Original Article

Evaluation of Prescribing Proton Pump Inhibitors among Hospital Inpatients in a Teaching Hospital: Report from Northwest of Iran

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ABSTRACT

Background:
Proton pump inhibitors (PPIs) are extensively used for managing gastrointestinal (GI) related disorders, but their inappropriate prescription remains a concern, leading to potential complications and increased healthcare costs. The current study was designed to evaluate the prescribing patterns of PPIs in hospital inpatients at Imam Khomeini Hospital.

Materials and Methods:
We conducted a cross-sectional study from May 2023 to July 2023 in a tertiary referral teaching hospital in Urmia, Iran. A total of 283 patients receiving PPIs were enrolled and classified into therapeutic and prophylactic groups. Prescriptions were further categorized as appropriate or inappropriate based on the protocol approved by the hospital's Rational Prescribing Committee. Demographic information, clinical outcomes, PPI indications, dosage, and administration route were collected.

Results:
80 out of 283 patients were assigned to the therapeutic group, in which 82.5% of prescriptions were compatible with the approved protocol, and the prophylactic group with 203 patients had 42.36% rational PPI administration. Oral form of PPIs was more commonly used (therapeutic: 55%, prophylactic: 87.7%). The following factors were found to be associated with appropriate prescriptions: a history of GI disorders (in the therapeutic group), pulmonary and rheumatological disorders, and the use of anticoagulants (in the prophylactic group). Inappropriate prescriptions were associated with neurological disorders (in the prophylactic group) and specific comorbidities such as hypertension and chronic obstructive pulmonary disease (in the therapeutic group).

Conclusion:
Our study revealed that inappropriate PPI prescriptions were common in this medical center. Despite having a protocol in place, continuous training for prescribers is essential. The persistence of this condition places a financial burden on healthcare systems and puts patients at risk of unintended drug-related complications.

Keywords: Proton Pump Inhibitors, Prescribing Pattern, Prophylaxis

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INTRODUCTION

Proton pump inhibitors (PPIs) are the most potent medications for inhibiting gastric acid secretion, which have been used to manage gastric-related disorders, such as gastroesophageal reflux disease (GERD), gastrointestinal bleeding (GIB), Zollinger-Ellison syndrome and stress-related ulcers (1, 2). PPIs were first discovered in the 1980s and introduced to the pharmaceutical market with the drug omeprazole. Pantoprazole, esomeprazole, rabeprazole, and lansoprazole are the other most common used ones (3). The mechanism of action of PPIs is through binding irreversibly to the proton pump, an ATPase pump responsible for the exchange of hydrogen (H^+) and potassium (K^+) ions located in the luminal surface of the gastric parietal cell membrane. This binding inhibits the proton pump function and blocks gastric acid secretion (4).

Stress ulcers are erosions that occur in the upper part of the Gastrointestinal (GI) tract, mainly in the esophagus, stomach, and duodenum, due to hospitalization. To be precise, these erosions originate from the lower part of the esophagus; however, as the duration of hospitalization increases, these erosions can progress deeper and extend into the stomach and duodenum (5,6). The underlying mechanism is thought to be decreased perfusion of the GI mucosa, which leads to increased gastric acid production and disruption of glycoproteins-mediated mucosal protection (7). Patients with stress ulcers often remain asymptomatic, but the most common manifestation is GI bleeding (8). However, studies have shown that this condition increases patient morbidity and mortality (9). Multiple risk factors make patients (especially critically ill patients in intensive care units) susceptible to stress ulcers. Two major risk factors include mechanical ventilation for more than 48 hours and coagulation disorders (platelets<50000/mm3 or INR≥1.5 or PTT >2 times the control value). The presence of each factor leads to a 3.7% increase in the risk of developing stress ulcers (10). Minor risk factors are as follows: sepsis, shock, heart failure with ejection fraction less than 40%, end-stage renal disease (ESRD) or a glomerular filtration rate (GFR) less than 15 mL/min, history of GI ulcer, history of GIB, more than three comorbidities, hypoperfusion, multiple traumas including head, spinal, and other injuries, burns exceeding 35% of the body surface area, organ transplant, antiplatelet medication use, and non-steroidal anti-inflammatory drugs (NSAIDs) (11). Therefore, it can be concluded that stress ulcer is a common complication in hospitalized patients (especially those in the intensive care unit) and can lead to GIB. Hence, it is necessary to use preventive medications as stress ulcer prophylaxis (SUP) in certain high-risk patients (12).

