PUBLIC HEALTH RESEARCH

Appropriateness of Proton Pump Inhibitors Prescription in Patients Admitted to a Malaysian Tertiary Hospital

Then Ru Fah[1], Tan Yi Jun[1], Pan Yan[2] and Chieng JinYu[3*]

[1] Medical Department, Serdang Hospital, Malaysia.
[2] Biomedical Science Department, the University of Nottingham Malaysia Campus, Malaysia.
[3] Medical Department, Faculty of Medicine and Health Sciences, Putra University of Malaysia, Malaysia.

**For reprint and all correspondence: Chieng Jin Yu, Medical Department, Faculty of Medicine and Health Sciences,*
Putra University of Malaysia, 43400 Serdang, Selangor, Malaysia.
Email: cjy511@yahoo.com

ABSTRACT

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Introduction Proton pump inhibitors (PPIs) are one of the commonest drug prescribed, however it is not without risk of adverse effects especially if the usage is inappropriate. We aimed to evaluate the frequency, indications and appropriateness of PPIs prescription among the medical inpatients, Serdang Hospital, which is a tertiary hospital in Malaysia.

Methods This is a cross sectional study consisting of 1184 patients admitted to medical ward and received PPI from 1st July 2016 to 31st March 2017, and their database were further analysed by SPSS Statistics 17.0. Unpaired t-test was performed to analyze the data collected. $P < 0.05$ (two-tailed) is considered significant. Their indications were cross-referenced against the indications adapted from the United States Food and Drug Administration (FDA).

Results About 23.9% (1184/4953) of inpatients were using PPIs, and 63.0% (746/1184) of them recently started on PPI in the ward, with mean age of 59.7 years. More male patients were commenced on PPIs during hospitalization (P value < 0.05). Based on the FDA guideline, only 21.8% patients were indicated, 32.2% were borderline indicated, and 46.0% patients were not indicated in prescribing PPIs. Stress ulcer prophylaxis was the commonest indication, while anaemia with no evidence of gastrointestinal bleed was the main non-indication in starting PPIs. Only 11% of patients had performed the oesophago-gastro-duodenoscopy (OGDS) during the hospital stay.

Conclusions 46.0% of inpatients were inappropriately prescribed PPIs according to FDA guideline. More efforts should be initiated to improve the current situation of PPIs overutilization in Malaysia.

Keywords Proton pump inhibitor - Overutilization - Appropriateness.

INTRODUCTION

Proton pump inhibitors (PPIs) are currently the most effective agents for acid-related disorders. PPIs have been used for treatment of *Helicobacter Pylori* infection, Gastro – Esophageal Reflux Disease (GERD), peptic ulcer disease and pathological hypersecretory conditions such as Zollinger–Ellison syndrome. For most indications, the patients should only take PPI for four to twelve weeks. However, the use of PPIs has significantly increased since the first PPI, omeprazole first came to market in 1980s. In a US study estimating the prevalence of visits in which patients used PPIs by SR Rotman et al., it was found that PPIs were prescribed in 4.0% of visits in 2002 and increased to 9.2% of visits in 2009 ($p < 0.001$), and more surprisingly that 62.9% of them were prescribed without clear indication.[1] The dramatic increase in PPIs prescription may be inappropriate and do not conform to evidence-based indications or even according to United States Food and Drug Administration (FDA) guideline on PPIs usage. Ample epidemiology studies over the past decade have reported the inappropriate PPIs prescription either inpatient or outpatient. And this even can lead to additional wastage of medical healthcare.[2,3] A questionnaire-based study which was done in an Irish regional hospital showed 45.0% of patients were on PPIs with no valid indication, and 31.0% of them were taking PPI for at least two years.[4] Additionally, a Peru study showed a 54.6% of PPIs overuse in two academic hospitals which was not based on Clinical Practice Guideline (CPG).[5] While in Asia, Christopher Chia TW et al.[6] had published a study which involved 477 inpatients in a Singapore Hospital that less than 50.0% of their patients were prescribed PPIs according to FDA guideline.

