PPIs and Safety Concerns – A Pending Verdict?

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Abstract
Proton pump inhibitors (PPIs) with a high therapeutic index have strong evidence to support their efficacy in the management of common gastrointestinal (GI) conditions such as gastroesophageal reflux (GERD), peptic ulcer diseases, H. pylori infection etc. Despite this, the list of adverse effects being cited across literature with chronic use of these drugs is on an upward trend. Studies and published literature have associated PPI use with risk of bone fractures, various micronutrient deficiencies, gastro-intestinal infection, pneumonia, cardiac complications, dementia, kidney disease, intestinal bacterial overgrowth and drug interactions. It is however of clinical interest to note that in most of the studies published, the risk association reported with PPIs is weak. Unfortunately, widespread media publicity around these studies has prompted discontinuation of the drug in patients in whom it is indicated and created generalized anxiety among its users 20 years later since their introduction.

The primary objective is to review the literature for an unbiased translation of the knowledge to appropriately guide decision in clinical practice.

Introduction
Proton pump inhibitors (PPIs) since their introduction in 1989 are the most frequently prescribed drugs in use for extended periods of time. Once considered to be relatively safe, recent studies have questioned their absolute safety especially on long-term use (Figure 1). Their alleged association with risk of life-threatening conditions such as heart disease, and the risk of chronic kidney disease (CKD) has caught the attention of practicing physician, media and the patients.¹

The recent in the controversy
A recent longitudinal observational cohort (Department of Veterans Affairs database study) by Xie et al, 2019 has evaluated the outcomes related to PPI intake and all-cause and cause specific mortality. They observed a small excess (45.20 deaths/1000 PPI users) of cause specific mortality due to cardiovascular (CV) disease (38.65%), neoplasms (28.63%), infections (9.29%), and genitourinary system (13.83%) diseases in a graded relationship to duration of drug exposure (Figure 2).

An analysis of the sub causes of death suggested an association between new users of PPI and excess of mortality from CV disease and CKD. They also reported a graded association between duration of PPI exposure and risk of renal outcome, risk of doubling of serum creatinine level, eGFR decline, and end-stage renal disease (ESRD).²

The present evidence does lack strength and there is inadequate evidence to establish causal relationships between PPI usage and adverse consequences.³,⁴

Hill’s criteria: A quick glance
The Hill criteria (Table 1) includes a list of 9 considerations to strengthen the notion between causation/exposure and association. Arriving at conclusions based on weak associations can be problematic and probably is the reason for the growing alarm over PPI prescription and long-term use.⁴

A brief overview of the PPIs
PPIs inhibit the H+/K+-ATPase via covalent binding to cysteine residue of the proton pump and reduce their acid secretory function.⁵ The elimination of all PPIs involves hepatic oxidation by the CYP450 enzyme; primarily CYP2C19.Omeprazole, esomeprazole, and lansoprazole have an enzymatic metabolism mainly through CYP2C19 and CYP3A44. Pantoprazole is also initially metabolized by CYP2C19 and CYP3A4.⁶ Rabeprazole is not strongly
Concerns associated with use of PPIs

**Acute interstitial nephritis (AIN)**

Isolated cases of acute interstitial nephritis have been attributed to PPIs very early on since their introduction. A 2014 observational case-control study by Blank et al, reported a 5-fold increased adjusted odds ratio for risk of acute interstitial nephritis amongst users of PPIs. However, the risk seems to be an idiosyncratic one with no clear underlying mechanism being identified for the association. The largest case series to-date has only included 18 cases and the effect seems to be a hypersensitivity reaction to the drug or one of its metabolites.

**Chronic kidney disease (CKD)**

Many retrospective and prospective studies have tried to establish the association between PPI use and risk of kidney disease. In a first major study carried out by Lazarus et al, two individual patient cohorts were evaluated and found a significant higher risk of 20-50% of incident CKD in persons using PPIs as compared to H2RA group. Similar results had been reported in the Geisinger Health System replication cohort and a large Swedish cohort study. Among the 322 baseline PPI users, the 10-year estimated absolute risk of CKD was 11.8% with absolute risk difference of 3.3%. As can be seen in the ARIC cohort and the replicated cohort, the patients were more likely to be obese, with hypertension and were on multiple medications including statins, hence at higher risk for CKD for reasons unrelated to their PPI use.

As mentioned earlier, study by Xie et al, expanded on the findings by Lazarus et al but the cohort included mostly older veterans and hence the results may not be generalized. The drug exposure was defined by the prescription records and by days of supply which by no means can necessarily be equivalent to days of use of the drug. The PPI group in the Veterans study (102692) was much larger than the control group (16101) with greater comorbidities and predisposition to develop conditions such as AKI or CKD in the former. The reported hazard ratios in the PPI group for an increased risk of incident eGFR, 60 ml/min per 1.73 m2 and of incident CKD, doubling of serum creatinine level, eGFR decline and of ESRD studied were quantitatively small at between 1.19 and 1.30. Another recent meta-analysis in 2017 by Wijarnpreecha et al, included 5 observational studies with 536902 participants also suggested a greater risk of CKD in PPI users compared to use of H2RA.