Despite evidence supporting the effectiveness and safety of PPIs, excessive and irrational prescriptions have been observed in many studies (13-18). Moreover, this inappropriate use can lead to several complications, including Clostridium difficile infection (19, 20), pneumonia (21,22), osteoporosis (23), and hypomagnesemia (24). Additionally, the widespread inappropriate prescription of PPIs in various medical settings imposes a significant financial burden on healthcare systems. A study conducted by Sattayalertyanyong and colleagues in Thailand in 2020 estimated that inappropriate PPI prescription among inpatients and outpatients costs $118,659 and $214,663 per year, respectively (25). Another study in Germany in 2023 with a large population (472,146 patients) showed that only 4.5% of treatments with PPIs were entirely by guidelines (26). Some studies have evaluated the PPI prescribed in Iran. Sohrevardi and co-workers reported that 63% of prescribed intravenous pantoprazole in patients staying in intensive care units and general wards was inappropriate due to either wrong indication, dose, or duration (27). Shahbazi and others found that 92.9% of patients receiving intravenous pantoprazole could tolerate the oral form of the medication. Therefore, 5029 vials of pantoprazole, prescribed inappropriately, imposed an additional cost of 17,822 US dollars to the healthcare system (28).

Because our country is a developing nation, we must maintain financial stability. We also have to prevent additional costs in the healthcare system caused by the inappropriate prescription of medications. Therefore, due to the lack of enough evidence supporting the PPI prescribing pattern in our hospital and country, we aimed to conduct a study to investigate the appropriateness of PPI prescriptions.

MATERIALS AND METHODS

Study setting and population

An observational and cross-sectional study was conducted in the academic hospital affiliated with Urmia University of Medical Sciences from May 1, 2023, to July 31, 2023. The study population was selected randomly from hospital inpatients receiving PPIs prescribed either in internal medicine wards or medical intensive care units (MICUs). The research was conducted in accordance with the guidelines outlined in the Declaration of Helsinki (29). The study protocol was approved ethically by the Ethics Committee of Urmia University of Medical Sciences (NO. IR.UMSU.REC.1400.471). All patients signed the written informed consent form before participating in the study. To minimize any possible selection biases related to physicians' rotation and patients with specific diseases, patients were enrolled randomly to study on different days of the week. All patients enrolled in the study were followed up until discharge. Patients with missing or unreliable data, those who did not complete the checklist, and patients admitted on their first day without laboratory data were excluded from the study. The primary study outcome was to determine the appropriateness of prescriptions based on therapeutic or prophylactic groups.

Protocol preparation and definition of appropriate prescription
Initially, a protocol for evaluating the rational prescription of PPIs was developed by a clinical pharmacist and a gastroenterologist based on the guidelines and previous studies (25, 30-47). Subsequently, this protocol was revised by the faculty members of the hospital's Gastroenterology Department and then finalized to be implemented in the study (Table 1). It was also approved by the hospital's Rational Prescribing Committee. Indications, dosage, route, and duration of use for PPIs were precisely identified within the prepared protocol. Since all patients enrolled in the study received pantoprazole, all the mentioned items in Table 1 are specified for this drug.

