the study. Demographic data including age, gender, diagnosis category, comorbidities, smoking status, alcohol consumption status, length of stay, and PPI status, were documented. Indication(s) for PPI prophylaxis or therapy, type of PPI, route of administration, PPI dose, and duration of therapy, as well as details relating to the use of concomitant aspirin, clopidogrel, other antiplatelets, heparin, warfarin, corticosteroids, and/or NSAIDs were also recorded and analyzed.

Furthermore, the indications for PPI use were registered and reviewed through the medical records or inquired from the patients. However, physicians who were responsible for the PPI prescriptions were blinded from the study and not questioned from the reviewers (i.e., researchers in this study) so that the obtained data were not altered from the physicians' awareness, resulting in the actual reflection of the real situation in PPI use.

Total costs of inappropriate PPI therapy in this study were determined from the price of PPIs, obtained from the hospital pharmacy records, multiplied with the total number of days using PPIs inappropriately from all participants in the randomly selected admissions. The total annual excessive cost of inappropriate PPI use was then proportionally estimated from the actual total number of internal medicine admissions in 2017 (i.e., during January to December) before converting to U.S. dollar ($).

Definition and criteria for appropriate and inappropriate PPI prescription

Indications, doses and duration of treatment for appropriate PPI prescription in this study were identified following the standard guidelines and previous review articles as listed in Table 1 [2–4, 31–35]. A PPI indication was considered

Table 1 Indications for and appropriate dose of proton pump inhibitors

Indications for proton pump inhibitors	Duration of treatment	Dose
Non-variceal bleeding	72 h	Double dose[b]
		High dose[d]
Dyspepsia	4–8 weeks	Standard dose[a]
Gastroesophageal reflux diseaseand its complication (e.g., esophagitis, Barrett's esophagus, peptic esophageal stricture)	4–8 weeks	Standard dose[a]
Helicobacter pylori infection	1–2 weeks	Double dose[c]
Treatment of peptic ulcer disease	4–8 weeks	Standard dose[a]
Treatment of Zollinger-Ellison syndrome	Lifelong	Standard dose[a]
Prevention of NSAIDs-related ulcer complications		
NSAIDs and patient history of ulcer/GIB	Until drug requiring prophylaxis is stopped	Standard dose[a]
NSAIDs and patient age > 60 years		
NSAIDs plus concomitant use of any of the following drugs: corticosteroids, antiplatelets, and/or anticoagulants		
Prophylaxis in high risk patients using antiplatelets		
Antiplatelets and patient history of ulcer/GIB	Until drug requiring prophylaxis is stopped	Standard dose[a]
Antiplatelets with more than one of the following risk factors: age > 60 years, or dyspepsia/GERD symptoms		
Antiplatelets plus concomitant use of any of the following drugs: corticosteroids, antiplatelets, NSAIDs, and/or anticoagulants		
Stress ulcer prophylaxis for high risk patient		
Coagulopathy (e.g. platelet count of < 50,000/mm^3, INR ≥ 1.5)	Until condition requiring prophylaxis is stopped	Standard dose[a]
Mechanical ventilation for > 48 h		

NSAIDs non-steroidal anti-inflammatory drugs; *GIB* gastrointestinal bleeding; *INR* international normalized ratio

[a]Standard dose: (i) for oral administration: omeprazole 20 mg daily, pantoprazole 40 mg daily, lansoprazole 30 mg daily, and rabeprazole 20 mg daily; (ii) for intravenous administration: omeprazole 40 mg daily

[b]Double dose: omeprazole 40 mg every 12 h for patients with non-variceal bleeding and clinical Rockall score ≤ 3

[c]Double dose: omeprazole 20 mg twice daily or 40 mg daily, pantoprazole 40 mg twice daily or 80 mg daily, lansoprazole 30 mg twice daily or 60 mg daily, and rabeprazole 20 mg twice daily or 40 mg daily

[d]High dose: pantoprazole 80 mg intravenous bolus followed by an infusion of 8 mg/hr for patients with non-variceal bleeding and clinical Rockall score > 3 or high risk ulcer (adherent clot, non-bleeding visible vessel, or active bleeding ulcer)

"appropriate" when the indication either in medical records or from patient interview fall within one of the criteria listed in Table 1. Doses and duration of the treatment were also taken into account for determination of appropriate use. When the indication was not explicitly mentioned in the documents, the researchers had to further explore details in medical records through the past medical history records, gastrointestinal endoscopies and histology findings before making the decision on the prescription. If there was no relevant information to the appropriate use, the prescription was then categorized into "no clear reason of PPI use found". On the other hand, the "inappropriate" prescription was determined when indications, doses and duration of treatment were not in agreement with the criteria in Table 1. The one with "no clear reason of PPI use found" was also regarded as "inappropriate" use.

