ORIGINAL ARTICLE

Appropriateness of Proton-Pump Inhibitor Usage among Hospitalised Patients in a Johor Government Hospital

Lee TC[a], Sim SJ[b], Tey WN[b], Deborah Ng PJ[b], Liong PZ[b]

[a]*Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia*

[b]*Department of Pharmacy, Sultan Ismail Hospital, Johor Bahru, Malaysia.*

ABSTRACT

INTRODUCTION: Proton pump inhibitors (PPIs) are potent and effective acid suppressant agents. There are emerging concerns that PPI overuse leads to escalating healthcare costs, drug-drug interactions, and adverse clinical outcomes. Exploring the appropriateness of PPI therapy among hospitalised patients in Malaysia is crucial. Thus, this study aims to determine the appropriateness of proton pump inhibitors utilisation in Sultan Ismail Hospital, Malaysia. **MATERIALS AND METHODS**: This single-center retrospective cross-sectional study was conducted at a public tertiary hospital situated in the Johore state of Malaysia. Patients recruited were 12 years and above who had received PPI in January 2017. Medical information was reviewed from electronic medical records. Patients were classified into three subgroups based on indications adopted from evidence-based guidelines. **RESULTS**: 422 patients were enrolled, 47.4% (n=200) fulfilled the Food Drug Administration (FDA) approved indications, 25.4% (n=107) had borderline indications, and 27.2% (n=115) had inappropriate PPI usage. Improper PPI therapy was observed with a similar fraction of patients in medical (24.5%, n= 58) and non-medical disciplines (30.8 %, n=57). Stress ulcer prevention in low-risk subjects and individuals with no apparent indication were reasons for PPI overuse. **CONCLUSION**: PPI overuse is prevailing in hospitalised adult patients. Promoting the awareness of guideline-based indications and adverse clinical events of PPI among clinicians is imperative in improving PPI prescribing.

Keywords
Proton pump inhibitor, indications, stress ulcer prophylaxis, appropriateness, overutilisation

Corresponding Author
Ms Sim Shi Jia,
Department of Pharmacy,
Hospital Sultan Ismail,
Jalan Persiaran Mutiara Emas Utama,
Taman Mount Austin,
81100 Johor Bharu, Johor , Malaysia
No Tel: +607-3565000
E-mail: simsj@hsi.gov.my

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INTRODUCTION

Proton pump inhibitors (PPIs) reduce gastric acid production through irreversible binding to the hydrogen-potassium ATPase pump found on gastric parietal cells. PPIs effectively treat erosive oesophagitis, non-erosive reflux disease, symptomatic peptic ulcer disease, functional dyspepsia, Zollinger-Ellison syndrome, and eradication of *Helicobacter pylori* infection.[1]

According to Malaysian Statistics on Medicines 2011-2014, the total utilisation of medications for the acid-related disorder was 6.9278 DDD/1,000 inhabitants/day in 2011. The total utilisation for subsequent years in 2012, 2013, and 2014 were 8.2432, 9.3200, and 10.3726 DDD/1,000 inhabitants/day, respectively.[2] The steady rise in PPI utilisation is likewise observed in advanced countries, including Australia, New Zealand, and the United Kingdom.[3-5]

PPIs overuse has been reported in Spain, Italy, Singapore, Australia, and United Kingdom.[6-9] There were few studies on PPIs overutilisation in Malaysia. Mohamad et al. reported inappropriate PPI therapy for stress ulcer prophylaxis (SUP) in 96.4% of elderly warded in a teaching university hospital in Malaysia.[10] Injudicious use of PPIs was revealed in over 50 % of patients receiving stress ulcer prophylaxis in the medical ward in Sarawak, Malaysia.[11] Then et al. reported inappropriate PPIs therapy in 46.0 % of medical inpatients in a tertiary hospital.[12]

Worldwide, it is estimated that between 25% to 70% of patients prescribed PPIs without justifiable indications. In 2006, expenditure on PPIs was £7 billion globally with losses amounted to £2 billion due to inappropriate PPIs use.[13]