There are also growing concerns about the possible side effects of PPIs which are increasing with longer and wider use of PPIs. The long-term safety of these medications, as well as potentially important drug interactions has become the subject of debate. Omeprazole is ranked on the top four among the highest expenditure of the most prescribed medicines in Malaysia.[7] Few recent studies had demonstrated inappropriate PPI prescription in Malaysian hospitals.[8-9] Therefore, we aimed to run this study to identify the prevalence, indications and appropriateness of PPIs prescription among the patients in general medical ward, Serdang Hospital, which is a tertiary hospital in Selangor, Malaysia.

METHODS

Our study is a cross sectional study design. All patients who were admitted to general medical ward from 1st July 2016 to 31st March 2017 (nine months period) and recently started on PPIs in the ward were recruited in our study, and their database (demography, presenting complains, working diagnosis, physical examinations, lab investigations and management plan) were further analysed by SPSS Statistics 17.0. Unpaired t-test was performed to analyze the data collected. χ^2 or Fisher's exact test, where appropriate, was used for analysis of categorical variables. $P < 0.05$ (two-tailed) is considered significant. Our hospital uses Electronic Medical Record (EMR) system in patient registry, and the patients' data can be completely kept and accessed over time. Furthermore, EMR system had the advantage that the type of PPIs given and the indications of the PPI including those already on PPIs before hospitalization were able to be reviewed base on the documentation of symptoms, endoscopy findings and clinical circumstances. Currently, there is no national guideline of prescription of PPIs in Malaysia. The United States FDA guideline for usage of PPIs had been applied in this study, and the indications for the use of PPIs were shown in Table 1. Those patients on PPIs were further categorised into three groups: (a) fulfilled the FDA indications; (b) no clear indications; and (c) borderline indications. This project was registered with the National Medical Research Register and approved by the Medical Research Ethics Committee, Malaysia prior to the commencement of the study.

Table 1 Indications for the use of PPIs accepted by United States FDA[10]

United States FDA accepted indications for the use of PPIs
Peptic ulcer disease
Erosive esophagitis
Helicobacter pylori
Gastro-esophageal reflux disease
Pathological hypersecretory conditions
Stress ulcer prophylaxis
Other accepted or off labelled usage of PPIs as per United States FDA
Risk reduction of NSAID-associated peptic ulcer disease in patients on NSAIDs with >2 of the following risk factors :
- Age >65 years old
- History of peptic ulcer disease or upper gastrointestinal tract bleeding
- High dose NSAID therapy

- Concomitant NSAID use with an anticoagulant, antiplatelet or glucocorticoid
Esophageal stricture (peptic)
Barret's esophagus
To improve pancreatic enzyme absorbtion in cystic fibrosis
Uninvestigated dyspepsia (short term trial, investigation required, if persistent)

RESULTS

A total of 4953 patients had been admitted to general medical ward from 1st July 2016 to 31st March 2017. Retrospectively, 23.9% (1184/4953) of them were using PPIs during their ward admission. Among 1184 patients, 37.0% of them already used a PPI even before their hospitalization, which was assumed to be initiated by their primary care physicians or during their previous hospital visits. Therefore, only those who were recently started on PPIs in the ward (n=746) were recruited in the current study. The mean age of patients was 59.7 years, with 45.6% (340/746) of the patients were of 60-79 year old age group, followed by 40.8% (304/746) of 30-59 year old age group. 58.2% of them were male. In terms of ethnics, the 746 patients comprised 371 Malays, 190 Chinese, 152 Indians and 33 others. An overview of demographics of the patients regarding their gender, ethnicity, and age group were summarized in Table 2.

Table 2 Socio-dermographic of inpatients on PPIs

Variables	Frequency, n (percentage, %)	
Gender		
Male	434 (58.2)	*P* value = 0.045
Female	312 (41.8)	
Ethnicity		
Malay	371 (49.7)	*P* value = 0.093
Chinese	190 (25.5)	
Indian	152 (20.4)	
Others	33 (4.4)	
Age group		
younger than 30 years old	44 (5.9)	*P* value = 0.979
30-59	304 (40.7)	
60-79	340 (45.6)	
More than 80 years old	58 (7.8)	
Total	746 (100.0)	

Pantoprazole and omeprazole accounted for 81% of overall PPIs prescriptions, as shown in Table 3.