Table 1. Therapeutic and prophylactic indications for PPI use

Therapeutic indications	Dose	Rout	Duration
Gastroesophageal reflux disease:			
Mild disease without erosive esophagitis (<2 episodes/week)	20 mg once daily[1]	Oral	8 weeks
Severe disease or erosive esophagitis (≥2 episodes/week)	40 mg once daily	Oral, IV[2]	8 weeks[3]
Non-variceal upper gastrointestinal bleeding, re-bleeding prevention	80-mg bolus and 8 mg/h infusion[4]	IV	72 hours
Barrett's esophagus	40 mg once daily	Oral	Long-term maintenance therapy is recommended
Dyspepsia	20 to 40 mg once daily	Oral	4-8 weeks
Zollinger–Ellison syndrome	80 mg twice daily[5]	Oral, IV[6]	As long as clinically indicated
Helicobacter pylori eradication	40 mg or 80 mg twice daily[7]	Oral	As part of a combination regimen with antibiotics
Prophylactic indications			
Concomitant use of NSAIDs with any of the following medications: Corticosteroids, antiplatelets, or anticoagulants Chronic use of NSAIDs with a history of gastrointestinal disorders Concomitant use of antiplatelets in patients with age> 60 years Stress ulcer prophylaxis	40 mg once daily	Oral, IV[8]	Until critical illness and risk factors are resolved
Risk factors for stress ulcer prophylaxis[9]:			
Major risk factors: Mechanical ventilation for >48 hours Coagulopathy (platelets<50000/mm3 or INR≥1.5 or PTT >2 times the control value) History of gastrointestinal bleeding or peptic ulcer in the last 12 months Head trauma or spinal trauma with GCS<10 More than 20% of the body surface area burn Minor risk factors: Sepsis[10] Hepatic failure[11] Renal insufficiency[12] Shock13 Organ transplant Use of NSAIDs Injury severity score >15 ICU stay for >1 week Occult gastrointestinal bleeding > 6 days Administration of 250 mg hydrocortisone or an equivalent dose Use of antiplatelets or anticoagulants in therapeutic doses[9] Being NPO for at least 5 days			

International Normalized Ratio = INR, Partial Thromboplastin Time = PTT, Intensive care unit = ICU, Per Os = PO, Non-steroidal anti-inflammatory drugs = NSAIDs, Glasgow Coma Scale= GCS, 1: Increase to 40 mg once daily, if needed, after 4 to 8 weeks; 2: For patients unable to take pantoprazole orally, given 40 mg once daily, then switch to oral administration, when possible; 3: Patients without severe erosive esophagitis or Barrett's esophagus can taper down to the lowest effective dose to manage symptoms and then stop acid suppression when asymptomatic. Patients with severe erosive esophagitis or Barrett's esophagus should continue long-term maintenance therapy with 40 mg once daily; 4: If re-bleeding occurs, diagnosed on clinical and/or endoscopic grounds, the patient may receive intravenous proton pump inhibitor for an additional 72 hours; 5: Titrate upward early in therapy to a maximum of 240 mg/day, given as 80 mg every 8 hours or 120 mg every 12 hours, if needed, 6: An IV form of pantoprazole is indicated for patients who cannot take it orally, given as 80 mg every 8 hours or 120 mg every 12 hours for a limited period (up to 6 days) and then switched to oral administration when possible; 7: The dose depends on the selected regimen; 8: An intravenous form of pantoprazole is indicated for patients who cannot take it orally and then switch to oral administration, when possible; 9: Stress ulcer prophylaxis is recommended for patients with one major risk factor or at least two minor risk factors; 10: An acute increase in total Sequential Organ Failure Assessment (SOFA) score of 2 or more points due to infection; 11: Cirrhosis proven by biopsy, history of variceal bleeding, or hepatic encephalopathy; 12: Needing intermittent or continuous renal replacement therapy; 13: Continuous infusion of vasopressors or inotropes, mean arterial blood pressure less than 70 mmHg, or plasma lactate level equal to or more than 4 mmol/L.

Patients' classification and data collection

The patients enrolled in the study were categorized based on their medication orders into two groups: therapeutic and prophylactic. Then, the rationality of the drug prescriptions was assessed according to the prepared protocol. Additionally, the form of medication received by the patients (oral or intravenous) was determined (Figure 1). This classification informs us precisely about physician awareness of therapeutic and prophylactic indications of PPIs.

