Long Term Risks of Proton Pump Inhibitor Administration: A Literature Review

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ABSTRACT

Proton pump inhibitor (PPI) has become drug of choice for acid related disease. However, PPI tend to be overprescribed and becoming one of the highest burden for health cost. Some studies showed that PPI are prescribed unnecessarily. Recent evidences showed raised concerns over long term effects of PPI consumption. Several long term side effects such as increased incidence of gastric polyps, micronutrient absorption disorders, infections, and osteoporosis have been yearly discussed. In recent years there has been increased attention to new side effects such as dementia, chronic renal failure, and cardiovascular disorders. Therefore, some health associations had issued warning and guidance regarding long term PPI prescription.

Keywords: *Proton pump inhibitor, long term side effect, polyp, infection, dementia, malabsorption, osteoporosis, chronic kidney disease, cardiovascular.*

ABSTRAK

Proton pump inhibitor (PPI) telah menjadi obat pilihan utama dalam pengobatan penyakit terkait asam lambung. Namun, seringkali PPI diresepkan secara berlebihan dan menjadi salah satu beban yang tinggi bagi biaya kesehatan. Beberapa penelitian menunjukan, bahwa PPI diresepkan secara tidak perlu. Bukti-bukti terbaru memunculkan kekhawatiran mengenai efek jangka panjang dari konsumsi PPI. Beberapa efek jangka panjang, seperti peningkatan insidensi polip gaster, gangguan penyerapan mikronutrien, infeksi serta osteoporosis telah dibahas setiap tahunnya. Dalam beberapa tahun terakhir telah ada peningkatan perhatian terhadap munculnya efek samping baru, seperti demensia, gagal ginjal kronis, dan gangguan kardiovaskular. Oleh karena itu, beberapa asosiasi kesehatan telah mengeluarkan peringatan serta panduan mengenai pemberian resep PPI jangka panjang.

Kata kunci: *proton pump inhibitor, efek jangka panjang, polip, infeksi, demensia, malabsorbsi, osteoporosis, gagal ginjal kronis, kardiovaskular.*

INTRODUCTION

Proton pump inhibitor (PPI) is the main therapeutic modality for disease caused by abnormal gastric acid production such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger-Ellison syndrome.[1] PPI is more effective in suppressing gastric acid secretion than H2 receptor antagonists (H2 blockers) through the mechanism of proton pump inhibition H^+ / K + ATPase in gastric parietal cells.[1,2]

The duration of PPI varies according to the diseases such as 8 weeks for GERD and more than 1 year in erosive esophagitis.[2,3] Long-term use may occur because inappropriate indication or purchased independently by the patients.[4] In 2009, PPI prescription was ranked the third largest drug classes in the United States with an estimated cost of $ 13.5 trillion / year.[4] The PPI use in more than 60 percent of hospitalized patients in Australia and UK was found to be inappropriate and burdening more health cost.[5]

Several studies have shown the side-effects in long-term use of PPI which are increased incidence of gastric polyps, micronutrient absorption disorders, infections, and osteoporosis.[2] In recent years there has been increased attention to new side effects such as dementia, chronic renal failure, and cardiovascular disorders.[6-8] This paper focused on the latest issues regarding side effects of PPI and reviewed based on latest evidences.

Hypergastrinemia, polyp, carcinoid and gastric carcinoma

Gastrin is a peptide hormone that stimulates gastric acid secretion from parietal cells.1 Gastric acid suppression due to PPI usage for more than 3 months may increase gastrin level.[1,9] Continuous elevation of gastrin level can cause hyperplasia of parietal cell and enterochromaffin-like-cell (ECL), the trophic effect was associated with the increased risk of polyps, carcinoids, and gastric carcinomas.[1,4,10]

Hyperplasia accompanied with parietal cell protrusion can obstruct isthmus and blood vessel flow, forming a cyst, eventually forming fundic gland polyps (FGP). The incidence of FGP in PPI usage for more than 12 months was 1-36%.[4,11] Jalving et al conducted an observational study in 599 patients and found that the use of PPI for more than 5 years increased the risk of FGP by four fold.[11] While termination of PPI may cause FGP regression. Jalving found one low grade dysplasia out of 107 FGP, while Graham found one low grade dysplasia from 6065 FGP.[10,11]

Systematic review by Lundell found that PPI usage for more than 3 years caused ECL hyperplasia but there was no carcinoid or gastric carcinoma found.[12] Cochrane meta-analysis showed that PPI usage for more than 6 months associated with ECL hyperplasia either diffuse or micronodular or linear but no dysplasia or neoplasia.[12, 13] It can be concluded that long-term use of a PPI may cause hypergastrinemia and FGP, but does not increase the risk of carcinoid and gastric carcinoma.