It is worth noting that the indication with prevention of NSAID- or antiplatelet-related gastroduodenal damage can be a bit complicated. If this indication was used in high risk patients (i.e., patients with either age over 60 years, or previous history of GIB/peptic ulcer, or concurrent use of corticosteroids/anticoagulants/NSAIDS/antiplatelets, or dyspepsia/GERD symptoms), it was defined as "appropriate" prescription. However, if it was prescribed in low risk patients (i.e., patients without any high risk factors mentioned above), it was considered as "inappropriate" use. Furthermore, stress-related mucosal disease (SRMD) which is an erosive process of the gastroduodenum normally occurs among most critical illness patients. Development of SRMD can be resulted from various conditions including splanchnic hypoperfusion, exposure of the gastric mucosa to acid, and following breakdown of the gastric mucosal defense system. Patients with respiratory failure necessitating mechanical ventilation greater than 48 h or coagulopathy will also be considered as having the highest risk of SRMD [36, 37]. Therefore, ulcer prophylaxis from SRMD as well as antiplatelets and NSAIDs were stated as "inappropriate" prescription when there were no longer conditions requiring for prophylaxis.

Definition of PPI dosages

PPIs available in this study included omeprazole, pantoprazole, lansoprazole, and rabeprazole with different recommended doses. For standard doses with oral administration, it is suggested to use omeprazole 20 mg daily, pantoprazole 40 mg daily, lansoprazole 30 mg daily, and rabeprazole 20 mg daily; whereas the standard dose with intravenous injection was only omeprazole 40 mg daily. Double doses were calculated by doubling the standard dose of individual PPI. Only pantoprazole 80 mg intravenous bolus followed by an infusion of 8 mg/h was considered as a high dose in this study.

Sample size

The sample size (n) in this study were calculated based on the formula using for the estimation of an infinite population proportion as follows

$$n = (z)^2 p(1 - p)/d^2 \quad (1)$$

where z = 1.96 as a confidence level of 95%; $p = 0.65$ as the prevalence of inappropriate PPI prescription in hospitalized patients in Thailand from the recent study (65% of the total patients receiving PPIs) [17]; d = 0.065 as a marginal of error with 10% of p. Therefore, the number of participants receiving PPIs recruited in our study for reliable data should be at least 207 patients. In case of any errors in the data correction, 20% of total patient was then added on top, suggesting that the suitable sample size for this study should be at least 250 patients.

Data analysis

Demographic and clinical characteristics of patients were summarized using descriptive statistics. Frequency and percentage were used to describe categorical variables. Continuous variables were reported as mean ± standard deviation for normally distributed variables, and as median and range for non-normally distributed variables. Kolmogorov–Smirnov test was used to test the normality of data distribution. Comparisons of categorical variables between the appropriate or inappropriate PPI groups were performed using Chi square test or Fisher's exact test. Continuous variables were compared using Student's *t* test or Mann–Whitney U test. Strength of association was evaluated using odds ratio (OR) and 95% confidence interval (95% CI). For all tests performed, a two-tailed $p < 0.05$ was considered statistically significant. PASW Statistics (SPSS) version 18.0 (SPSS, Inc, Chicago, II, USA) was used to perform all statistical analyses.

Results

A total of 456 patients admitted in the internal medicine wards of Siriraj Hospital were screened during the study period. Only 265 patients (58.1%) were prescribed PPIs at admission or during hospitalization and got enrolled for the further investigation, whereas 191 patients who did not receive PPI prescription were not pursued for any further analyses. Half (49.4%) of these 265 patients had PPI treatment initiated in the hospital, and the other 50.6% started PPI treatment earlier admission. A summary of PPI prescription before or during admission, at discharge, and during

follow-up at the outpatient department (OPD) is shown in Fig. 1. Of the 265 enrolled patients, 134 (50.6%) had inappropriate PPI prescriptions. Of those, 67 (50.0%) started PPIs prior to admission, and the other 50.0% started PPIs during hospital admission. Regarding the 196 patients that were prescribed PPIs at hospital discharge, 102 (52.0%) received PPIs inappropriately. Of those, 57 (56.0%) started PPIs prior to admission, and 45 (44.0%) started PPIs during hospital admission. At the 1-month follow-up in our OPD, 129 patients were prescribed PPIs at discharge. Continuation of PPIs treatment was not recommended in 61 patients (47.3%), of which 45 (73.8%) were patients that started PPIs prior to hospital admission, and the other 16 (26.2%) started treatment during admission.