Table 3 Types of PPIs prescription during ward admission

Type of PPIs	Frequency, n (percentage, %)
Omeprazole	289(38.8)
Pantoprazole	315(42.2)
Esomeprazole	136(18.2)
Lansoprazole	6(0.8)
Total	746 (100.0)

It was alarming that only 11% (82/746) of the patients had performed the oesophago-gastro-duodenoscopy (OGDS) during the hospital stay for justification for being on PPIs.

Based on the United States FDA guideline for usage of PPIs, 21.8% (163/746) patients were indicated, 32.2% (240/746) were borderline indicated and 46.0% (343/746) patients were not indicated in prescribing PPIs (see Figure 1).

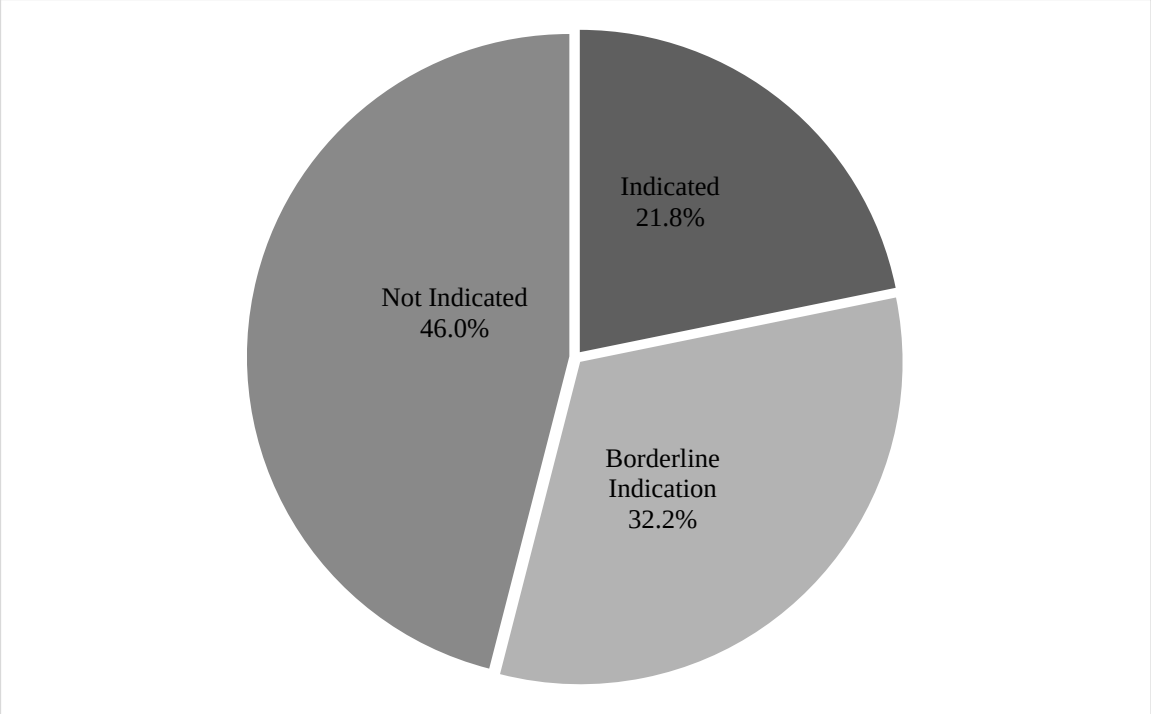

Figure 1 Proportion of patients started on PPIs during ward admission according to the United States FDA guideline

As illustrated in Figure 2, among the 163 patients who were indicated for PPIs, stress ulcer prophylaxis (64.4%, n=105) was the commonest indication in starting PPIs. Most of them were started PPIs in view of critically ill condition during admission where they were intubated requiring invasive ventilation. Peptic ulcer disease (28.2%, n=46) was the second commonest indication for PPIs prescription, followed by erosive esophagitis (5.5%, n=9) and GERD (2.0%, n=3) respectively.