Malabsorption of micronutrients

PPIs is working by covalently bind to H+/K+ ATPase, which serve as the final common pathway for gastric acid secretion. On the other hand, gastric acid plays major role in the physiologic pathways for most micronutrients absorption. Exposure to long-term gastric acid inhibition may interfere with the absorption of many vitamins and minerals, particularly iron, calcium, magnesium and vitamin B_{12}.[14, 15]

Iron

Dietary iron is mostly in non-soluble non-haem iron form. Thus, ferric iron needs to be oxidized into soluble form for better absorption in duodenum. This process is facilitated by gastric juice. Some studies reported significant association between chronic use of PPI and presence of anemia, shown by decrease of most hematological indexes from baseline.[14, 16]

Sarzynski et al.[17] conducted a retrospective cohort study to explore the association between chronic PPI use (at least 1 year) and iron deficiency anemia. This study shown that PPI users had significant decreases in mean hemoglobin and hematocrit ($P < 0.01$ for both). The adjusted odds ratio (OR) for hemoglobin decrease >1 g/dL was 5.03 (95% CI: 1.71-14.78) and hematocrit decrease >3% was 5.46 (95% CI: 1.67-17.85).[17]

Shalev et al.18 conducted study to examine whether treatment with PPIs can decrease iron absorption in iron overload cases (congenital dyserythropoietic anemia type I/CDA I). Eight CDA I patients aged 12-18 years with mild iron overload received 20mg/d omeprazole for 6 months. Blood samples analysis was performed at baseline, at the end of intervention and 6 months after its cessation. Ferritin level decreased from 585 ± 180 ng/ml at baseline to 522 ± 172 ng/mL at the end of 6-month treatment and 660 ± 256 ng/mL 6 months after cessation of omeprazole treatment ($p = 0.009$). There was non-significant reduction in the mean iron level (iron 159 ± 42, 136 ± 54, 167 ± 34 µg/dL, $p = 0.302$) but significant reduction in hemoglobin level

(Hg 10.0 ± 0.8, 9.55 ± 1.0, 10.4 ± 10.7 g/dl, p=0.002).[18]

Despite the results above, the correlation between PPIs therapy and development of iron deficiency anemia should be studied further. The evidence of correlation remains poor because of some limitations such as small sample size, limited serial ferritin levels to properly determine iron-deficiency anemia and the inability to exclude number of potential confounders. In clinical practice, routine investigation of anemia is not recommended, but association between long term PPI treatment and anemia should be considered after excluding all other main causes. Furthermore, most cases of iron malabsorption can be managed clinically with the use of iron supplement that are absorbed independent of gastric acid.[14,16,17]

Magnesium

Magnesium (Mg2+) is second most copious element inside human cells and fourth most abundant positively charged ion in the human body.19 Hypomagnesemia associated with PPIs may manifest as tremor of the extremities, convulsions (40%), muscle cramps and spasms (20%), weakness and lethargy (30%), tetany (17%), loss of consciousness, numbness, anxiety, hallucinations, agitation (20%), dizziness and nausea (36%). Hypomagnesemia also induces endothelial dysfunction that could promote atherosclerosis. Theoretically, this could be one of the reasons for the observed relationship between PPI use and increased risk of major cardiovascular events.[19]

In 2014, William et al conducted a study by measuring 24-hour urine magnesium excretion of 278 patients as part of nephrolithiasis evaluation.[20] PPI use was documented in 15% (n = 50) of all study subjects. This study found 11 mg lower daily magnesium excretion in PPI users than non-users (p = 0.05). Another study shown that resolution of magnesium levels was evident after discontinuance of PPIs, and in few cases which the patients were re-challenged with PPI, the hypomagnesemia reoccured.[16]