Current evidence, therefore, shows only a weak association between PPIs and kidney disease. The American Gastroenterology Association recommends against routine screening/monitoring of serum creatinine in patients on PPI therapy.

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**Table 1: Hill criteria (the nine aspects of association)**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Aspects to determine causality/association</th>
</tr>
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<tbody>
<tr>
<td>Strength of association</td>
<td>Is the association of high magnitude?</td>
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<tr>
<td>Consistency</td>
<td>Are the findings reproducible?</td>
</tr>
<tr>
<td>Specificity</td>
<td>Is the outcome predicted based only on the exposure to PPIs?</td>
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<tr>
<td>Temporality</td>
<td>Does the use of PPI precede the observed outcome?</td>
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<tr>
<td>Biological gradient</td>
<td>Is there a direct relationship between dose or duration of PPI use and the outcome?</td>
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<tr>
<td>Biological plausibility</td>
<td>Is there a rational and theoretical basis for the proposed association?</td>
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<tr>
<td>Coherence</td>
<td>Any conflicts with what is known about the natural history and biology of the disease?</td>
</tr>
<tr>
<td>Experiment</td>
<td>Are the data based on experiments?</td>
</tr>
<tr>
<td>Analogy</td>
<td>Are there features of association similar to other associations judged to be causal?</td>
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</tbody>
</table>
Cardiovascular events

Use of PPIs has been linked to risk of acute cardiovascular events and myocardial infarction (MI) by either competing with P450 isoenzyme activation of clopidogrel or by a direct increase in the vascular resistance by inhibition of nitric oxide synthase activity.\(^9\) Platelet reactivity in patients undergoing angioplasty and on concomitant PPI and clopidogrel was seen to be significantly higher compared to those on only clopidogrel.\(^{10}\)

However, as different PPIs inhibit CYP2C19 to varying degrees, the interaction may vary between PPIs prescribed, with omeprazole being the most potent inhibitor of the isoenzyme.\(^{6,11}\) (Figure 4)

In the 9862 patients 17.9% vs. 25.0% amongst only clopidogrel vs. clopidogrel-PPI therapy experienced a major adverse cardiovascular event post percutaneous coronary intervention (PCI) (\(p<0.0001\)) with similar results in another meta-analysis.\(^8\) Each PPI (omeprazole, esomeprazole, pantoprazole, and lansoprazole) assessed showed similar associations of increased risk with the PPIs.\(^{12,8}\)

In contrast, use of PPIs having minimal interaction with the enzyme pathway in a cohort study of over 20000 patients with CV disease, there was no significant increase in serious CV events.\(^1\) Population-based epidemiological studies and meta-analyses have tested plausible or weakly plausible mechanisms on the risk associations between PPI use and MI.\(^{1,14}\) The COGENT trial (despite its limitations) showed no clinically significant evidence of a PPI-clopidogrel interaction (4.9% vs. 5.7%; PPI vs. Placebo for CV events).\(^{10}\)

One of the other mechanisms by which PPIs pose a cardiac risk is by directly blocking vascular nitric oxide synthase and promoting vascular contraction. This has been reported by ex-vivo findings and by a recent publication wherein GERD patients on PPIs had a 1.16-fold increased association with MI irrespective of clopidogrel use. Overall, current evidence suggests only a weak evidence of PPI and CV risk.\(^3\)

Whatever the controversy or conflicting results, the pharmacodynamic and pharmacokinetic interaction between clopidogrel and CYP2C19 specific PPIs cannot be overlooked. In lieu of this, Food and Drug Administration (FDA) in March 2010 announced that in patients identified as CYP2C19 poor metabolizers, clopidogrel should not be used in combination with PPIs. A black-box warning in 2009 warrants against the use of omeprazole or esomeprazole with clopidogrel.\(^{13}\) PPIs are also reported to reduce the antiplatelet effect of acetylsalicylic acid (ASA).\(^{14}\) PPIs may also increase statin action due to competitive inhibition of P450 cytochromes.\(^{15}\)

It may, therefore, be reasonable to choose a PPI with minimal inhibitory effect on CYP2C19 enzyme e.g. Rabeprazol in combination therapy with cardiac drugs which has shown positive evidence.\(^{5,7,16,17}\) Rabeprazole has also been shown to prevent severe bleeding and MACE events in a retrospective study in patients on clopidogrel and aspirin after stent implantation.\(^{18}\)

Coronary heart disease being a major health concern requires the use of antiplatelet and anticoagulant agents. Increase in the gastrointestinal bleeding risk with these drugs has led to the recommendation of co-prescription of PPIs.\(^{11}\) Therefore, guidelines (2012) from the American College of Cardiology Foundation and American Heart Association (ACCF/ AHA) do not prohibit the use of PPI agents in appropriate clinical settings.\(^5\)

The relevant CYP knowledge is a useful tool in managing these patients and a PPI with less CYP2C19 inhibitory capacity may be optimal option in such conditions.