Baseline demographic, clinical, and medication data of 265 included patients are shown in Table 2. The mean age of patients was 65.8 ± 18.3 years, and 135 (50.9%) were males. Most patients reported being a non-smoker (68.3%), and a non-drinker of alcohol (66.8%). The average hospital length of stay (LOS) was 11 days. Regarding concomitant medications, 216 patients (81.5%) were coprescribed PPIs with at least one of the following drugs: aspirin 27.2%, clopidogrel 3%, aspirin plus another antiplatelet 12.8%, corticosteroids 19.6%, anticoagulants 17.7%, and NSAIDs 1.1%. Of the 4 PPIs prescribed among patients included in this study, 95% (n = 252) were for omeprazole, 4.2% (n = 11) were for pantoprazole, 0.4% (n = 1) was for lansoprazole, and 0.4% (n = 1) was for rabeprazole. Regarding route of PPI administration, 65.3% was prescribed in oral form, and 34.7% was prescribed in intravenous form. Regarding PPI dosage, 76.2% was prescribed in standard dose, 20.4% in double dose, and 3.4% in high dose. All high-dose prescriptions were ordered/written for patients diagnosed with upper GIB.

Of the 134 patients (50.6%) that were inappropriately prescribed PPIs, 106 (79.1%) had no indication for PPIs, 18 (13.4%) were prescribed the incorrect dose, and 10 (7.5%) were prescribed PPIs for the incorrect duration. The median duration of inappropriate PPI treatment in hospital