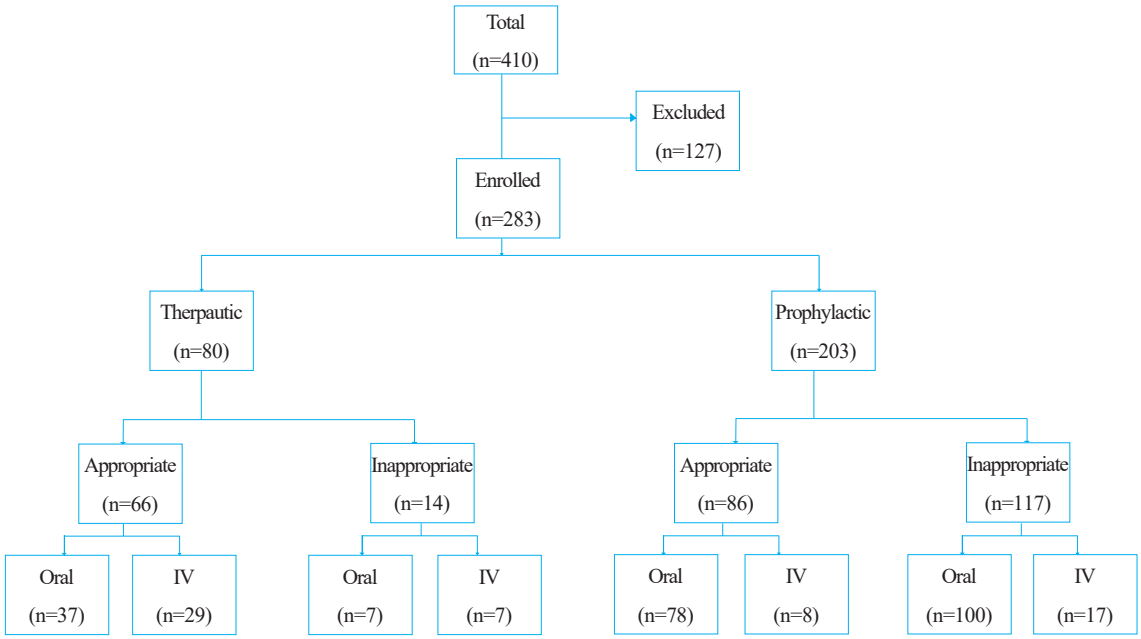

Figure 1. Flowchart illustrating patient enrollment and categorization based on therapeutic and prophylactic treatment approaches

The data collection process included initial assessment and discharge. The data were obtained through patient records, staff reports, interviews with the patient or their companion, and laboratory data. Patients' demographic data, cause (major diagnosis) and duration of hospitalization, history of previous use of PPI, the clinical outcome of the patient (death or discharge), the indication of PPI prescription for prophylaxis or therapy, dose, and the number of consumed vials and tablets of PPI, route of administration, comorbidities, [oral or non per oral (NPO)], diet form during hospitalization, other concurrent medications prescribed during PPI administration, especially concomitant antiplatelets (aspirin, clopidogrel), NSAIDs, anticoagulants, steroids, were recorded. Two well-trained medical students conducted the entire data collection process, which was subsequently double-checked by a clinical pharmacist and a gastroenterologist.

In order to minimize biases related to the rationality of drug prescribing and accurately demonstrate the prescription patterns in the hospital, the attending physicians and residents responsible for drug prescriptions were kept uninformed and blinded regarding the study's implementation.

After reviewing each patient's medical records (including endoscopy reports) and related laboratory tests (and interviewing with the patient's companion if needed), the PPI prescription was considered "appropriate" if the prescribed drug met the criteria defined in the protocol. If the indication of the prescribed medications, dosage, route, or duration did not conform to the protocol, the prescription was deemed "inappropriate." When there was no clear information about the rationality of drug prescription, the medicine was classified as "without clear indication." All patients classified as "without clear indication" were also considered inappropriate.

Sample size calculation

The sample size for our study was determined using the formula for estimating an infinite population proportion. We employed a 95% confidence level (z = 1.96), a prevalence rate (p) of 0.65 based on the study by Sirivunnabood and colleagues on inappropriate PPI prescriptions, and a margin of error (d) of 0.065. This calculation indicated that a minimum of 207 patients was needed. We increased the sample size by 20% for potential data collection errors. This raised the minimum required number of patients to approximately 249. Ultimately, our study included 283 patients receiving PPIs, surpassing the calculated minimum. This ensures the reliability of our data and

provides sufficient statistical power for analysis.

$$n=\frac{z^2_{(1-\alpha/2)}\times P(1-p)}{d^2}$$

Statistical analysis

Descriptive statistics were used to present the demographic and clinical characteristics of the patients. The normality of the data distribution was evaluated using the Kolmogorov-Smirnov test. Categorical variables were reported using frequency and percentage. In contrast, continuous variables were presented as mean ± standard deviation for normally distributed variables and median and range for non-normally distributed variables. In therapeutic and prophylactic groups, the Chi-square or Fisher's exact test was used to compare categorical variables between the appropriate and inappropriate subgroups. Student's t test or Mann-Whitney U test was employed to compare continuous variables between the appropriate and inappropriate subgroups. A P value of less than 0.05 was considered statistically significant in all conducted tests. All statistical analyses were performed using SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA) and Microsoft Office Excel 2019.