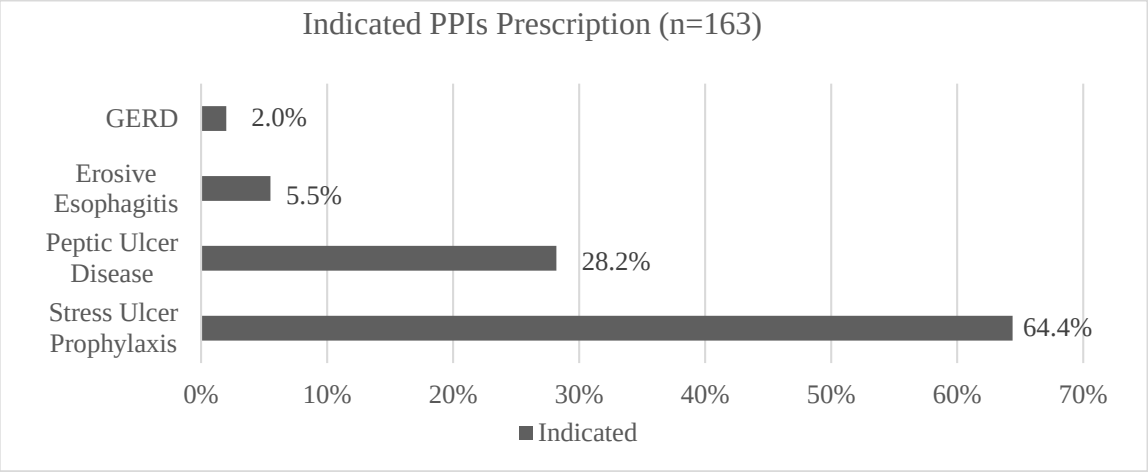

Figure 2 Patients on PPIs which were indicated according to the FDA guideline

With regard to borderline indications in starting PPIs for this study, Figure 3 demonstrated in descending frequency were non- steroidal anti-inflammatory agents (NSAIDs) or antiplatelet agents such as aspirin or clopidogrel with the age more than 65 years (48.3%,n=116), post critical care (19.2%, n=46), anaemia with risk of gastrointestinal bleed (12.9%, n=31), double antiplatelet with anaemia (8.3%,n=20), uninvestigated dyspepsia (5.4%,n=13), double antiplatelet agents (4.2%, n=10) and endoscopy (1.7%, n=4).