Short term PPI use is not associated with hypomagnesaemia. PPI associated hypomagnesaemia usually remains undetected and very rare, onset usually occurs after 5 years of PPI use. The primary absorption of magnesium is through passive pathway in small intestine, but the mechanism for magnesium depletion is still unknown. In absence of symptoms, identification of PPI related hypomagnesemia was purely dependent of chance.[16]

FDA recommends health care provider should consider checking magnesium levels to whom are anticipated to be treated with long-term PPIs. But this is not practical, especially for the over-the-counter market. In case of patients who were presented with profound hypomagnesemia or ongoing magnesium loss, it may be reasonable to follow up magnesium levels more closely.16

Vitamin B_{12}

Vitamin B_{12} absorption is depend on gastric acid, therefore long-term PPI use may impair the absorption of vitamin B_{12}. Gastric acid is facilitating release of vitamin B_{12} from B_{12}-R protein complex and subsequently B_{12} can be absorbed in the terminal ileum once bound to intrinsic factor.[16]

Lam et al conducted case-control study within the Kaiser Permanente Northern California population. Lam et al.[21] compared 25.956 patients diagnosed with vitamin B_{12} deficiency between January 1997 and June 2011 versus 184.199 patients without B_{12} deficiency. Among patients diagnosed with B_{12} deficiency, 12% (n = 3.120) were exposed to PPIs therapy for two or more years. Among patients without B_{12} deficiency, 7.2% (n = 13.210) were exposed to PPIs therapy for two or more years. Both group were associated with an increased risk for vitamin B_{12} deficiency, especially for patients whose taking doses more than 1.5 PPI pills/day were more strongly associated (OR = 1.95; 95% CI: 1.77-2.15).[21]

This result was supported by the result of Jung *et al.*[22] systematic review and meta-analysis. The purpose of this study is to evaluate the association between prolonged acid lowering agent use and vitamin B_{12} deficiency from four case-control studies and one observational study. They found that long-term use of acid lowering agent significantly associated with the development of vitamin B_{12} deficiency (HR = 1.83; 95% CI: 1.36-2.46, p = 0.00).[22]

These findings do not recommend to avoid acid suppression therapy for patients with clear indication for treatment, but clinicians should evaluate the risk/benefit of any medical therapy for each unique individuals. Clinicians should always bear in mind that every therapy should be appropriate, dose and timing should be directed accordingly along with monitoring of long term therapy with regular laboratory test for nutrients/minerals level whose absorption might be impaired.[14-22]

Osteoporosis

Recently, reports of adverse effect on PPIs use associated with increased bone fractures receive much attention. A prospective study that included patients aged 18 to 58 receiving PPIs with symptomatic and endoscopic findings of GERD, reported that bone mineral density in both the vertebra and femur were reduced significantly after the patients received long-term PPIs treatment.[23] Yang et al conducted a nested case-control, which consisted of PPI users and the non-users of acid suppression drugs who were > 50 years old and included all patients with an incident hip fractures between 1987-2003. This study showed that PPIs taken for longer than 1 year were associated with an increased risk of hip fractures almost 1.5 times compared to non users.[24] Furthermore, PPIs use were also found associated to increased fracture in young adults aged 18-29 years old (RR = 1.39; 95% CI:1.26-1.53) and reported a dose-response effect with increased total exposure to PPIs, in a case control study by Freedberg et al which included 124.799 cases and 605.643 controls.[25] Also, In recent meta-analysis study which included 18 observational studies with a total of 244.109 fractures, reported a higher risk of hip fractures (RR = 1.26; 95% CI: 1.16–1.36), spine fractures (RR = 1.58, 95% CI: 1.38–1.82), and for fractures at any site (RR = 1.33; 95 % CI: 1.15–1.54) not only after long-term treatment but also in case of PPIs use for less than 1 year.[26]