RESULTS

After an initial assessment of 410 hospital inpatients receiving PPIs in internal medicine wards and MICUs of Imam Khomeini Hospital, 283 were enrolled in the study after excluding 127 patients. Out of 283 enrolled patients, 80 and 203 were categorized into therapeutic and prophylactic groups, respectively, based on the appropriateness of their treatments. In the therapeutic group, 66 patients (82.5%) received appropriate treatment, while 14 (17.5%) received inappropriate treatment. The prophylactic group comprised 86 patients (42.36%) who received appropriate treatment and 117 patients (57.64%) who received inappropriate treatment. Furthermore, in the therapeutic group, 44 patients (55%) received the medication orally, and 36 (45%) received the medication intravenously. The prophylactic group consisted of 178 patients (87.6%) who received the oral form and 25 patients (12.4%) who received the intravenous form of the medication. The only drug in the PPIs class that the patients in the study received was pantoprazole. Among the patients with inappropriate prescriptions, 18 received the wrong form of medication, and nine received the incorrect dosage (Table 2).

Table 2. Baseline demographic, clinical, and pharmacological data of the enrolled patients

Demographic data and characteristics of patients	Therapeutic			Prophylactic		
	Appropriate	Inappropriate	P value	Appropriate	Inappropriate	P value
Number of patients	66 (82.5)	14 (17.5)		86 (42.36)	117 (57.64)	
Age (mean± SD)	53.45 ± 16.15	53.5 ± 21.12	13 (54.20 %)	0.993	58.35 ± 17.90	0.310
Male sex n (%)	29 (43.9)	6 (42.9)	0.941	50 (58.1)	59 (50.4)	0.276
BMI (mean± SD)	25.82 ± 5.28	25.50 ± 5.29	0.843	26.73 ± 5.57	26.02 ± 5.52	0.361
Duration of hospitalization (days), median (P25, P75)	9 (5, 14.5)	7.5 (5.75, 10.25)	0.161	11 (7.75, 18)	10 (7, 17)	0.083
Prior PPI usage n (%)	43 (65.2)	4 (28.6)	0.012	36 (41.9)	40 (34.2)	0.264
Clinical outcome n (%)						
Discharge	63 (95.5)	14 (100)	0.416	81 (94.2)	110 (94.1)	0.960
Death	3 (4.5)	0 (0)		5 (5.8)	7 (5.9)	
Diet n (%)						
NPO	20 (30.3)	7 (50)	0.157	7 (8.1)	4 (3.4)	0.142
PO	46 (69.7)	7 (50)		79 (91.9)	113 (96.6)	
Rout of administration n(%)						
Oral	37 (56.1)	7 (50)	0.679	78 (93)	100 (85.5)	0.263
Intravenous	29 (43.9)	7 (50)		8 (7)	17 (14.5)	

Table 2. Baseline demographic, clinical, and pharmacological data of the enrolled patients