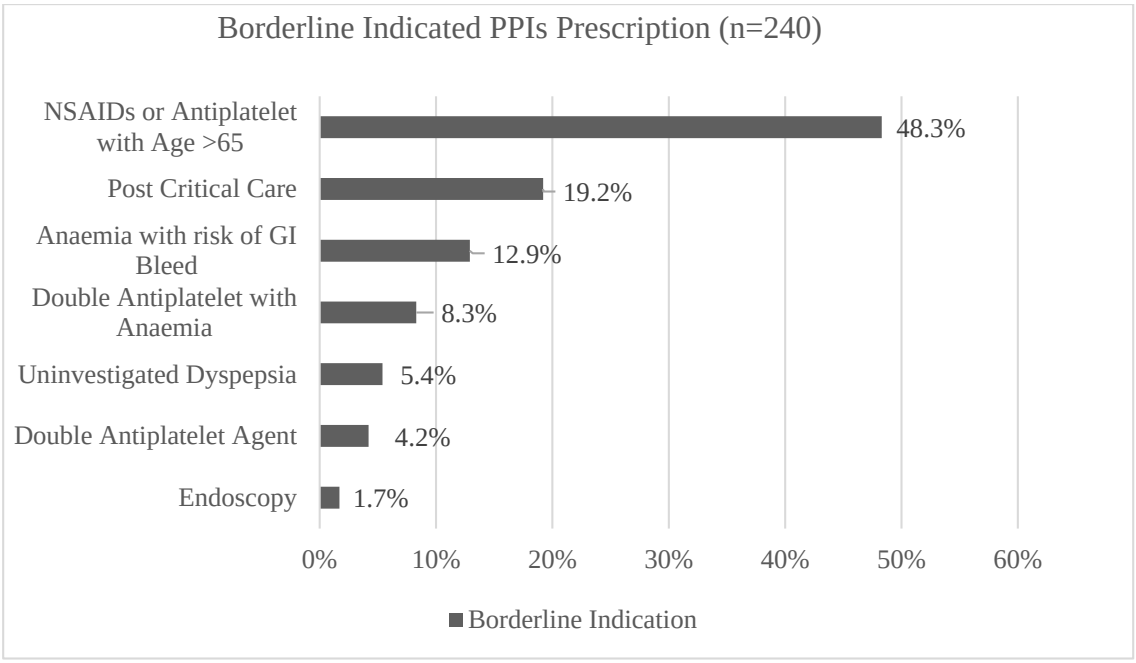

Figure 3 Patients on PPIs which were Borderline Indicated according to the FDA guideline

Anaemia with no evidence of gastrointestinal bleed was the main non-indication in starting PPIs and consisted of 37.6% (129/343). Other non-indication in starting PPIs in our study were NSAIDs or antiplatelet agents with age less than 65 years old (15.2%, n=52), steroid (14.0%, n=48), anticoagulant (7.9%, n=27) and biological treatment (0.3%, n=1). Surprisingly, up to 25.0% of the patients were started on PPIs with no apparent indication at all. The administration of PPIs (with no apparent indication) had been further confirmed by searching through our medical electronic record together with the pharmacy records.

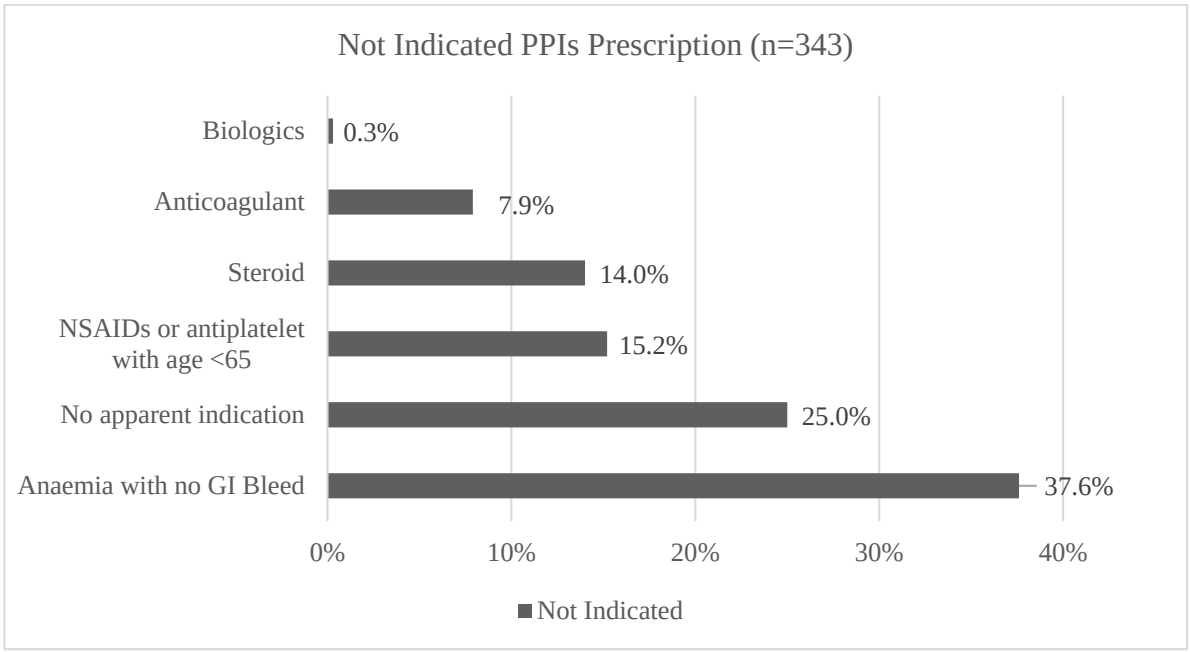

Figure 4 Patients on PPI which were not indicated according to the FDA guidelines

DISCUSSION

Our study showed that 23.9% of the consecutive medical inpatients were using PPIs. This prevalence was lower if compared with Ireland (79.0%),[4] Singapore (46.5%)[6] and United States (70.0%).[11] In Serdang Hospital, all the inpatients must be reviewed by a consultant physician at least once during the hospitalization. And most of the PPIs in

our hospital are of List A, which meant that the valid prescription of PPIs could only be made by a physician with qualification of specialist level and above. This pattern of strict prescription is believed to limit the prescription of PPIs in our hospital setting.