National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia received 468 reports (823 adverse events) between the years 2000-June 2015.[15] Majority of adverse drug reactions (ADRs) occurred within two weeks of initiating PPIs, including pruritus, maculopapular skin rash, abdominal discomfort, and Steven-Johnson Syndrome/ Toxic Epidermal Necrolysis (SJS/TEN) overlap.[15] PPI-related hypersensitivity reactions range from mild symptoms to life-threatening disorders. Cutaneous manifestations are primarily mild, including pruritus, urticaria, maculopapular rash, and erythroderma. Serious hypersensitivity reactions reported in the literature include Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis.[16]

Numerous observational studies and meta-analyses have suggested probable links between PPI use and various adverse clinical events, specifically decreased bone density, osteoporotic fracture, hypomagnesaemia, micronutrient deficiencies, pneumonia, kidney dysfunction, spontaneous bacterial peritonitis, and *Clostridiodes difficile* infections.[17-20] However, the definite association between PPI use and the serious adverse effects has not been established convincingly by these retrospective observational studies due to confounding factors and biases.

Most studies on PPIs therapy in Malaysia are limited to patients admitted to the medical ward. The appropriateness of PPI prescriptions in non-medical wards remains largely unknown. We aimed to extend our study to patients in non-medical disciplines.

MATERIALS AND METHODS

Study Design and Ethical Consideration

A retrospective cross-sectional study was conducted in a public tertiary hospital located in the Johore state of Malaysia. Patients aged more than 12 years old receiving any PPIs during their hospitalisation in January 2017 were recruited. Ethical approval was obtained from Malaysian National Medical Research Register (NMRR ID 17-1780-35243). Medical information was extracted from hospital electronic medical records (EMR), including patient demographic information, presenting complaints, working diagnosis, endoscopy findings, and information on PPI (type, dose, route of administration, frequency, and indication of PPI).

Currently, no published national guideline on PPIs therapy is available in Malaysia. Instead, we have adopted approved indications for PPIs use from several international societies. Patients receiving PPIs were classified into three main categories according to their indications : (a) those who fulfilled FDA [21] and American Society of Health-System Pharmacists (ASHP)[22] approved indications ; (b) those with "borderline indications"; and (c) those without explicit or inappropriate indications. "Borderline indications" were defined as indications that were considered appropriate based on guidelines published by the National Institute for Health and Clinical Excellence (NICE) [23] and the American College of Gastroenterology (ACG).[24] Appropriate PPIs use considered if patients meet approved indications or "borderline indications." Table I shows the various indications for PPIs use.

All medical data extracted was transferred into the individual data collection form before analysing them using SPSS version 18.0. Continuous data were expressed as mean ± standard deviation, while the median (range), frequency, and percentages were calculated for categorical data.

RESULTS

A total of 3968 patients, 12 years old and above, had been admitted to Sultan Ismail Hospital in January 2017. Four-hundred twenty two (10.6 %) patients received PPI during hospitalisation; 57.3% (n=242) were male, and 31% (n=131) were above 65. Majority was Malay (52.8%, n=223), followed by Chinese (32.2%, n=136), Indian (10.4 %, n=44), and others 4.5% (n=19). Commonly prescribed PPIs were pantoprazole (63.3%), Omeprazole (30.6%), and Esomeprazole (6.2%). 15.9 % of patients (n=67) undergone endoscopy examination during hospitalisation.

Table I: Indications for the use of PPIs [21-24]

Approved indications [21]	Peptic ulcer disease Erosive esophagitis Helicobacter pylori Gastro-oesophageal reflux disease (GERD) Pathological hypersecretory conditions Stress ulcer prophylaxis
Borderline indications [23-24]	Endoscopy (pangastritis/erosions) Double antiplatelet agents Anemia (high risk, clinically unstable /possible history of GI bleeding) Double antiplatelet and anemia Uninvestigated dyspepsia
Indications for stress ulcer prophylaxis [22]	Mechanical Ventilation > 48 hours Coagulopathy (platelet count <50,000/mm3) History of GI ulceration/ bleeding < 1 year before admission Thermal injury (>35% body surface area) Multiple trauma (injury severity score > 16) Severe head or spinal injury Perioperative transplant period Low intragastric pH Major surgery (lasting > 4 hours) Acute lung injury ***Two or more of the following***: Sepsis syndrome ICU stay > 1 week Occult bleeding > 6 days High dose corticosteroid (250mg of hydrocortisone equivalent) Hepatic failure Renal insufficiency Hypotension

Patients in medical wards contributed to 56.2% (n= 237) of total PPI prescriptions, followed by surgery (22%, n=93), orthopaedic surgery (9.0%, n=38) and oncology (6.9 %, n=29), as shown in table 2. Out of 422 patients, 200 (47.4%) fulfilled the FDA-approved indications, 107 (25.4%) had borderline indications and 115 (27.2%) had inappropriate indications, as represented in Figure 1.