Demographic data and characteristics of patients	Therapeutic			Prophylactic		
	Appropriate	Inappropriate	P value	Appropriate	Inappropriate	P value
Sum of consumed medicines n						
Vial	562	77	0.040	339	371	0.821
Tablet	349	69		1012	1086	
Major cause of hospitalization n (%)						
Gastrointestinal disease	22 (33.4)	5 (35.6)	0.029	10 (11.7)	22 (18.8)	0.175
Pulmonary disease	10 (15.1)	4 (28.6)	0.254	22 (25.6)	15 (12.8)	0.028
Neurological disease	3 (4.5)	0 (0)	1.000	9 (10.4)	27 (23.1)	0.025
Hematology & Oncology disease	16 (24.2)	3 (21.4)	1.000	19 (22.2)	25 (21.3)	1.000
Endocrine disease	1 (1.5)	0 (0)	1.000	2 (2.3)	8 (6.8)	0.193
Nephrological disease	8 (12.2)	1 (7.2)	1.000	18 (20.9)	19 (16.3)	0.466
Rheumatological disease	6 (9.1)	1 (7.2)	1.000	6 (6.9)	1 (0.9)	0.044
Comorbidities n (%)						
Hypertension	2 (3)	5 (35.7)	0.001	9 (10.4)	14 (11.9)	0.824
Chronic obstructive disease	7 (10.6)	12 (85.7)	0.000	7 (8.1)	3 (2.5)	0.102
Diabetes mellitus	2 (3)	2 (14.2)	0.139	10 (11.6)	12 (10.2)	0.823
Cerebrovascular disease	0 (0)	0 (0)	-------	7 (8.1)	10 (8.5)	1.000
Chronic kidney disease	3 (4.5)	0 (0)	1.000	3 (3.4)	5 (4.2)	1.000
Coronary artery disease	2 (3)	2 (14.2)	0.139	0 (0)	1 (0.9)	1.000
Concurrent medication n(%)						
Aspirin	12 (18.1)	3 (2.1)	0.720	26 (30.2)	21 (17.9)	0.064
Aspirin plus other antiplatelets	1 (1.5)	0 (0)	1.000	8 (9.3)	3 (2.5)	0.058
Anticoagulant	9 (13.6)	1 (7.1)	0.683	6 (5.1)	0.000	0.361
Corticosteroids	6 (9.1)	1 (7.1)	1.000	21 (24.4)	16 (13.6)	0.068
NSAIDs	1 (1.5)	0 (0)	1.000	2 (2.3)	4 (3.4)	0.702

Body mass index = BMI, Proton pump inhibitor = PPI, Non-Per Os = NPO, Per Os = PO, Non-steroidal anti-inflammatory drug = NSAID

Therapeutic group:

In the therapeutic group, the average age of patients was 53.46 ± 16.97, with 35 (43.75%) being male and a mean BMI of 25.76 ± 5.25. The median duration of hospitalization was 9 (5, 12.75) days. Before hospitalization, 47 (58.75%) patients had a history of PPI usage. 77 (96.25%) patients were discharged, and three (3.75%) patients passed away. In terms of dietary intake, 53 (66.25%) patients were on a per

os (PO) diet, and 27 (33.75%) were on a non-per os (NPO) diet. The leading causes of hospitalization were GI diseases (33.33%), followed by oncological (24.24%), pulmonary (15.15%), nephrological (12.12%), rheumatological (9.09%), neurological (4.54%), and endocrine diseases (1.51%), respectively. The prevalence of comorbidities is as follows: Chronic obstructive pulmonary disease is notably high at 51.35%; hypertension (18.91%); diabetes mellitus (10.81%); coronary artery disease (10.81%); and chronic kidney disease (8.10%). Prior PPI usage (P=0.012), sum of consumed vials (P=0.040), and GI disorders (P=0.029) were significantly higher in appropriate subgroups, highlighting their significance as leading causes of hospitalization.

Prophylactic group:

In the prophylactic group, there were 109 (53.69%) male patients with an average BMI of 26.32±5.54 and an average age of 56.87±17.67. The median length of hospital stay was 11 (7, 17) days. Among the patients, 76 (37.43%) had used PPIs before admission. 12 (5.92%) patients passed away, while 191 (94.08%) were discharged. Regarding dietary intake, 192 patients (94.58%) were on a PO diet, and 11 patients (5.42%) were on a NPO diet. 21.67% of hospitalizations were due to oncological disorders, with the remaining cases attributed to rheumatological diseases (3.44%), neurological issues (17.73%), pulmonary conditions (18.22%), nephrological problems (18.22%), GI issues (15.76%), and endocrine disorders (49.26%). Additionally, the prevalence of comorbidities is as follows: chronic obstructive disease (12.34%), chronic renal disease (9.81%), cerebrovascular disease (20.98%), hypertension (28.39%), diabetes mellitus (27.16%), and coronary artery disease (1.23%). GI disease (P=0.028) and rheumatological disease (P=0.044) as major causes of hospitalization were significantly higher in the appropriate group. Meanwhile, neurological disease (P=0.025) as a notable cause of hospitalization and anticoagulant use (P=0.000) as a concurrent medication was higher in the inappropriate group.