However, among those who were initiated on PPIs, 46.0% of them were not complied with United States FDA guidelines. Anaemia with no evidence of gastrointestinal bleed was the main reason PPIs were being prescribed inappropriately. This finding was similar to some other Asian study in where anaemia was the main reason for inappropriate prescription of PPIs.[6, 7] According to guideline, the patients with anaemia are not recommended to be routinely initiated with PPI as it may result in hyposecretion of gastric acid that may affect the iron absorption.[12]

It was noted that more than half of patients in this study using PPIs were above 60 years old. This was reported in many other studies demonstrating increasing PPIs prescription among elders as well.[4, 8, 9,13] However, in general, the age itself was not accepted as the independent factor for PPI prescription because the elders are always more susceptible to illness requiring hospitalization. The evidence suggesting potential for inappropriate PPIs prescription in elders is high in addition to the increased risk for developing *clostridium difficile* infections (CDI) and can lead to osteoporosis and fractures if the PPI was used longer than eight weeks in the elders.[14] As an effort to reduce the unnecessary prescription of PPIs in elders, the American Geriatrics Society (AGS) had added PPI to the 2015 AGS Bears Criteria as potentially inappropriate medication use in elders.[14]

More male patients were commenced on PPIs during hospitalization (P value < 0.05), meaning that the gender was significant associated with PPIs prescription. This could be explained by the relative higher risk of male patients to get peptic ulcer disease,[15] *Helicobacter Pylori* infection[16] and other acid-related disorders.

Most of our patients didn't perform any OGDS during the hospital stay. In fact, endoscopic examination should be performed to justify the need for PPIs, especially in those with long term prescription.

PPIs have been used a lot over the years for treatment of certain gastrointestinal disorder due to the effectiveness of the drug. However, there are growing concerns on overuse of PPIs in terms of adverse effect as well as healthcare cost. Since 2010, FDA has issued safety warnings regarding the long-term use of PPIs. PPIs are reported to be associated with enteric infection such as *clostridium difficile*, osteoporotic bone fractures, increased risk of pneumonia, disturbance of antiplatelet function, or nutritional deficiencies. Few studies[17, 18] have demonstrated an increased risk of *clostridium difficile* infections in those with PPIs. This could be explained by a higher gastric pH which leads to a more virulent strain of bacteria. It was reported a 41.0% reduction in calcium absorption after two weeks of omeprazole therapy.[19,20] Long term PPIs is potentially associated with higher risk of bone fracture.[21] Previous studies[22,23] have identified an increased rate of hospital-acquired pneumonia and recurrent community-acquired pneumonia in those receiving any form of acid suppression therapy, but the risk appears to be greater in patients receiving PPIs than in those receiving H2 receptor antagonists.[24] The role of acid suppression in increasing risk for pneumonia remains unclear. Patients with multiple comorbidities and polypharmacy who take long term PPIs are at high risk of drug-drug interactions. The alteration of pH in the gastrointestinal tract may affect the drug absorption, and PPIs inhibit cytochrome (CYP) p450 and the p-glycoprotein pathway.[25] Gilard et al. had found a reduction in the platelet reactivity index in 140 patients who took clopidogrel together with omeprazole for a week.[26]

Furthermore, Angiolillo DJ et al.[27] had demonstrated the attenuating effects of concomitant omeprazole treatment on platelet response to clopidogrel, but not between clopidogrel and pantoprazole. In 2010, American College of Cardiology, American College of Gastroenterology, and American Heart Association (ACCF/ACG/AHA) released a consensus statement[28] suggesting the use of PPIs to reduce the risk of upper gastrointestinal haemorrhage in patients on dual antiplatelet therapy (DAPT). PPI was recommended in high risk patients on DAPT, especially those of advanced age, previous upper gastrointestinal haemorrhage history, *H. pylori* infection, or concurrent utilization of NSAIDs, steroids, or anticoagulants.