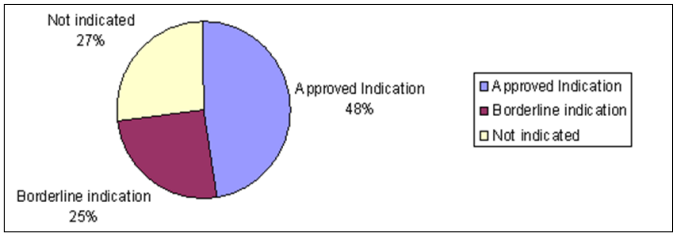

Figure 1 Distribution of inpatients on proton pump inhibitors PPIs (n=422)

Stress ulcer prophylaxis (SUP) was the commonest approved indication for initiating PPIs (48%, n=96) followed by peptic ulcer disorders (44.5%, n=89), GERD (3.0 %, n= 6) and erosive oesophagitis (2.5%, n=5) (Figure 2). Mechanical ventilation (39.6%) and multiple risk factors for stress-induced gastric mucose injury (39.6%) were the valid reasons for SUP in the intensive care unit (ICU).

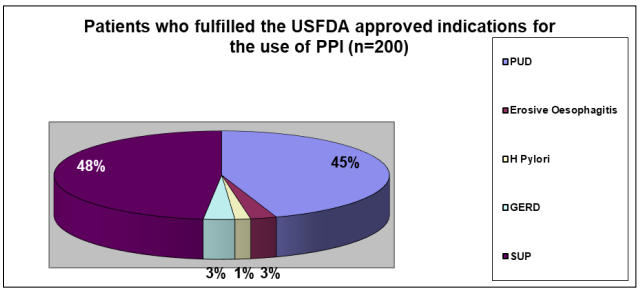

Figure 2 Patients who fulfilled the USFDA approved indications for the use of PPI

107 (25%) had borderline indications based on expert consensus guidelines other than FDA-approved indications. PPIs used in this category were patients with anaemia and high risk of gastrointestinal haemorrhage (55.1%, n=59), dual antiplatelet therapy (29.9%, n=32), and uninvestigated dyspepsia (6.5%, n=7) (Table II).

Table II. Patients with borderline indications for the use of PPI (n=107)

Borderline indication	Number (n)	Percentage (%)
Anaemia (high risk, clinically unstable/ with a possible history of gastrointestinal bleeding)	59	55.1
Double antiplatelet agents	32	29.9
Investigated dyspepsia	7	6.5
Endoscopy (pangastritis/erosions)	6	5.6
Double antiplatelet + anaemia	3	2.8

115 (27%) patients considered having inappropriate PPI use, as shown in Figure 3. Inappropriate PPI prescriptions were observed in an equal proportion of patients in medical and non-medical wards (24.5% vs. 30.8%).

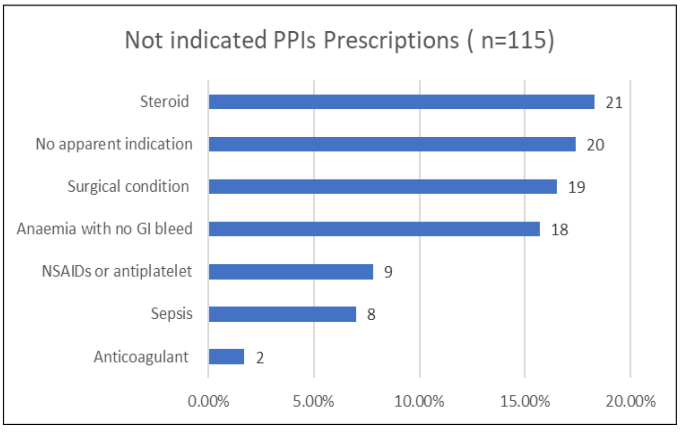

Figure 3 Patients with inappropriate proton pump inhibitors prescriptions (n=115)