Prescription pattern & co-prescription

Therapeutic group:

In the therapeutic group, aspirin was used by 18.2% of appropriately treated patients compared with 21.4% of inappropriately treated patients. Steroids were used by 13.6% of patients receiving appropriate treatment versus 7.1% of those receiving inappropriate treatment. Anticoagulants, including warfarin and heparin, were used in 9.1% of appropriately treated patients and 7.1% of inappropriately treated patients. Combination therapy aspirin plus other antiplatelets and NSAID usage was low across both subgroups (Figure 2).

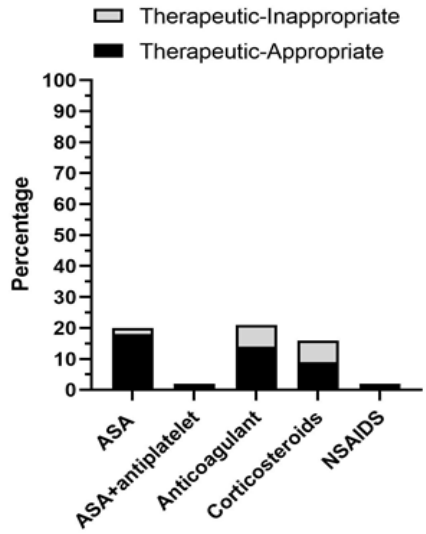

Figure 2. Comparison of therapeutic indications for appropriate and inappropriate PPI prescriptions

Prophylactic group:

30.23% of patients in the prophylactic group who received appropriate treatment used aspirin, compared with 17.94% of patients who received inappropriate treatment. Compared with 5.12% of patients receiving inappropriate treatment, 26.74% of patients receiving appropriate treatment received anticoagulants, warfarin, and heparin. Corticosteroid use was 13.67% in patients receiving inappropriate treatment and 24.41% in patients receiving appropriate treatment. In both groupings, the use of NSAIDs and combination therapies (aspirin with additional antiplatelets) was minimal (Figure 3).

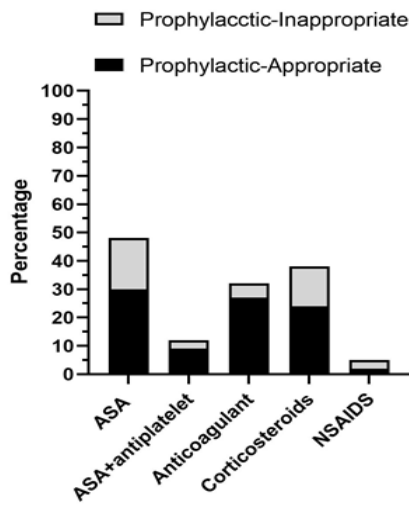

Figure 3. Comparison of prophylactic indications for appropriate and inappropriate PPI prescriptions

Indications:
In the appropriate group, the most common indication for PPI prescription was GERD, followed by NSAIDs use and coagulopathy. In most patients with inappropriate PPI prescriptions, there was no clear indication. NASID use and renal insufficiency were the other predominant indications of PPI prescription (Table 3).

Table 3. PPIs indications compared between the appropriate and the inappropriate PPI prescription group.

	n
Appropriate PPI prescription (n=152)	
Gastroesophageal reflux disease, erosive or non-erosive	54
Use of NSAIDs	41
Coagulopathy (platelets<50000/mm3 or INR≥1.5 or PTT>2 times the control value)	33
Use of anticoagulants in therapeutic doses	32
Hepatic failure	30
Administration of 250 mg hydrocortisone or an equivalent dose	27
Concomitant use of NSAIDs with corticosteroids, antiplatelets or anticoagulants	24
Upper gastrointestinal bleeding	12
Mechanical ventilation for >48 hours	9
Concomitant use of antiplatelets in patients with age> 60 years	7
Renal insufficiency	7
Sepsis	5
Chronic use of NSAIDs with history of gastrointestinal disorders	3
Head trauma or spinal trauma with GCS<10	2
Organ transplant	2
Being NPO for at least 5 days	2
Shock	1
Inappropriate PPI prescription (n=131)	
Without clear indication	
Use of NSAIDs	56
Renal insufficiency	28
Administration of 250 mg hydrocortisone or an equivalent dose	19
Gastroesophageal reflux disease, erosive or non-erosive	17
Use of anticoagulants in therapeutic doses	10
Upper gastrointestinal bleeding	7
Hepatic failure	4
Concomitant use of NSAIDs with corticosteroids, antiplatelets or anticoagulants	2
Concomitant use of antiplatelets in patients with age> 60 years	2
Mechanical ventilation for >48 hours	2
Coagulopathy (platelets<50000/mm3 or INR≥1.5 or PTT>2 times the control value)	1
Sepsis	1
Shock	1
Chronic use of NSAIDs with history of gastrointestinal disorders	1
	1