Normally, calcium contained in foods is absorbed throughout the whole gut by paracellular transport and also by a transcellular pathway via the transient receptor potential vailloid-6-channel at the level of the apical membrane of the duodenum and proximal jejunum. The gastric acid secretion plays important role in conducting effective calcium absorption.[27] Acidic environment in the stomach facilitates the release of ionized calcium from insoluble calcium salts to be absorbed into serum, which inhibition of gastric acid by PPIs will lead to calcium malabsorption.[28,29] Later on, the hypocalcemia will induce parathormone production, give rise to bone resorption, and eventually causing osteoporosis and bone fractures.[29-31] Vitamin B_{12} malabsorption also thought as mechanism which will increase the homocysteine levels and reduces the osteoblastic activity with subsequent effects on bone formation and strength.[32]

In 2010, the Food and Drugs Administration (FDA) issued warning about possible increased risk of fractures of hip, wrist and spine with the use of PPIs. Patients using PPIs for at least 1 year or using high dose PPIs had the most risk with the incidence of fractures. FDA recommended that patients at risk for osteoporosis should increase dietary calcium intake and if necessary, prefer calcium supplements that are not influenced by gastric acid for absorption, such as calcium citrate.[33]

Dementia and Alzheimer Disease

Gomm et al in 2016 conducted prospective cohort study regarding the relationship between long term use of PPI in geriatric patient and dementia event. This study involved over 70,000 patients aged over 75 years old. Routine PPI use was defined as at least one time PPI prescription at each quarter during 18 months follow up period. Almost 3000 patients (4%) fulfilled the criteria as routine PPI user and had history of polypharmacy. During study period, 29,510 patients were diagnosed for dementia. Gomm et al found 44% increased risk for dementia in patients using PPI routinely. Increased beta-amyloid related with PPI usage is proposed as the underlying mechanism. The limitation of this study is the patients in PPI group are having more risk factors for dementia. Also this study is not controlling the comfounding factors such as hypertension, lifestyle, apolipoproteinE which are established as dementia risk factors.[34]

Recent published studies showed different results which found that PPI are not associated with increased risk of dementia or Alzheimer Disease. Goldstein et al conducted observational longitudinal study with over 10,000 people aged older than 50 years old and normal cognitive function at baseline. Goldstein concluded that elderly who continuously or intermittently using PPI were associated with lower risk of decline in cognitive function (HR = 0,78, p = 0.005 and HR = 0.82; p = 0.001, respectively).[36] Other study published in 2017 by Taipale et al confirmed that PPI usage was not associated with risk of Alzheimer disease and also not associated with dose-response relationship. Taipale conducted Finish nationwide nested case-control study (MEDALZ) which included 70,718 newly diagnosed Alzheimer disease during 2005-2011 and matched control of 282,858 individuals. The strengths of this study are the diagnosis of Alzheimer is confirmed by specialist and evaluated with established diagnosis protocol; Also the data regarding PPI usage was based on prescription register, not claim based.[36] Although recent studies showed negative findings regarding PPI use and dementia, PPI should be used judiciously and more prospective studies are needed.

acute interstitial nephritis (AIN) and chronic kidney disease (CKD) progression review published in 2007 found 63 cases of AIN associated with PPI use, with the average duration of PPI use until nephritis confirmed was 13 weeks.[37] Nested case control involved 184,480 subjects by Klesper et al, found that the use of PPI was associated with two times increased risk for developing acute kidney injury (AKI).38 According to several published case report, the duration of PPI use until AIN developed was varied between one week to 9 months.[39]

Recent studies showed that PPI usage also associated with increased risk for developing and accelerating the CKD progression. Lazarus et al, in 2016 conducted observational study which using two databases in United States, which are Atherosclerosis Risk in Communities (ARIC) and Geisinger Health System. These databases involved 10,482 and 248,751 participants, respectively. ARIC data showed 50% increased incidence of CKD in PPI group, while Geisinger data showed increased incidence for 17%. Twice daily use of PPI was related with higher increased of developing CKD compared to once daily use (HR = 1.46 vs. 1.15).[7]

Another study that involved 173,231 PPI and 20,270 H_2 blocker user, found that PPI usage was associated with 28% higher increase risk for developing CKD, 53% higher risk for having double increased creatine serum, 32% higher for developing decrease of glomerular filtration rate more than 30%, and 96% higher risk for developing end stage renal disease. The incidence for CKD and progression of CKD stage were associated with the PPI duration usage.[40] However, this study was an observational study, therefore direct causative effect could not be established from the result. More well-designed prospective and interventional studies are needed.