Lack of clear documented indications is a common issue in PPI therapy. PPIs were often prescribed for patients on corticosteroids, anticoagulants, and anaemia without gastrointestinal blood loss in medical and oncology disciplines. PPIs usage was deemed unwarranted in surgical disorders such as acute cholecystitis, pancreatitis, oesophageal varices, and lower gastrointestinal bleeding.

Table III: Distribution of Patients according to Disciplines and Indications

Discipline	Number of Patients(%)	Approved Indications and Borderline indications(%)	Inappropriate indications (%)
Medicine	237 (56.2)	179 (75.5 %)	58 (24.5%)
Surgery	93 (22.0)	68 (73.1%)	25(26.9 %)
Orthopaedic	38 (9.0)	21 (55.2%)	17 (44.7%)
Oncology	29 (6.9)	15 (51.7%)	14 (48.3%)
ICU	11 (2.6)	11 (100%)	0 (0%)
Others	14 (3.3)	13 (92.9 %)	1(7.1%)
Total	422	307 (72.7%)	115 (27.3%)

DISCUSSION

Proton pump inhibitors (PPI) are among the most widely prescribed drugs in ambulatory care and hospital settings. PPIs have a trusted safety profile and tolerability, with minor adverse events occurring at a rate of 1-3%. Common adverse effects are headaches, nausea, flatulence, abdominal pain, diarrhoea, rash, and dizziness.[25] Despite proven effectiveness and tolerability, there are emerging concerns about its long-term effects. PPIs affect several pathophysiological pathways, leading to cardiovascular morbidity, nephrotoxicity, immune response and infections, nutritional disorders, fracture, and cognitive dysfunction.[26] PPIs are frequently used "off label" for an extended period, leading to safety threats yet offering little benefits in many subjects.

10.2% of hospitalised adult patients in this cohort were prescribed PPIs, as compared to studies in Singapore (46.5%),[8] Australia (45%),[16] and United States (70%).[27] The differences in PPI prescriptions reflect the diversity of study populations and variation in prescribing practices. Stress ulcer prophylaxis in critically ill patients (22.5%, n=96) constituted the commonest reason for PPIs initiation. There are several well-established predisposing factors for stress-related mucosal damage, including respiratory failure, coagulopathy, acute hepatic failure, sepsis, shock, major head or spinal cord injury, burns, and a history of gastrointestinal haemorrhage.[28] PPIs are potent and preferred acid suppression agents for stress ulcer prevention. Gastro-oesophageal reflux disease was less common and contributed to only 2.5% (n=11) of PPI prescriptions. In comparison, GERD was the commonest indication for PPI therapy in Australia (68.2%)[29], likely reflecting ethnic and geographical differences in the prevalence of GERD.[30]

Improper PPI use is common, ranging from 24% to 80% in western countries.[6-7,9] Over a quarter of patients (27%, n=115) in our cohort failed to conform to evidence-based indications for PPI utilisation. A higher prevalence (46%) of inappropriate PPI use was reported in a separate study in Malaysia.[12] The vast variation in prevalence is attributed to differences in usage criteria, medical practices, and diverse study populations. It is noteworthy that improper PPIs use occurred in approximately equal proportion of patients in non-medical disciplines (24.5% and 30.8 %).

Stress ulcer prophylaxis in low-risk patients was a common reason for non-compliant prescriptions. Physicians often co-administer PPI and glucocorticoid to minimise the theoretical risk of developing peptic ulcers. In reality, corticosteroid does not directly cause damage to the gastroduodenal mucosa, although they can enhance the gastrointestinal risk associated with non-steroidal anti-inflammatory drugs (NSAID) use. Peptic ulcer disorder is an infrequent complication of corticosteroid therapy, occurring between 0.4-1.8 % of patients.[31] Anticoagulants, either vitamin K antagonists or direct-acting anticoagulants, do not directly cause gastric mucosa injury; hence, gastroprotection is not warranted unless with concomitant antiplatelet and NSAID prescription. Physicians often over-prescribe PPIs in patients with anaemia without evidence of gastrointestinal bleeding .[7,11] Gastric acid hyposecretion induced by PPIs may result in iron and vitamin B12 malabsorption, further aggravating the anaemia.[32]