Healthcare cost is another point of discussion in terms of prescription of PPIs which is not according to guideline. Undoubtedly, the alarmingly high and inappropriate prescription of PPIs will definitely cause increase in healthcare cost. Thomas L et al. had published a retrospective study showing that 68.8% of the patients in a managed care organization at United States, were prescribed a PPI inappropriately at hospital discharge, with the cost of inappropriate prescription of PPIs up to $3,013,069.[29] Malaysia is a developing country, and the public healthcare is fully subsidized by the *government*. In the 2018 National Budget, RM27 billion was allocated for the healthcare industry. Malaysia's current budget for the healthcare is about 4.0% of GDP, but this is still lower than the World Health Organisation (WHO) recommendation. The rapidly rising cost of drug therapy is for sure a great concern to our healthcare provider. Therefore, there is a need for us to improve our standard in prescribing PPIs according to

guidelines. With much wastage of unnecessary PPI prescription cost, it could be used for other much beneficial indications in terms of improving our healthcare.

As always, education is the key. This had been proven in a study performed in West Glouchester, United Kingdom showing a reduction in PPIs prescription and saving of 1.13 million pound after an educational intervention done.[30] In addition, the primary care improvement program which was done in Padua, Italy had shown a reduction of PPIs prescription and lowering of cost in healthcare as well.[31] Health care workers (HCWs) should be educated appropriately for management of gastrointestinal disorder via continuous medical education (CME) and also guidance in prescribing PPIs according to guidelines. The pharmacists in the hospital can aid in the improvement of PPIs prescription. A dedicated pharmacist can be assigned during ward rounds as well as to monitor the prescription of PPIs on daily basis. Currently, we do not have our own clinical guideline of prescription of PPIs in Malaysia, except a statement published by Malaysian Society of Gastroenterology and Hepatology (MSGH) on the use of antiplatelet therapy and PPIs in the prevention of gastrointestinal bleeding in 2013. A national consensus or guideline is warranted to guide in prescription of PPIs, not only to clinicians, but should be extended to clinical and community pharmacists and patients.

There were few limitations in our study. The sample size of the study had been limited due to the short duration of the study. The sample data that we obtained was from a single hospital which could not represent the situation of all hospitals in Malaysia.

CONCLUSION

PPI therapy is not without risk of adverse effects, especially if the usage is inappropriate. Our study had demonstrated 46.0% of our medical inpatients were inappropriately prescribed PPIs. More evidence is required to further identify the association between long term PPIs and risk of adverse effects.