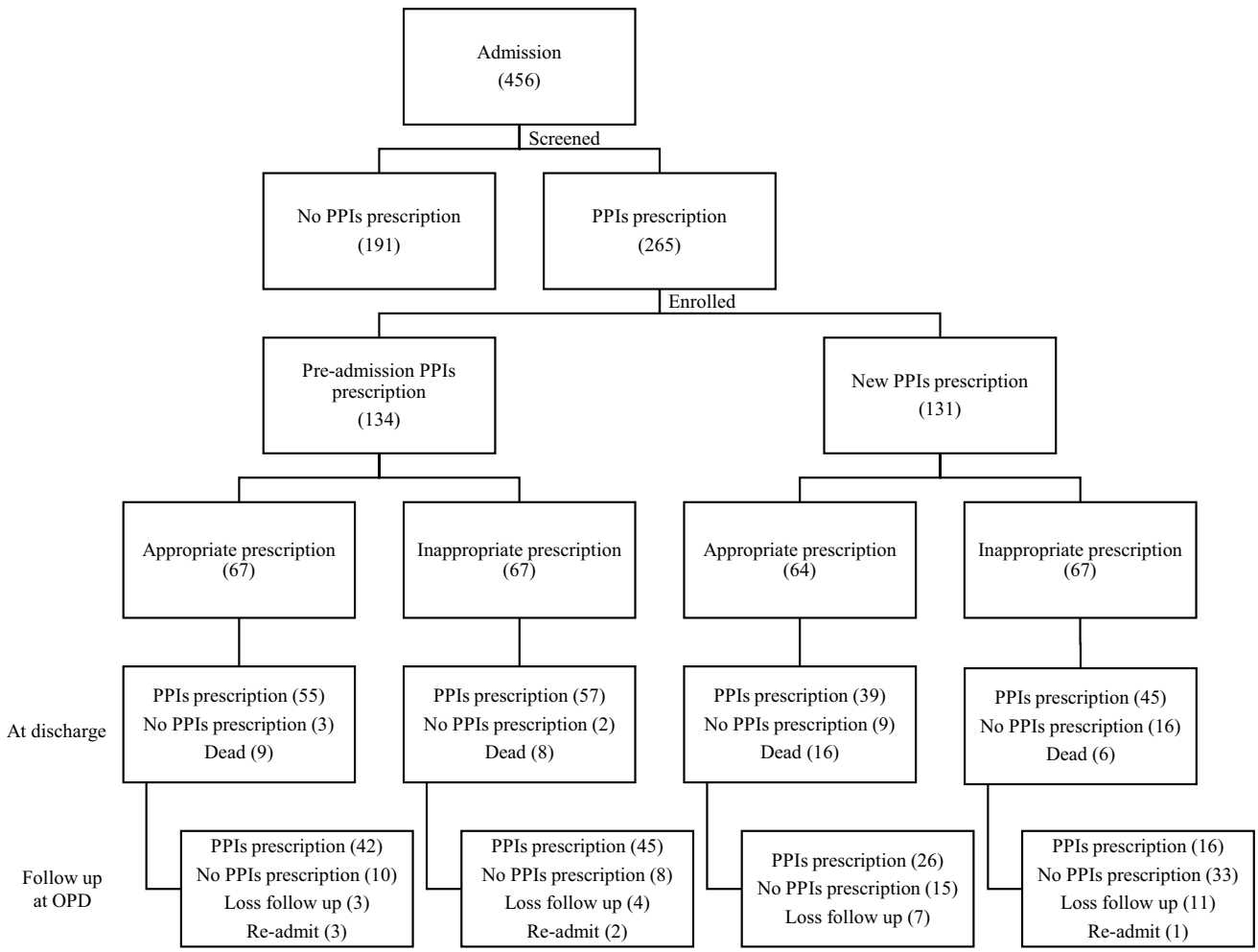

Fig. 1 Summary of proton pump inhibitor (PPI) prescription before or during admission, at discharge, and -month follow-up at the outpatient department (OPD)

Table 2 Baseline demographic, clinical, and medication data of included patients

Patient characteristics	(N = 265)
Male gender, n (%)	135 (50.9%)
Age (mean ± SD)	65.8 ± 18.3
Non-smoker, n (%)	181 (68.3%)
No alcohol consumption, n (%)	177 (66.8%)
Length of stay (days), median (P_{25}, P_{75})	11 (6, 18)
Principal diagnosis, (n (%)	
Pulmonary disease	64 (24.2%)
Infectious disease	49 (18.5%)
Cardiac disease	40 (15.1%)
Gastrointestinal disease	34 (12.8%)
Neurological disease	27 (10.2%)
Malignancy	13 (4.9%)
Comorbidity, n (%)	
Hypertension	167 (63.0%)
Diabetes mellitus	99 (37.4%)
Dyslipidemia	114 (43.0%)
Coronary artery disease	69 (26.0%)
Cerebrovascular disease	47 (17.7%)
Cirrhosis	19 (7.2%)
Chronic kidney disease	77 (29.1%)
Concurrent medications, n (%)	
Aspirin	72 (27.2%)
Clopidogrel	8 (3.0%)
Aspirin plus other antiplatelets	34 (12.8%)
Corticosteroids	52 (19.6%)
Warfarin	25 (9.4%)
Heparin	22 (8.3%)
NSAIDs	3 (1.1%)
PPIs prescribed, n (%)	
Omeprazole	252 (95.1%)
Pantoprazole	11 (4.2%)
Lanzopraole	1 (0.4%)
Rabeprazole	1 (0.4%)
Indications for PPIs at admission (n = 265), n (%)	
Inappropriate use	134 (50.6%)
Indications for PPIs at discharge (n = 196), n (%)	
Inappropriate use	102 (52.0%)
Indications for PPIs at follow-up (n = 129), n (%)	
Inappropriate use	61 (47.3%)

SD standard deviation; *P* percentile; *NSAIDs* non-steroidal anti-inflammatory drugs; *PPIs* proton pump inhibitors

was 8.5 days. Two type PPIs prescribed inappropriately, 133 (99.3%) were for omeprazole and 1 (0.7%) were for lanzoprazole. Regarding route of PPI administration, 71% was prescribed in oral form, 29% was prescribed in intravenous form. Regarding PPI dosage, 84% was prescribed in standard dose and 16% in double dose.

Table 3 Protein pump inhibitor (PPI) indications compared between the appropriate PPI prescription group and the inappropriate PPI prescription group (N = 265)

	n (%)
Appropriate PPI prescription (n = 131)	
Prophylaxis against ulcer complications in high risk patients	83 (63.4%)
Antiplatelet use	54 (41.2%)
NSAID use	1 (0.8%)
Stress ulcer prophylaxis	28 (21.4%)
Non-variceal bleeding	43 (32.8%)
Dyspepsia	15 (11.5%)
Peptic ulcer disease	13 (9.9%)
Gastroesophageal reflux disease	8 (6.1%)
Helicobacter pylori infection	2 (1.5%)
Inappropriate PPI prescription (n = 134)	
Prophylaxis against ulcer complications in low risk patients	102 (76.1%)
Antiplatelet use	49 (36.6%)
NSAID use	1 (0.7%)
Corticosteroids use	30 (22.4%)
Anticoagulants use	9 (6.7%)
Stress ulcer prophylaxis	13 (9.7%)
Non-variceal bleeding	2 (1.5%)
Dyspepsia	7 (5.2%)
Peptic ulcer disease	2 (1.5%)
No clear reason of PPI use found	21 (15.7%)

NSAID non-steroidal anti-inflammatory drug

The most inappropriate use of PPI was for gastrointestinal ulcer prophylaxis in low risk patients (102 patients, 76.1%) in which the major populations were patients taking antiplatelets (49 patients, 36.6%), and corticosteroids (30 patients, 22.4%), whereas the predominant indication for appropriate PPI prescription was for prevention of antiplatelet-induced ulcer or GIB in high risk patients (54 patients, 41.2%), followed by treatment of non-variceal bleeding (43 patients, 32.8%) (Table 3).