Yang et al in 2017 conducted meta analysis regarding the relationship between PPI usage and risk of AKI. They found seven observational studies which consist of five cohort studies and two case control studies. Six included studies were having good quality, while one study regarded as fair quality study. All these studies involved over 2.4 million participants. The statistical analysis found that patients with PPI were associated with increased 61 percent risk for developing AKI. Further analysis showed that individuals younger than 60 years old and PPI naive were having increased AKI risk due to PPI. However, several limitations from this meta analysis were the high heterogeneity among studies, and unexplained causality effect due to observational studies as the source of data.[41]

Cardiovascular Event

Some studies have been showed increased cardiovascular event risk related with PPI usage. Charlot et al performed retrospective study using medical records from all hospitals in Denmark between 1997-2006. The inclusion criteria were all patients aged older than 30 years surviving 30 days after first myocardial infarction and treated with aspirin. After one year follow up, they found 3,366 of 19,925 (16.9%) of the participants experienced recurrent cardiovascular event. Over 22.9% patients treated with PPI vs. 15.2% without PPI treatment were experiencing cardiovascular death, myocardial infarction, or stroke. Analysis using propensity score matched Cox proportional hazard regression analysis showed increased risk for 1.61 ($p < 0.001$). While the use of H_2 receptor blocker are not associated with increased cardiovascular risk.[42] Despite the large sample size, this observational study had some weakness which are the investigators not excluding the confounding factors such as smoking habit and obesity which may affecting the cardiovascular event. Also, the result could not be generalized in other ethnics, as this study performed in only one country.[42]

Other study by Shah et al in 2015 using clinical documents from various sources which included 2.9 million patients, showed 1.16 fold increased myocardial risk and 2.0 fold increased cardiovascular mortality in GERD patients treated with PPI. Because of this study is a-data-mining study, the confounding factors cannot be excluded and controlled such as PPI dosage or over-the-counter PPI usage.[8]

Recent mechanism underlying cardiovascular effects of PPI that being proposed is increased serum concentration for asymmetric dimethylarginine (ADMA), which act as nitric oxide (NO) synthase inhibitor. NO physiologically known as vasodilator and exerts protective effects. PPI inhibited dimethylarginine dimethylaminohydrolase (DDAH), enzyme that responsible for ADMA degradation, therefore resulting increased ADMA concentration and decreasing NO production.[43] However, other studies showed that the increased concentration of ADMA due to PPI usage were not clinically significant in human bodies and blood circulation.[44,45]

With current evidence, the use of PPI for gastrointestinal bleeding prevention can still be given to patients with cardiovascular disorders who receive antiplatelet. PPI should be prescribed based on the consideration of greater benefits compared to existing risks.[46]

PPI use and Infections

Clostridium difficile

A retrospective study conducted by Garg et al to determine the asscociation between PPI use and the increase of Clostridium-difficile Associated Diarrhea (CDAD) infection. This study included 400 random patients with CDAD which separated into three groups: hospital-acquired CDAD, long-term care facility (LTCF)-acquired CDAD, and community-acquired CDAD. They found that many LTCF patients were on PPIs, with 24% of the patients has no indication for the use of PPIs. This study revealed LTCF patients had the largest presentation on CDAD infection (46.1%), followed by community-acquired (33.3%) and hospitalized patients (20.6%).[47]

Continuous PPI use is also associated with recurrent *Clostridium difficile* infection (CDI). McDonald et al found increased risk for CDI in patient whose receiving PPI for at least 75% of days in the hospital in those who remained hospitalized or had been prescribed PPI drug for more than 90 days after the initial PPI treatment. (HR = 1.5; 95% CI: 1.1-2.0).[48] However, other factors such as antibiotic exposure, and bad handwashing techniques which allow passage of the spores between persons should also be considered in hospitalized patients with CDI. [49]

Travelers' Diarrhea

A long term use of PPI can reduce in acid production. The effect of hypochlorhydria can increased bacterial or parasitic infections. Through various mechanism, PPIs is associated with increased risk to the following bacterial enteropathogen: Salmonella, *Campylobacter jejuni*, invasive strains of *Escherichia coli*, vegetative cells of *Clostridium difficile*, *Vibrio cholerae* and *Listeria*. However, the studies conducted to see increased incidence rate of travelers diarrhea in patients who consumed PPIs has not been shown to be significant. Still, chronic PPIs use on travellers departing for areas with high incidence of diarrhea should be considered.[49,51]