REFERENCES

1. Rotman SR, Bishop TF. Proton pump inhibitor use in the U.S. ambulatory setting,2002-2009. PLoS One. 2013; 8(2):e56060.
2. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. AM J Manag Care.2010; 16:e228-234.
3. Eid SM, Boueiz A, Paranji S, Mativo C, Landis R, Abougergi MS. Patterns andpredictors of proton pump inhibitor overuse among academic and non-academichospitalists. Intern Med. 2010; 49:2561-2568.
4. Muhammad H, Faiza Y, Syed KMG, Fahd A, Frank W. Inappropriate use of protonpump inhibitors among medical inpatients: a questionnaire-based observational study. JRSM Short Rep. 2013; 4:2042533313497183.
5. Bustamante Robles KY, Ticse AR, Canepa RIF, Costta HCG, Vasquez KS, Soto AL, Sosa VH. Frequency of proton pump inhibitor prescription based in clinical practice guidelines in hospitalized patients in two academic hospitals in Lima, Peru. Rev Gastroenterol Peru. 2012; 32:44-49.
6. Christopher Chia TW, Lim WP, Charles Vu KF. Inappropriate use of proton pump inhibitors in a local setting. Singapore Med J. 2014; 55:363-366.
7. Lim L, Mohamed Izham MI. Selection of proton pump inhibitors (PPIS) for formulary inclusion using an objective scoring system in Malaysia. J Appl Pharm Sci. 2012; 2:17–24.
8. Mohamed HE Mohamad HNM, Amirul H, Rabiatul NK. Evaluation of Proton Pump Inhibitors Prescribing among Non-Critically Ill Hospitalized Patients in a Malaysian Tertiary Hospital. Journal of Applied Pharmaceutical Science 7 (12); 2017:077-083.
9. Kirubakaran R and Loo JH. The Appropriateness of Acid Suppressive Medications' Use in a Tertiary Hospital in Kedah. Ijppr.Human, 2016; 6 (4):719-728.
10. FDA Center for Drug Evaluation and Research. New Drug Application (NDA) Nexium (esomeprazole magnesium) delayed release capsules. AstraZeneca LP. Application Number 21-153 & 21-154 [online]. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/ nda/2004/021153Orig1s008.pdf.
11. Gupta R, Garg P, Kottoor R, et al. Overuse of acid suppression therapy in hospitalized patients. South Med J. 2010; 103:207–11.
12. Ali T, Roberts DN, Tierney WM. Long-term Safety Concerns with Proton Pump Inhibitors. Am J Med. 2009; 122:896–903.
13. Orlaith B. Kelly, Catherine Dillane, Stephen E. Patchett, Gavin C. Harewood, Frank Murray. The Inappropriate Prescription of Oral Proton Pump Inhibitors in the Hospital Setting: A Prospective Cross-Sectional Study. Dig Dis Sci. 2015 Aug; 60(8): 2280-6.
14. American Geriatric Society 2015 Beers Criteria Update Expert Panel (2015). American Geriatrics Society 2015 Updated

Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Journal of American Geriatric Society, 63, 2227-2246.

15. Kurata JH, Haile BM, Elashoff JD. Sex differences in peptic ulcer disease. Gastroenterology. 1985 Jan; 88(1 Pt 1):96-100.
16. De Martel C, Parsonnet J. Helicobacter pylori infection and gender: a meta-analysis of population-based prevalence surveys. Dig Dis Sci. 2006 Dec; 51(12):2292-301.
17. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol. 2007; 102:2047-2056.
18. 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 Jul; 107(7):1011-9.
19. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci N. Y.* 2011; 56(4): 931-950.
20. Chubineh S, Birk J. Proton pump inhibitors: the good, the bad, and the unwanted. *South Med J*. 2012; 105(11): 613-618.
21. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006; 296:2947-2953.
22. 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; 292:1955-1960.
23. Eurich DT,Sadowski CA,Simpson SH,Marrie TJ,Majumdar SR.Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs.Am J Med. 2010; 123(1): 47–53.
24. Herzig SJ,Howell MD,Ngo LH,Marcantonio ER.Acid-suppressive medication use and the risk for hospital-acquired pneumonia.JAMA.2009;301(20):2120–2128.
25. Polasek TM, Lin FP, Miners JO *et al*. Perpetrators of pharmacokinetic drug-drug interactions arising from altered cytochrome P450 activity: a criteria-based assessment. *Br J Clin Pharmacol*2011;71:727–736.
26. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, Mansourati J, Mottier D, Abgrall JF, Boschat J. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol. 2008; 51:256–260.
27. Angiolillo DJ, Gibson CM, Cheng S, Ollier C, Nicolas O, Bergougnan L, Perrin L, LaCreta FP, Hurbin F, Dubar M. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. Clin Pharmacol Ther. 2011; 89:65–74.
28. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, Furberg CD, Johnson DA, Kahi CJ, Laine L, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Circulation. 2010; 122:2619–2633.
29. 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; 16:122-129.
30. Valori RM, Brown CM, Strangeways P, Bradburn M. Reducing community dyspepsia drug costs: a controlled trial. Gut. 2001; 49:495-501.
31. Cardin F, Zorzi M, Bovo E, Guerra C. Bandini F, Polito D, Bano F, Grion AM, Toffanin R. Effect of implementation of a dyspepsia and Helicobacter pylori eradication guideline in primary care. Digestion. 2005; 72:1-7.