Regarding our analysis for factors significantly associated with the inappropriate prescription of PPIs, only aspirin use [odds ratio (OR): 2.29, 95% confidence interval (CI) 1.31–4.02; $p = 0.030$] and corticosteroid use (OR: 1.93, 95% CI 1.03–3.6; $p = 0.038$) were found to be significant predictors of incorrect use of PPIs. There were 47 (35.1%) aspirin users and 33 (24.6%) corticosteroid users in the inappropriate PPI prescription group, and 25 (19.1%) aspirin users and 19 (14.5%) corticosteroid users in the appropriate PPI prescription group. Aspirin with other antiplatelets use ($p < 0.001$) and heparin use ($p < 0.001$) were found to be significant predictors of appropriate prescription of PPIs (Table 4).

Table 4 Characteristics of patients prescribed proton pump inhibitors (PPIs) compared between the appropriately prescribed and inappropriately prescribed groups

Characteristics	Appropriate PPI use (n = 131)	Inappropriate PPI use (n = 134)	*p*-value
Gender, n (%)			
Male	66 (50.4%)	69 (51.5%)	0.856
Female	65 (49.6%)	65 (48.5%)	
Age (mean ± SD)	66.7 ± 17.0	64.9 ± 19.5	0.420
Length of stay (days), median (P_{25}, P_{75})	10 (5, 20)	11 (6, 17)	0.956
Concurrent medications, n (%)			
Aspirin	25 (19.1%)	47 (35.1%)	0.030
Aspirin plus other antiplatelet	32 (24.4%)	2 (1.5%)	< 0.001
Clopidogrel	4 (3.1%)	4 (3.0%)	0.974
Corticosteroid	19 (14.5%)	33 (24.6%)	0.038
Warfarin	16 (12.2%)	9 (6.7%)	0.126
Heparin	19 (14.5%)	3 (2.2%)	< 0.001
NSAID	2 (1.5%)	1 (0.7%)	0.619
PPI prescription, n (%)			
New PPI prescription	64 (48.9%)	67 (50.0%)	0.852
Pre-admission PPI prescription	67 (51.1%)	67 (50.0%)	
PPIs duration (days), median (P_{25}, P_{75})	9 (5, 19)	8.5 (5, 15)	0.261

SD standard deviation; *P* percentile; *NSAID* non-steroidal anti-inflammatory drug

The drug costs obtained from the hospital pharmacy stated that omeprazole 20 mg was $0.2 per tablet and omeprazole 40 mg was $7 per vial. The median duration of inappropriate PPI use in the hospital was 8.5 days. Regarding the total expenses based on 456 admissions in this study, the costs of inappropriate PPI therapy in hospitalized patients and ambulatory patients were $2865 and $5183, respectively. With respect to the annual total excessive costs in 2017 with 18,886 admissions in the internal medicine in our institute, the estimation of those costs for inpatients and outpatients was $118,659 and $214,663, respectively.

Discussion

Fifty-eight percent of randomly selected inpatients in our internal medicine wards were prescribed a PPI. Moreover, the number of patients receiving these treatments prior to admission was similar to those who started treatment at admission (50.6% vs. 49.4%). Our study revealed a high rate of inappropriate PPI prescription among hospitalized patients (50.6%), which is consistent with the findings of other studies (range 50–86%) [7–18].

Regarding PPI prescriptions at discharge, 196 patients in our study were prescribed PPIs when they were released from the hospital. Of those, 102 patients (52%) received PPIs inappropriately, which is similar to the 52% finding from a study from Germany [8]. A recent Spanish study found that 55% of patients in a tertiary hospital received PPIs at discharge, and 80% of those patients had no indications for PPIs [38]. Overuse of PPIs was reported in other European hospital cohorts [39], and a large cohort study conducted in Pittsburgh found that 68.8% of patients (n = 20,197) were inappropriately prescribed a PPI at hospital discharge [40].