Pneumonia

Nested-case-control trial was conducted by Laheij et al to examine the association between acid suppression drugs and the development of community-acquired pneumonia (CAP). The study population include 364,683 individuals who developed 5551 first occurrences of pneumonia during follow-up. The incidence rates of pneumonia in non-acid-suppressive drug users and acid-suppressive drug users were 0.6 and 2.45 per 100 person-years, respectively. The adjusted RR for pneumonia among persons currently using PPIs compared with those who stopped using PPIs was 1.89 (95% CI:1.36-2.62).[52]

Another study was conducted by Hermos et al, using the linked pharmacy and administrative databases of the New England Veterans Healthcare System. They included 71985 of newly prescribed patients with PPI between 1998 and 2007 and 1,544 patients met criteria for CAP with PPI initiation, also 15,440 controls were matched through risk-set sampling by age and time under observation. The study found that PPI use will increase the risk of developing CAP significantly. (adjusted OR, = 1.29; 95% CI: 1.15-1.45). However, several confounding factors such as dementia (n = 85; p = .062 for interaction) and sedative/tranquilizer use (n = 224; p = .049 for interaction) might affect the result which increased the PPI-CAP association. Furthermore, this study also found that PPI exposures between 1 and 15 days increased CAP risks compared to longer exposures, and higher PPI doses (>1 dose/day) will increase the CAP risk. In addition, several studies of acid suppression support the theory that aspirated gastric contents (colonized in the absence of acid) may cause an increased rate of ambulatory pneumonia in long-term PPI users.[49,53]

The Rational Use of PPI

Regarding a number of adverse effect associated with the use of PPIs that were explained and supported with numerous studies above, the appropriateness of PPIs use should be considered more carefully. The Canadian Family Physician (CFP) recommends de-prescribing the PPIs, which is defined by reducing dose, stopping, or using "on-demand" dosing in adults who have completed a minimum of 4 weeks of PPI treatment for heartburn or mild to moderate gastroesophageal reflux disease or esophagitis, and whose symptoms are resolved. However, this recommendation is not addressed for patients with Barrett esophagus, severe esophagitis grade C or D, or documented history of bleeding gastrointestinal ulcers.54 In April 2014, National Institute for Health and Care Excellence (NICE) clinical guideline (CG) recommends that patients requiring long-term management of symptoms for dyspepsia, should have an annual review of their condition, encouraging them to try stepping down or stopping treatment.55

The American Gastroenterological Association

(AGA) also recommends that patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them, and patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. In case of Barrett's esophagus and symptomatic GERD, the patients should take a long-term PPI and the dose of long-term PPIs should be periodically reevaluated to the lowest effective PPI dose. Also, PPIs should be taken in patients at high risk for ulcer-related bleeding from NSAIDs if they continue to take NSAIDs. [56]

CONCLUSION

PPI has become main therapy in acid related diseases. However, PPI tends to be overprescribed. While more high quality studies are needed, Long term PPI use has been associated with several possible risk of side effects. Therefore, practitioners should only prescribed PPI as long as indicated. Recommendations that published by several Health Associations can be used as guidance.