Bone fractures

A warning on the possible risk of bone fractures inserted on the PPI label in 2010 was retracted in 2011 owing to lack of evidence that short-term low-dose PPI use was associated with bone density changes.\(^{13}\) Studies that have assessed bone mass have shown conflicting results.\(^3\) While a systematic review and meta-analysis of 18 observational studies reported on a moderate increase in the risk of hip, spine and any-site fracture with PPI use for over a year, the observational studies included could have influenced the results by confounders and bias.\(^{22}\)

The available evidence linking PPI use and fracture risk is weak. The negative effects on the bone health are attributed more to the nutritional deficiencies rather than a cause effect of the drugs. Neither is a routine monitoring of BMD or calcium supplementation recommended nor is a warning on the label for risk of osteoporosis and fracture mandated by FDA.\(^3\)

Nutritional deficiencies

One of the adverse effects implicated with chronic PPI use is the occurrence of various micronutrient deficiencies. However, it is highly plausible that these deficiencies correlate to additional risk factors in the patient and not solely due to PPI use. While PPIs may theoretically cause malabsorption of vitamin B12, results from studies have been conflicting.\(^3\) While a case control study found use of PPI and H2Ras to be associated with an increased risk of deficiency of the vitamin, other studies found no difference in the risk of deficiency between PPI users and non-users.\(^{3,4,23}\) The AGA does not recommend a regular monitoring or supplementation with the vitamin in patients on PPI therapy.\(^3\)

Malabsorption of iron is seen as a consequence of acid suppression by PPIs. A case control study by Kaiser Permanente Northern California health system showed that PPI intake for 2 or more years had an Attributable risk(AR) of 48 to 71 incident cases over
1000-patient years (OR 2.49, 95% CI, 2.35–2.64). The risk was seen to increase with higher daily doses and duration of intake.4 Findings from a retrospective study by Sarzynski et al, observed that PPI use for over 12 months results in the participants having lower hemoglobin, hematocrit and mean corpuscular volume values.3

A randomized placebo-controlled study by O’Connell 2005 et al, reported on a significant decrease in fractional calcium absorption in elderly women after 1 week of PPI therapy. In the opinion of few other authors, alterations in the gastric pH caused by PPIs are insufficient to impair calcium absorption from the gut. Best Practice Advice issued by AGA recommends against additional calcium intake in patients on PPI therapy.3

PPIs are proposed contributors to hypomagnesemia, an otherwise common occurrence in critically ill patients. The FDA issued a drug safety communication in this regard in 2011.24

Dementia

PPI use was first linked to dementia by a population-based observational cohort study that examined the incident cases of dementia in nearly 74000 patients over the age of 75 years. Compared with the general population, the adjusted HR of developing dementia was 1.44 vs. 1.16 with regular PPI use vs. intermittent use. However, conclusions from this may not be considered valid given that the age factor, polypharmacy, and type of dementia were overlooked and the whole population studied was overall less healthy.25

Goldstein et al, assessed development of mild cognitive impairment and progression to Alzheimer’s disease in a prospective cohort of 10,486 volunteers which included 2800 PPI users. Regular PPI use was associated with low risk of transition to mild cognitive impairment or dementia caused by any etiology and no association with Alzheimer’s. Intermittent use of PPI did not show any association with mild cognitive impairment or dementia by any etiology.22 Further, Taipale et al in a case-control design found no association of PPI use (over 3 years) and at higher doses with Alzheimer’s after adjusting for covariates.3

Infections

PPI use has been reported to increase risk of infections attributable to long-term acid suppression and alteration in the gut flora. A meta-analysis of 50 controlled observational studies by Cao et al, and a systematic review and meta-analysis of 16 observational studies showed significant association between PPI therapy and increased risk of C. difficile infection even after adjustment for age and other potential cofounders.3

In another systematic review by Tleyjeh et al, a 1.51 adjusted pooled RR for C. difficile infection was noted. The evidence was low quality and the number needed to harm (NNH) was 3935 (AR 0.25/1000 patient-years) compared to a NNH of 50 for patients who completed 2 weeks of antibiotics.22