Non-steroidal anti-inflammatory drugs = NSAIDs, International normalized ratio = INR, Partial thromboplastin time = PTT, Glasgow Coma Scale = GCS, Non-Per Os = NPO, Proton pump inhibitors=PPI

DISCUSSION:

In summary, our results indicated that 17.5% of therapeutic and 57.64% of prophylactic PPI prescriptions were inappropriate. This high rate of inappropriate use in the prophylactic group is concerning, as it suggests that many patients are receiving PPIs without a clear medical indication. This aligns with previous studies (48-50) indicating widespread misuse of PPIs, often driven by a tendency to over-prescribe these medications for stress ulcer prophylaxis in patients without significant risk factors.

Previous studies (25,48,50) have generally assessed PPI use as a single category, potentially masking important differences between these two types of use. By separately analyzing these categories, our study identified that inappropriate prescriptions are predominantly found in the prophylactic rather than the therapeutic group.

The study identified several factors associated with inappropriate PPI prescriptions. Patients with hypertension and chronic obstructive pulmonary disease were more likely to receive inappropriate PPI therapy, possibly due to a lack of clear guidelines or awareness among prescribers regarding the specific indications for PPI use. In contrast, appropriate

prescriptions were more common in patients with documented GI disorders and those on concurrent anticoagulant or corticosteroid therapy. This suggests that when clear indications are present, adherence to guidelines is better, underscoring the importance of clinical protocols and education.

The analysis shows that prior PPI usage was significantly higher in the therapeutic group and the appropriate subgroup. This suggests that patients who had previously been prescribed PPIs were more likely to receive them appropriately when hospitalized, particularly for therapeutic purposes. This finding could imply that prior exposure and familiarity with PPI treatment protocols among patients and physicians leads to more guideline-compliant prescribing practices in therapeutic contexts.

Our study revealed that neurological disease was more prevalent as the major cause of hospitalization in the prophylactic inappropriate subgroup. The overuse of PPIs in this subgroup highlights the need for more adherence to prescribing guidelines. Neurological patients, especially those in critical care settings, may be perceived as vulnerable to stress ulcers and GIB, prompting prophylactic PPI use.

Several strategies should be implemented to address the high rate of inappropriate prophylactic PPI prescriptions. Continuous education programs for healthcare providers about the appropriate indications for PPI use, distinguishing between prophylactic and therapeutic contexts, are essential. Developing and enforcing guidelines that clearly delineate when PPIs should be used prophylactically versus therapeutically will help ensure compliance. Regular audits of PPI prescribing patterns are necessary to monitor adherence to guidelines and identify areas for improvement.

The study has several limitations. It was conducted in a single tertiary referral teaching hospital, which may limit the generalizability of the findings. The study's observational nature does not allow for establishing causal relationships between identified factors and inappropriate PPI use. Additionally, our study was initially designed as a clinical trial, and we intended to implement the PPI prescription protocol in the departments, train the staff on the correct prescription methods, and then subsequently review the PPI prescription pattern again to determine the effectiveness of our intervention. However, this was not achieved due to the hospital's lack of interdepartmental cooperation. Due to insufficient information in the patients' medical records or their unavailability, 127 patients who met the inclusion criteria for the study were subsequently excluded. Future studies should investigate the long-term effects of interventions aimed at reducing inappropriate prophylactic PPI prescriptions. Expanding research to multiple centers would also provide a broader perspective on PPI prescribing practices and help validate our findings across different healthcare settings.

CONCLUSION:

Our study found a high rate of inappropriate PPI prescriptions in hospital inpatients, particularly for prophylactic use. This misuse poses risks and financial burdens. Inappropriate prescriptions were often due to unclear indications and specific comorbidities. Stricter guidelines and regular audits could improve prescription practices and reduce costs. Healthcare providers need education on proper PPI use, and further research is required to explore long-term outcomes.

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