PPIs therapy was inappropriate in patients with liver cirrhosis and hypertensive gastropathy, acute pancreatitis, and stress ulcer prophylaxis in low-risk individuals.[33] PPIs are metabolised by cytochrome CYP450 in the liver, reducing drug clearance and prolonged half-life in liver cirrhosis. PPIs promote alteration in gut microbiota and translocation of gut bacteria; hence, predisposing to spontaneous bacterial peritonitis, hepatic encephalopathy, acute on chronic liver failure, and higher mortality.[34-35] PPI use also does not alter the clinical outcomes of patients with severe acute pancreatitis, including length of hospitalisation and hospital mortality.[31,36]

Only 15.9 % (n=67) of patients on PPIs in this cohort underwent endoscopy examination, a finding accordant with other studies conducted in Malaysia (11%).[12] Endoscopy examination is desirable to justify prolonged PPI use in some subjects. PPI therapy without clear documented indications was commonly observed, resulting in unjustifiable long-term or indefinite continuation.[37]

There are few plausible explanations for PPIs overutilisation. Firstly, non-awareness towards the evidence-based recommendations on PPIs use. Second, prescribers generally consider PPIs a safe and effective drug and are unaware of potential long-term adverse effects related to PPIs. Third, physicians seldom document PPI indications and intended treatment duration, leading to inappropriate long-term PPIs use. Qualitative research on the knowledge of prescribers and attitudes toward prescribing is desired to identify factors contributing to PPIs overuse, a prerequisite for developing effective interventions.

Numerous observational studies and meta-analyses have reported several cardiovascular and non-cardiovascular adverse outcomes in PPI therapy.[17-20] A US-based longitudinal observational study examined mortality in a database of more than 6 million US veterans over 5.7 years, reported a small but statistically significant excess of cause-specific mortality.[38] However, more recent well–designed, randomised, prospective studies have demonstrated no clear association between PPI use and the previously documented adverse events reported in numerous observational studies.[39-40] Nevertheless, non -judicious use of PPIs would translate into increased healthcare costs, drug interactions, and significant long-term adverse outcomes.

Several approaches can be adopted to reduce PPI risks and overutilisation. Adverse outcomes associated with PPIs occur predominantly among patients receiving long-term therapy. Minimising the dose, frequency, and therapy duration by regularly reviewing a patient's requirement for acid-suppressive therapy could eliminate or reduce the undesirable adverse clinical outcomes. Collaboration between physicians and pharmacists to develop hospital-specific guidelines and conduct regular audits could improve safe prescription practices. The educational intervention aimed to promote awareness of prescribers on approved indications, and adverse effects of PPIs could further minimise inappropriate usage .[41] Clinical practice guideline recommends deprescribing PPIs in adults where therapy is no longer needed to reduce medication burden and harm. [42] Safe deprescribing involves stopping, stepping down, or reducing doses with intermittent or on-demand PPI use. A systemic review of 21 studies to deprescribe inappropriate PPIs in the elderly has demonstrated that population-wide education, promotion strategies, and geriatrician-led deprescribing are effective.[43] Ideally, PPI therapy should be based on evidence-based indications, effectiveness, patient preference, risks, and benefits assessment.[37]

LIMITATIONS

Our single-center retrospective study identified several limitations. The selected study consisted of adults hospitalised inpatients; hence, the findings could not be generalised to ambulatory care settings. There are some limitations on the completeness of electronic medical records, particularly relating to proper indications for PPIs prescription. Many patients had no clear documentation of reasons for PPIs treatment, which may have led to overestimating inappropriate prescribing. We also did not investigate the appropriateness of PPI therapy duration according to guideline recommendations. This study could serve as a preliminary study and potentially provide insights for

future studies.