Rodriguez et al found a significant association between PPI use and increased risk of bacterial gastroenteritis, irrespective of duration of treatment. Like-wise a systematic review by Leonard et al, reported an increased risk of enteric infections in patients using acid suppressant agents. However, one retrospective analysis of almost 2 million patients (350000 under PPI treatment) observed almost 3.1 to 6.9 - fold higher rates of Campylobacter and Salmonella infections amongst them even prior to initiation of treatment. Further data from 2 randomized controlled trials that had a 12- and 5-year follow up failed to find any significant differences in enteric infections between PPI users and non-users. On reviewing Hill criteria, the available evidence is of moderate strength, temporality, consistency, and plausibility.3,4

Another aspect is the increased risk of spontaneous bacterial peritonitis (SBP) especially in the patients with liver disease and cirrhosis. Both a recently published meta-analysis by Dam et al, and a systematic review and meta-analysis by Xu et al, found an increased risk of SBP in PPI users compared to nonusers. However, Yu et al, in a meta-analysis of 10 case-control and 6 cohort studies found an association of PPIs with SBP only in case-control studies but no association between PPI intake and 30-day mortality. Overall, the current evidence has a weak strength and does not support the denial of PPIs to patients with liver disease if indicated.5

Pneumonia

Several studies published between the 1990s and 2000s, suggested use of PPI to be associated with the risk of pneumonia.3 A pharmaco-epidemiologic cohort of 35000 patients found PPIs to be associated with higher rates of pneumonia among mechanically ventilated patients.20 The incidence of pneumonia was also seen to be high in patients with acute stroke on PPI therapy in another retrospective study.26 While the mechanism and overall association seem biologically plausible, the overall quality of evidence is low. An interesting finding from a large meta-analysis including 26 studies and 200000 patients by Lambert et al, and another study by Sarkar et al, reported that treatment with PPI for less than a month was associated with the highest risk of CAP with the risk decreasing and losing statistical significance as the duration of PPI therapy increased.3 On evaluation of the Hill criteria, current evidence from the studies has a weak strength and only plausibility is present.3,4

Gastric cancer

PPIs are said to increase gastric enterochromaffin like (ECL) cells in the gastric fundic mucosa with potential for development of gastric neuroendocrine tumors. However, post clinical use of these drugs there have not been any reliable reports to support the association.3 Meanwhile, few observational studies have suggested an increase in gastric cancer in patients treated with PPIs for H. pylori infection with a hazard ratio value of 4.29 per 10000 person years. Cheung et al reported excess gastric cancer risk among PPI users of 4.29 per 10000 person years.27 Meta-analysis by Wan et al, found long term PPI use to be associated with a two-fold increase of gastric cancer with an odds ratio of 2.10.28 However, there are studies that present contrasting findings making it difficult to reach a conclusion on the actual risk.5

Drug interactions

Many commonly used drugs including the PPIs are metabolized by the CYP2C19 enzyme. Concerns have been raised on the potential of PPIs to decrease the level of degradation of co-prescription drugs sharing the enzyme pathway with resultant augmentation or inhibition of pharmacological effects of the latter. Competitive inhibition of hepatic cytochrome P (CYP) 450 enzymes involved in drug metabolism
which may pose an increased risk for adverse effects. In addition, the competitive inhibition of hepatic cytochrome P (CYP) 450 enzymes by certain PPIs as one of the major causes for drug interactions is often ignored. Due consideration to pharmacokinetics and pharmacogenetic alterations can also aid in optimal and safe therapy with the PPIs.

Table 2: Drugs metabolized by the CYP450 enzyme pathway

<table>
<thead>
<tr>
<th>Class/Therapy</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitors (PPIs)</td>
<td>Omeprazole, esomeprazole, pantoprazole, lansoprazole</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Clopidogrel, ASA, ticagrelor, prasugrel</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>Citalopram, escitalopram, diazepam, donepezil, selegiline</td>
</tr>
<tr>
<td>Neurology</td>
<td>Clozapine, lamotrigine, phenytoin</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Drospirenone, ethinylestradiol</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>Nelfinavir (antiviral), voriconazole (antifungal)</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>Carisoprodol</td>
</tr>
<tr>
<td>Antidiabetic medications</td>
<td>Meglitinide-class, sulfonylureas, thiazolidinediones, and metformin (insignificant)</td>
</tr>
<tr>
<td>Statins</td>
<td>Atorvastatin, simvastatin, Fluvastatin, lovastatin, cerivastatin</td>
</tr>
</tbody>
</table>

Table 3: PPIs and associated drug interactions

<table>
<thead>
<tr>
<th>PPI</th>
<th>Co-prescription drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Nifedipine, tacrolimus, phenytoin, carbamazepine, diazepam, clopidogrel, digoxin, warfarin, methotrexate, theophylline.</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Phenytoin, diazepam, clopidogrel, digoxin, warfarin</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Theophylline, tacrolimus</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Nifedipine, digoxin</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>No interaction with clopidogrel, diazepam, phenytoin, theophylline, warfarin, ASA, metformin, tacrolimus.</td>
</tr>
</tbody>
</table>

References