REFERENCES

1. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. Eur J Clin Pharmacol 2008;64:935-51.
2. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. Expert rev clin pharmacol 2013;6:443-51.
3. Scholten T. Long-term management of gastroesophageal reflux disease with pantoprazole. Ther Clin Risk Manag 2007;3:231-43.
4. Sheen E, Triadafilopoulos G. Adverse Effects of Long-Term Proton Pump Inhibitor Therapy. Dig Dis Sci 2011;56:931-50.
5. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ 2008;336:2-3.
6. Gomm W, von Holt K, Thome F, Broich K, Maier W, Fink A, et al. Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis. JAMA neurology 2016;73:410-6.
7. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, et al. Proton Pump Inhibitor Use and Risk of Chronic Kidney Disease. JAMA Intern Med. 2016;176:238-46.
8. Shah NH, LaPendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, et al. Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population. PloS One 2015;10:e0124653.
9. Thomson ABR, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. World J Gastroenterol 2010;16:2323-30.
10. Graham DY, Genta RM. Long Term Proton Pump Inhibitor Use and Gastrointestinal Cancer. Current gastroenterology reports 2008;10:543-7.
11. Jalving M, Koornstra JJ, Wesseling J, Boezen HM, S DEJ, Kleibeuker JH. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. Aliment Pharmacol Ther 2006;24:1341-8.
12. Lundell L, Vieth M, Gibson F, Nagy P, Kahrilas PJ. Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. Aliment Pharmacol Ther 2015;42:649-63.
13. Song H, Zhu J, Lu D. Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions. Cochrane Database Syst Rev. 2014 Dec 2;(12):CD010623.
14. Yadlapati R, Kahrilas P. The "dangers" of chronic proton pump inhibitor use. J Allergy Clin Immunol 20. dafpus 12Eusebi L, Rabitti S, Artesiani M, Gelli D, Montagnani M, Zagari R et al. Proton pump inhibitors: Risks of long-term use. J Gastroenterol Hepatol 2017;32:1295-302.
15. Keller J, Layer P. The Pathopysiology of Malabsorption. Viszeralmedizin. 2014;30:7-7.
16. Johnson DA, Oldfield IV EC. Reported Side Effects and Complication of Long-term Proton Pump Inhibitor Use: Dissecting the Evidence. Clin Gastroenterol Hepatol 2013;11:458-64.
17. Sarzynski E, Puttarajappa C, Xie Y, Grover M, Laird-Fick H. Assocaiton Between Proton Pump Inhibitor Use and Anemia: A Restropective Cohort Study. Dig Dis Sci 2011;56:2349-53.
18. Shalev H, Quider AA, Harosh MB, Kapelushnik J. Proton pump inhibitors use suppresses iron absorption in congenital dyserythropoietic anemia. Pediatr Hematol Oncol 2016;33:457-61.
19. Pisani LF, Filippi E, Vavassori S, Munizio N, Vecchi M. Effect of proton pump inhibitors on magnesium balance: is there a link to cardiovascular risk? Magnesium Research 2016;29:1-10.
20. William JH, Nelson R, Hayman N, Mukamal KJ, Danziger J. Proton-pump inhibitor use is associated with lower urinary magnesium excretion. Nephrology (Carlton) 2014;19:798-801.
21. Lam JR, Schneider JL, Zhao *et al*. Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Use and Vitamin B_{12} Deficiency. *JAMA* 2013;310:2435-42.
22. Jung SB, Nagaraja V, Kapur A, Eslick GD. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Internal Med J 2015;45:409-16.
23. Ozdil K, Kahraman R, Sahin A, Calhan T, Gozden EH, Akyuz U, et al. Bone density in proton pump inhibitors users: a prospective study. Rheumatology international 2013;33: 2255-60.
24. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pumps inhibitor therapy and risk of hip fracture. JAMA 2006; 296:2947-53.
25. Freedberg DE, Haynes K, Denburg MR, Zemel BS, Leonard MB, Abrams JA, et al. Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26:2501-7.
26. 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.
27. Recker RR. Calcium absorption and achlorhydria. N Engl J Med 1985;313:70–3.
28. Lau AN, Tomizza M, Wong-Pack M, Papaioannou A, Adachi JD. The relationship between long-term proton pump inhibitor therapy and skeletal frailty. Endocrine 2015;49:606-10.