After discharge at the 1-month follow-up, 129 patients were prescribed PPIs to continue their discharge PPI prescription. Of those, 47.3% had no indications for PPIs. Only a few studies evaluated continuation of PPI prescriptions after discharge. A study in 31 primary care practices in Germany found that non-indicated PPIs were continued by general practitioners in 58% of patients for at least 1 month [8]. An American study found that after discharge, 46–80% of patients were still on PPIs after 3 months, and 50% were still on PPIs after 6 months [20]. Rates similar to the immediately aforementioned American study were found in an Italian hospital [19]. Remarkably, we observed similar rates of continuation of non-indicated PPI prescriptions among different studies, countries, and healthcare systems.

The reasons that PPIs are overprescribed in hospitals are neither well studied nor well understood. Physicians may have inaccurate or insufficient understanding about the risk of ulcer development during hospitalization, and they prescribe PPIs with good intent to prevent ulcer development even though they are not in compliance with existing PPI guidelines. Some physicians routinely continue PPIs considering them safe, long-term medications, without assessing risks and benefits of long-term therapy [11]. Other recent studies showed that physicians do not review and document PPI indications in a large number of cases, which often results in their long-term or indefinite

continuation [11, 41, 42]. In our study, the majority of inappropriate PPI prescriptions were ordered/written for prophylaxis against ulcer complications from antiplatelets and corticosteroids use in low risk patients. This finding is similar to that from a previous study conducted in Germany that found low-dose aspirin, NSAIDs in low risk patients, corticosteroid therapy, and oral anticoagulant treatment to be the most common incorrect indications for the prescription of PPIs [9, 17]. Furthermore, the most common indication for appropriate PPI prescription was prevention of antiplatelet-induced gastric ulcers in high risk patients. It is important to highlight that using PPI for ulcer prophylaxis from antiplatelets can be considered as either appropriate or inappropriate ways depending on individual patient's characteristics. Patients receiving antiplatelets with one of risk factors (e.g., age > 60 years, co-prescription with antiplatelets/anticoagulants/NSIADs/corticosteroids, and present symptoms of dyspepsia or GERD) were defined as "high risk patients" who are suitable for PPI prescription. On the contrary, patients taking antiplatelets without those risk factors were defined as "low risk patients" who are unsuitable for PPI prescription. Besides that, patient monitoring is also sensible to periodically evaluate the necessity of using PPIs. If the drug required for prophylaxis is discontinued, the PPI prescription should also be discontinued.

We observed that a high proportion of non-indicated PPI therapy was continued, particularly in patients who received PPIs prior to hospital admission. During discharge, 56% of patients who received inappropriate PPIs were patients that received PPIs prior to admission. The same was observed after discharge at the 1-month follow-up. The majority of patients (73.8%) that were inappropriately prescribed PPIs were patients who started treatment prior to hospital admission, and it was part of their usual medication. Previous study revealed the strongest factor associated with non-indicated continuation of PPIs was having PPI prescription prior to hospital admission [8]. Possible explanations include trust in the judgment of the physician who initially prescribed PPIs, and a failure to reassess indications for PPI since it was a part of the patient's normal medication prior to admission.

Inappropriate prescription of PPIs is an important issue for several reasons. First, the administration of unnecessary medication leads to polypharmacy, resulting in side effects and pharmacological interactions. Second, PPI use is found to be significantly associated to community-acquired pneumonia [22, 23] and *Clostridium difficile*-associated diarrhea [24, 25]. Moreover, a long-term PPI therapy is suspected to be associated with an increased risk of hip fracture [26–28]. Finally, the unnecessary prescription of any drugs unnecessarily exhausts resources either from private individuals, public healthcare systems, or insurance companies/funds/schemes.

The cost of this inappropriate use of PPIs has grown substantially and needs to be controlled. Our calculations revealed excess costs of $118,659 per year for inpatients, and $214,663 per year for outpatients. It should be emphasized that these estimates reflect only excess costs generated in internal medicine wards, so the institution-wide costs would be expected to be substantially higher. Sonchai et al. [17] reported the excess cost of inappropriate PPI prescriptions in hospitalized patients to be $210,000 per year. Moreover, the cost of inappropriate PPI use in the outpatient setting is even more alarming. The fact that most inappropriate PPI prescriptions were influenced by a physician's decision to provide prophylaxis against ulcer complications in low risk patients caused by antiplatelets suggests that many, if not most, patients could be expected to be on PPIs for their entire life. In addition to the potential drug interaction and side effect-related risks, this will place a significant financial burden on our healthcare system.