CONCLUSION

PPI overutilisation is prevalent in clinical practices, and there is a strong clinical need to optimise PPI prescribing. Inappropriate PPI therapy is observed in over a quarter of patients in our cohort, inclusive of non-medical disciplines. Many PPI prescriptions had no clear documented indications and plans, leading to improper long-term continuation. Stress ulcer prophylaxis in low-risk individuals being unwarranted and discouraged. Effective and practical strategies to optimize PPI therapy could curb healthcare costs and minimise drug-related adverse outcomes.

REFERENCES

1. Strand DS, Kim D, Peura DA. 25 years of proton pump inhibitors: A comprehensive review. Vol. 11, Gut and Liver. 2017;11:27-37.
2. Pharmaceutical Services Division Ministry of Health Malaysia.Malaysian statistics on medicine 2011-2014. Kuala Lumpur; 2017.
3. Hollingworth S, Duncan EL, Martin JH. Marked increase in proton pump inhibitors use in Australia. Pharmacoepidemiol Drug Saf. 2010;19:1019-24.
4. Nishtala PS, Soo L. Proton pump inhibitors utilisation in older people in New Zealand from 2005 to 2013. Intern Med J. 2015;45:624-9.
5. Othman F, Card TR, Crooks CJ. Proton pump inhibitor prescribing patterns in the UK: a primary care database study. Pharmacoepidemiol Drug Saf. 2016;25:1079-87.
6. Ramirez E, Lei SH, Borobia AM, Piñana E, Fudio S, Muñoz R, et al. Overuse of PPIs in patients at admission, during treatment, and at discharge in a tertiary Spanish hospital. Curr Clin Pharmacol. 2010;5:624-9.
7. Lodato F, Poluzzi E, Raschi E, Piccinni C, Koci A, Olivelli V, et al. Appropriateness of Proton Pump Inhibitor (PPI) prescription in patients admitted to hospital: Attitudes of general practitioners and hospital physicians in Italy. Eur J Intern Med. 2016;30:31-6.
8. Chia CTW, Lim WP, Vu CKF. Inappropriate use of proton pump inhibitors in a local setting. Singapore Med J. 2014;55:363-6.
9. Batuwitage BT, Kingham JGC, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. Postgrad Med J. 2007;83:66-8.
10. Mohamad MS, Shamsuddin N, Tan KM. Appropriateness of stress ulcer prophylaxis among older adults admitted to general medical wards in a university hospital. Eur Geriatr Med. 2015;6:119-23.
11. Oh AL, Tan AG, Phan HS, et al. Indication of acid suppression therapy and predictors for prophylactic use of proton pump inhibitors vs. histamine 2 receptor antagonist in a Malaysian tertiary hospital. Pharm Pract (Granada). 2015;13:633.
12. Then RF, Tan YJ, Pan Y, Chieng JY. Appropriateness Of Proton Pump Inhibitors Prescription In Patients Admitted To A Malaysian Tertiary Hospital. Int J public Heal Res. 2019;9:1043 -50.
13. Elnaem MH, Mohamed MHN, Nazar AH, Ibrahim RNK. Evaluation of proton pump inhibitors prescribing among non-critically ill hospitalized patients in a Malaysian tertiary hospital. J Appl Pharm Sci. 2017 Dec 1;7(12):77–83.
14. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ. 2008;336:2-3.
15. National Pharmaceutical Regulatory Agency, Ministry of Health Malaysia. REAKSI drug safety news. Petaling Jaya; 2016 Mar.
16. Lombardo C, Bonadonna P. Hypersensitivity Reactions to Proton Pump Inhibitors. Current Treatment Options in Allergy. 2015;2:110-23.
17. Yu EW, Bauer SR, Bain PA, Bauer DC. Proton pump inhibitors and risk of fractures: A meta-analysis of 11 international studies. Am J Med. 2011;124:519-26.
18. Zhou B, Huang Y, Li H, Sun W, Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int. 2016;27:339-47.
19. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, et al. Proton pump inhibitors linked to hypomagnesemia: A systematic