29. Sipponen P, Harkonen M. Hypochlorhydric stomach: a risk condition for calcium malabsorption and osteoporosis? Scand J Gastroenterol 2010;45:133–8.
30. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Current gastroenterology reports 2010;12:448-57.
31. Insogna KL. The effect of proton pump-inhibiting drugs on mineral metabolism. Am J Gastroenterol 2009;104:S2-4.
32. Sheraly AR, Lickorish D, Sarraf F, Davies JE. Use of gastrointestinal proton pump inhibitors to regulate osteoclast-mediated resorption of calcium phosphate cements in vivo. Curr Drug Deliv 2009;6:192–8.
33. Food and Drug Administration. Use of Proton Pump Inhibitors and Risk of Bone Fractures in Adults USA: FDA; 2010 [serial online] [cited 2017 October 30]. Available from: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM399631.pdf.
34. Gomm W, von Holt K, Thomé F, Broich K, Maier W, Fink A, et al. Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis. JAMA Neurol 2016;73:410-6.
35. Goldstein FC, Steenland K, Zhao L, Wharton W, Levey AI, Hajjar I. Proton Pump Inhibitors and Risk of Mild Cognitive Impairment and Dementia. J Am Geriatr Soc 2017 ;65:1969-74.
36. Taipale H, Tolppanen AM, Tiihonen M, Tanskanen A, Tiihonen J, Hartikainen S. No Association Between Proton Pump Inhibitor Use and Risk of Alzheimer's Disease. Am J Gastroenterol 2017;112:1802-8.
37. Sierra F, Suarez M, Rey M, Vela MF. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther 2007;26:545-53.
38. Klepser DG, Collier DS, Cochran GL. Proton pump inhibitors and acute kidney injury: a nested case-control study. BMC Nephrol 2013;14:150.
39. Brewster UC, Perazella MA. Acute kidney injury following proton pump inhibitor therapy. Kidney Int 2007;71:589–93.
40. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD. J Am Soc Nephrol 2016;27: 3153–63.
41. Yang Y, George KC, Shang WF, Zeng R, Ge SW, Xu G. Proton-Pump Inhibitors Use, and Risk of Acute Kidney Injury: A Meta-Analysis of Observational Studies. Drug Des Devel Ther 2017;11:1291–9.
42. Charlot M, Ahlehoff O, Norgaard ML, Jørgensen CH, Sørensen R, Abildstrøm SZ, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. Ann Intern Med 2010;153:378-86.
43. Ghebremariam YT, LePendu P, Lee JC, Erlanson DA, Slaviero A, Shah NH, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation 2013;128:845-53.
44. Kruszelnicka O, Świerszcz J, Bednarek J, Chyrchel B, Surdacki A, Nessler J. Asymmetric Dimethylarginine versus Proton Pump Inhibitors Usage in Patients with Stable Coronary Artery Disease: A Cross-Sectional Study. Int J Mol Sci 2016;17:xx-xx.
45. Ghebremariam YT, Cooke JP, Khan F, Thakker RN, Chang P, Shah NH, et al. Proton pump inhibitors and vascular function: A prospective cross-over pilot study. Vasc Med 2015;20:309-16.
46. Vaduganathan M, Bhatt DL, Cryer BL, Liu Y, Hsieh WH, Doros G, et al. Proton-Pump Inhibitors Reduce Gastrointestinal Events Regardless of Aspirin Dose in Patients Requiring Dual Antiplatelet Therapy. J Am Coll Cardiol 2016;67:1661-71.
47. Garg S, Mirza YR, Girotra M. Epidemiology of *Clostridium difficile*-Associated Disease (CDAD): A Shift from Hospital-Acquired Infection to Long-Term Care Facility-Based Infection. Dig Dis Sci 2013;58:3407-12.
48. McDonald EG, Milligan J, Frenette C, Lee TC. Continuous Proton Pump Inhibitor Therapy and the Associated Risk of Recurrent Clostridium difficile Infection. JAMA Intern Med 2015;175:784-91.
49. Metz DC. Long term use of proton-pump inhibitor therapy. Gastroenterology & hepatology 2008;4:322-5.
50. Metz DC. *Clostridium difficile* Colitis: Wash Your Hands Before Stopping the Proton Pump Inhibitor.
51. Bavishi C, DuPont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther 2011;34:1269–81.
52. Laheij RJ et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004;292:1955-60.
53. Hermos JA et al, Risk of community-acquired pneumonia in veteran patients to whom proton pump inhibitors were dispensed. Clin Infect Dis 2012;1:54:33-42.
54. Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, et al. Deprescribing Proton Pump Inhibitors. Can Fam Physician 2017;63:354-64.
55. NICE Clinical Guideline 184. Dyspepsia and gastro-oesophageal reflux disease. September 2014 [serial online] [cited 2017 October 30]. Available from: https://www.nice.org.uk/guidance/cg184/resources/gastrooesophageal-reflux-disease-and-dyspepsia-in-adults-investigation-and-management-pdf-35109812699845
56. Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology 2017;152:706-15.