This study has a number of limitations. First, this was an observational prospective study, so we collected the data by chart review and patient interview. The decision was made not to source data from physicians at wards or the OPD in order to minimize potential bias. Our method of research also relied upon adequate documentation in patient records. This limited the study certainly as pertinent results were not always readily available. Secondly, the data for this study came from a single center with medical residents writing orders for all medications, so it is possible that our results and conclusions may not be generalizable to other care settings. Despite these limitations, our results are consistent with the current literature, and they enhance the existing body of knowledge about this topic. The strengths of this study include its prospective design, the random weekly time periods during which patients were enrolled in order to reduce potential selection bias.

Conclusion

The results of this study revealed high rates of inappropriate PPI prescriptions in patients admitted to internal medicine wards at our center. Moreover, we found that this practice gets perpetuated at discharge and during outpatient follow-up care. The majority of inappropriate PPI prescriptions were written/ordered to provide prophylaxis against ulcer complications due to antiplatelet and corticosteroid use in low risk patients. Aspirin use and corticosteroid use were the factors found to be significantly associated with higher probability of inappropriate prescription of PPIs. The cost of this excessive and inappropriate use of PPIs is high and must be controlled. Physicians should carefully, accurately, and critically review their practice of recommending PPIs to ensure appropriate use of this important medication.

Acknowledgements The authors gratefully acknowledge the patients that generously agreed to participate in this study, and Ms. Khemajira Karaketklang of the Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University for assistance with statistical analysis. We would like to thank Mr. Kevin P. Jones (medical research manuscript editor) for proofreading this article.

Funding This study was supported by a grant from the Siriraj Hospital Research Fund, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Conflicts of interest All authors declare that they have no conflict of interest.

References

1. Ford AC, Moayyedi P. Current guidelines for dyspepsia management. Dig Dis. 2008;26(3):225–30.
2. Talley NJ, Vakil N. Practice parameters committee of the American College of G. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005;100(10):2324–37.
3. Lanza FL, Chan FK, Quigley EM. Practice parameters committee of the American College of G. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104(3):728–38.
4. Niaz SK, Quraishy MS, Taj MA, Abid S, Alam A, Nawaz AA, et al. Guidelines on gastroesophageal reflux disease. J Pak Med Assoc. 2015;65(5):532–41.
5. Mohebbi L, Hesch K. Stress ulcer prophylaxis in the intensive care unit. Bayl Univ Med Cent Proc. 2009;22(4):373–6.
6. Morneau KM, Reaves AB, Martin JB, Oliphant CS. Analysis of gastrointestinal prophylaxis in patients receiving dual antiplatelet therapy with aspirin and clopidogrel. J Manag Care Pharm. 2014;20(2):187–93.
7. Villamanan E, Ruano M, Lara C, Suarez-de-Parga JM, Armada E, Alvarez-Sala R, et al. Reasons for initiation of proton pump inhibitor therapy for hospitalised patients and its impact on outpatient prescription in primary care. Rev Esp Enferm Dig. 2015;107(11):652–8.
8. Ahrens D, Behrens G, Himmel W, Kochen MM, Chenot JF. Appropriateness of proton pump inhibitor recommendations at hospital discharge and continuation in primary care. Int J Clin Pract. 2012;66(8):767–73.
9. Ahrens D, Chenot JF, Behrens G, Grimmsmann T, Kochen MM. Appropriateness of treatment recommendations for PPI in hospital discharge letters. Eur J Clin Pharmacol. 2010;66(12):1265–71.
10. Akram F, Huang Y, Lim V, Huggan PJ, Merchant RA. Proton pump inhibitors: are we still prescribing them without valid indications? Australas Med J. 2014;7(11):465–70.
11. Haroon M, Yasin F, Gardezi SK, Adeeb F, Walker F. Inappropriate use of proton pump inhibitors among medical inpatients: a questionnaire-based observational study. JRSM Short Rep. 2013;4(8):1–6.
12. Perwaiz MK, Posner G, Hammoudeh F, Schmidt F, Neupane N, Enriquez D, et al. Inappropriate use of intravenous PPI for stress ulcer prophylaxis in an inner city community hospital. J Clin Med Res. 2010;2(5):215–9.
13. Shin S. Evaluation of costs accrued through inadvertent continuation of hospital-initiated proton pump inhibitor therapy for stress ulcer prophylaxis beyond hospital discharge: a retrospective chart review. Ther Clin Risk Manag. 2015;11:649–57.
14. Eid SM, Boueiz A, Paranji S, Mativo C, Landis R, Abougergi MS. Patterns and predictors of proton pump inhibitor overuse among academic and non-academic hospitalists. Intern Med. 2010;49(23):2561–8.
15. Martin-Echevarria E, Pereira Julia A, Torralba M, Arriola Pereda G, Martin Davila P, Mateos J, et al. Assessing the use of proton pump inhibitors in an internal medicine department. Rev Esp Enferm Dig. 2008;100(2):76–81.
16. Reid M, Keniston A, Heller JC, Miller M, Medvedev S, Albert RK. Inappropriate prescribing of proton pump inhibitors in hospitalized patients. J Hosp Med. 2012;7(5):421–5.
17. Sirivunnabood S, Barameerungsikul C. Proton pump inhibitors for stress ulcer prophylaxis in general wards. R Thai Air Force Med Gaz. 2011;57(2):1–5.
18. Savarino V, Dulbecco P, de Bortoli N, Ottonello A, Savarino E. The appropriate use of proton pump inhibitors (PPIs): need for a reappraisal. Eur J Intern Med. 2017;37:19–24.
19. Parente F, Cucino C, Gallus S, Bargiggia S, Greco S, Pastore L, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. Aliment Pharmacol Ther. 2003;17(12):1503–6.
20. Zink DA, Pohlman M, Barnes M, Cannon ME. Long-term use of acid suppression started inappropriately during hospitalization. Aliment Pharmacol Ther. 2005;21(10):1203–9.
21. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA. 2009;301(20):2120–8.
22. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk in PPI. Am J Gastroenterol. 2009;104(Suppl 2):S27–32.
23. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004;292(16):1955–60.
24. Howell MD, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M, et al. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. Arch Intern Med. 2010;170(9):784–90.
25. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. JAMA. 2005;294(23):2989–95.
26. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2011;106(7):1209–18 **(quiz 19)**.
27. Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. Calcif Tissue Int. 2006;79(2):76–83.
28. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006;296(24):2947–53.
29. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. Ther Adv Drug Saf. 2013;4(3):125–33.
30. Ladd AM, Panagopoulos G, Cohen J, Mar N, Graham R. Potential costs of inappropriate use of proton pump inhibitors. Am J Med Sci. 2014;347(6):446–51.
31. Freston JW. Review article: role of proton pump inhibitors in non-H pylori-related ulcers. Aliment Pharmacol Ther. 2001;15(Suppl 2):2–5.
32. Wilcox CM, Hirschowitz BI. Treatment strategies for Zollinger-Ellison syndrome. Expert Opin Pharmacother. 2009;10(7):1145–57.
33. Bhatt DLSJ, Abraham NS, Antman EM, Chan FK, Furberg CD, et al. ACCF/ACG/AHA2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. J Am Coll Cardiol. 2008;52(18):1502.