review and meta-analysis of observational studies. Ren Fail. 2015;37:1237-41.
20. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of clostridium difficile infection with acid-suppressing drugs and antibiotics: Meta-analysis. Am J Gastroenterol. 2012;107:1011-9.
21. Centers for Medicare and Medicaid Services. Proton pump inhibitors: Food and Drug Administration-approved indications and dosages for use in adults. Department of Health and Human Services.2013.
22. Armstrong TA, Coursin DB, Devlin J, Duke JS, Fish D, Gonzalez ER, et al. ASHP therapeutic guidelines on stress ulcer prophylaxis. American Journal of Health-System Pharmacy. 1999;56:347-79.
23. National Institute for Clinical Excellence. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management Clinical guideline [Internet]. 2014. Available from: www.nice.org.uk/guidance/cg184.Accessed December 26, 2021.
24. Lanza FL, Chan FKL, Quigley EMM, et al. Guidelines for prevention of NSAID-related ulcer complications. American Journal of Gastroenterology. 2009;104:728-38.
25. Yibirin M, De Oliveira D, Valera R, Plitt AE, Lutgen S. Adverse Effects Associated with Proton Pump Inhibitor Use. Cureus. 2021 ;13:e12759.
26. Corsonello A, Lattanzio F. Cardiovascular and non-cardiovascular concerns with proton pump inhibitors: Are they safe? Trends Cardiovasc Med. 2019;29:353–60.
27. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. JAMA Internal Medicine. 2016;176:172-4.
28. Quenot JP, Thiery N, Barbar S. When should stress ulcer prophylaxis be used in the ICU? Current Opinion in Critical Care. 2009;12:139–43.
29. Yap MH, Yip G, Edwards A, D'Intini V, Tong E. Appropriateness of proton pump inhibitor use in patients admitted under the general medical unit. J Pharm Pract Res. 2019;49:447-53.
30. Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: A systematic review. J Neurogastroenterol Motil. 2011;17:14–27.
31. Dorlo TPC, Jager NGL, Beijnen JH, Schellens JHM. [Concomitant use of proton pump inhibitors and systemic corticosteroids]. Ned Tijdschr Geneeskd. 2013;157:A5540 [Dutch].
32. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: Evidence and clinical implications. Ther Adv Drug Saf. 2013;4:125-33.
33. Scarpignato C, Gatta L, Zullo A, Blandizzi C. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016;14:149.
34. Dam G, Vilstrup H, Watson H, Jepsen P. Proton pump inhibitors as a risk factor for hepatic encephalopathy and spontaneous bacterial peritonitis in patients with cirrhosis with ascites. Hepatology. 2016;64:1265–72.
35. De Roza MA, Kai L, Kam JW, et al. Proton pump inhibitor use increases mortality and hepatic decompensation in liver cirrhosis. World J Gastroenterol. 2019;25:4933–44.
36. Murata A, Ohtani M, Muramatsu K, Matsuda S. Effects of proton pump inhibitor on outcomes of patients with severe acute pancreatitis based on a national administrative database. Pancreatology. 2015;15:491–6.
37. Yadlapati R, Kahrilas PJ. When is proton pump inhibitor use appropriate? Vol. 15, BMC Medicine. 2017;15:36.
38. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Risk of death among users of Proton Pump Inhibitors: A longitudinal observational cohort study of United States veterans. BMJ Open. 2017;7: e015735.
39. Moayyedi P, Eikelboom JW, Bosch J, et al. Pantoprazole to Prevent Gastroduodenal Events in Patients Receiving Rivaroxaban and/or Aspirin in a Randomized, Double-Blind, Placebo-Controlled Trial. Gastroenterology. 2019;157:682-91.
40. Hoff M, Skovlund E, Skurtveit S, Meyer HE, Langhammer A, Søgaard AJ, et al. Proton pump inhibitors and fracture risk. The HUNT study, Norway. Osteoporos Int. 2020;31:109-18.
41. Mcdonald EG, Jones J, Green L, Jayaraman D, Lee TC. Reduction of inappropriate exit prescriptions

for proton pump inhibitors: A before-after study using education paired with a web-based quality-improvement tool. J Hosp Med. 2015;10:281-6.
42. Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors. Can Fam Physician. 2017;63:354–64.
43. Wilsdon TD, Hendrix I, Thynne TRJ, Mangoni AA. Effectiveness of Interventions to Deprescribe Inappropriate Proton Pump Inhibitors in Older Adults. Drugs and Aging. 2017;34:265–87.