34. Zeitoun A, Zeineddine M, Dimassi H. Stress ulcer prophylaxis guidelines: are they being implemented in Lebanese health care centers? World J Gastrointest Pharmacol Ther. 2011;2(4):27–35.
35. Ferguson CB, Mitchell RM. Non-variceal upper gastrointestinal bleeding. Ulster Med J. 2006;75(1):32–9.
36. Monnig AA, Prittie JE. A review of stress-related mucosal disease. J Vet Emerg Crit Care (San Antonio). 2011;21(5):484–95.
37. Khalili H, Dashti-Khavidaki S, Hossein Talasaz AH, Tabeefar H, Hendoiee N. Descriptive analysis of a clinical pharmacy intervention to improve the appropriate use of stress ulcer prophylaxis in a hospital infectious disease ward. J Manag Care Pharm. 2010;16(2):114–21.
38. Elena R, Su HL, Alberto MB, Enrique P, Salvador F, Raul M, et al. Overuse of PPIs in patients at admission, during hospitalisation, and at discharge in a tertiary Spanish hospital. Curr Clin Pharmacol. 2010;5(4):288–97.
39. van Vliet EPM, Otten HJAM, Rudolphus A, Knoester PD, Hoogsteden HC, Kuipers EJ, et al. Inappropriate prescription of proton pump inhibitors on two pulmonary medicine wards. Eur J Gastroenterol Hepatol. 2008;20(7):608–12.
40. Thomas L, Culley EJ, Gladowski P, Goff V, Fong J, Marche SM. Longitudinal analysis of the costs associated with inpatient initiation and subsequent outpatient continuation of proton pump inhibitor therapy for stress ulcer prophylaxis in a large managed care organization. J Manag Care Pharm. 2010;16(2):122–9.
41. Batuwitage BT, Kingham JG, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. Postgrad Med J. 2007;83(975):66–8.
42. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol. 2012;5(4):219–32.