



Adverse effects of proton pump inhibitors: fact or fake news?

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Purpose of review

The present review summarizes the past year's literature, both clinical and basic science, regarding potential adverse effects of proton pump inhibitors.

Recent findings

Proton pump inhibitors are amongst the most widely prescribed and overprescribed medications worldwide. Although generally considered well tolerated, epidemiologic studies mining large databases have reported a panoply of purported serious adverse effects associated with proton pump inhibitors, including chronic kidney disease, cognitive decline, myocardial infarction, stroke, bone fracture and even death. It should be noted that the quality of the evidence underlying these associations is very low and these studies, by design, cannot ascribe cause and effect. Nonetheless, these associations have been sensationalized in the media and misinterpreted by patients and providers. Unintended consequences of the fake news are that patients are not being prescribed and/or taking clinical guideline-recommended proton pump inhibitors to prevent and treat complications from gastroesophageal reflux disease and upper gastrointestinal bleeding precipitated by NSAIDs and dual antiplatelet therapies. In addition, physicians, who already have limited time to interact with their patients, are spending an inordinate amount of additional time placing these findings into proper perspective and reassuring their patients when initiating treatment as well as on every follow-up visit.

Summary

Most of the recent highly publicized serious adverse effects ascribed to proton pump inhibitors are not based on demonstrable evidence. Nevertheless, when proton pump inhibitors are prescribed long-term, they should be used at the lowest effective dose and the need for their use periodically reassessed.

Keywords

acid secretion, antiseecretory, histamine H2 receptor, proton pump inhibitor

INTRODUCTION

Gastric acid secretion is precisely regulated to maximize benefits and minimize harms. Acid kills ingested microorganisms, renders the stomach and small intestine relatively sterile, modulates the gut microbiome, assists in protein digestion and facilitates the absorption of nonheme iron, calcium and vitamin B₁₂, and enhances the bioavailability of certain medications (e.g. ketoconazole, itraconazole, thyroid hormone and atazanavir). However, when levels of acid (and pepsin) overwhelm mucosal defense mechanisms, gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) may occur.

The development of proton pump inhibitors (PPIs; omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole and dexlansoprazole), medications that block the parietal cell acid pump, has revolutionized the management of GERD and PUD.

These potent antiseecretory medications have reduced complications and hospitalizations as well as improved the quality of life for patients suffering from acid-peptic disorders. PPIs have also become the gold standard in the prevention of NSAID-induced gastroduodenal ulcer, prevention of NSAID-induced upper gastrointestinal (UGI) bleeding and *Helicobacter pylori* eradication regimens. Consequently, PPIs are one of the most commonly

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KEY POINTS

- Although proton pump inhibitors are generally overprescribed, due to negative publicity, they are underutilized in patients at a high risk for UGI bleeding.
- Proton pump inhibitors should be used at the lowest effective dose and the need for their continued use should be periodically assessed and reassessed.
- Although proton pump inhibitors are well tolerated drugs, trolling of large observational databases has reported numerous potential adverse associations. The data supporting many of these associations, however, are very weak and often inconsistent.
- Evidence is relatively strong linking proton pump inhibitors with alterations in gut microbiome, micronutrient deficiencies, fundic gland polyps and enteric infection.
- There is evolving evidence, both basic science and clinical, linking proton pump inhibitors to carcinogenesis that is mediated via proton pump inhibitor-induced hypergastrinemia.
- Evidence is very weak or nonexistent linking proton pump inhibitors to chronic kidney disease, cognitive dysfunction, myocardial infarction, stroke, bone fracture and death.
- It is our responsibility as investigators, academicians, reviewers and clinicians to avoid sensationalized conclusions when publishing and interacting with the media. Findings derived from mining databases need to be placed in proper context and caution exercised regarding misinterpretation.

prescribed (and overprescribed) medications. In the United States, nearly 15% of adults have used a PPI within the last year, with even greater use in the elderly [1^{••},2[•]]. The use and overuse of PPIs is a world-wide phenomenon, with similar results reported in a drug-utilization study conducted in Iceland [3]. Over a 13-year period, the overall outpatient prescription for PPIs doubled and patients were increasingly treated with higher doses for longer durations than recommended by clinical guidelines.

Although PPIs have long been considered well tolerated medications, there have been numerous recent publications purporting potential harms. These reports, published in the medical literature and sensationalized in the media, have caused alarm and angst amongst patients and providers. An unintended consequence of the adverse publicity is that PPIs are now often underprescribed for conditions necessitating their use such as erosive esophagitis and prevention of NSAID-induced UGI bleeding,

particularly in patients taking dual antiplatelet therapies.

There is now a long list of dozens of potential serious adverse effects associated with PPI therapy, including alterations in gut microbiome, enteric infection, micronutrient deficiencies, fundic gland polyps, gastrointestinal malignancy, chronic kidney disease (CKD), cognitive dysfunction, myocardial infarction (MI), bacterial overgrowth, bacterial peritonitis, pneumonia, bone fracture, drug interactions and death. There is relatively strong evidence, including biologic plausibility, linking PPIs with alterations in gut microbiome, micronutrient deficiencies (e.g. magnesium, vitamin B₁₂, iron and calcium), fundic gland polyps and enteric infection. Increasing basic science data suggest a possible association with carcinogenesis that is mediated by PPI-induced hypergastrinaemia [4–7]. The quality of the evidence, however, underlying the other associations is very low and often inconsistent [8^{••},9^{••}]. The aim of this chapter is to critically review the recent literature, published within the past year, regarding potential adverse effects of PPIs and place the findings in proper perspective.

POTENTIAL ADVERSE EFFECTS OF PROTON PUMP INHIBITORS

It should be noted that most, if not all, studies maligning PPIs are retrospective observational studies that, by design, can generate hypotheses but cannot ascribe cause and effect [1^{••},9^{••}]. These large database studies have inherent limitations, as the studies were not designed to answer a specific question, information was not collected with a specific hypothesis in mind, PPIs were not assigned at random, experimental and control groups are not comparable, level of exposure (dose, duration and date of initiation) to PPI is not known and unaccounted biases and confounding variables persist, even after multivariable regression and propensity weighting. PPIs users tend to be older, sicker, hospitalized more frequently and taking more medications. Although the greater the magnitude of the association, the more likely that the relationship may be causal, when effect sizes are small [odds ratio (OR) or hazard ratio < 3], as is the case in all the studies, it is not possible to determine whether the association is valid or due to residual bias and confounding variables. Expressing risk in terms of relative risk (OR or hazard ratio), instead of absolute risk or number needed to harm, is misleading and overestimates the risk to an individual, particularly when adverse events are uncommon.

There is little or no biological plausibility linking PPIs to the potential adverse effects to be

reviewed (except for alterations in gut microbiome, enteric infection, micronutrient deficiency, fundic gland polyps, and possibly carcinogenesis and interference with drug absorption), as PPIs are in the bloodstream for only a relatively short time period (elimination half-life ~1 h) and peak plasma concentrations are relatively low. The reason PPIs cause prolonged inhibition of acid secretion has little to do with blood concentrations but rather is due to the fact that PPIs become concentrated and trapped within the secretory canaliculus of the parietal cell wherein they covalently bind to cysteine residues on the lumenally exposed α -subunit of the $H^+K^+-ATPase$ to inactivate the acid pump. Recovery of acid secretion depends upon de-novo synthesis of pump protein, a process that takes 54 h in rat.

Gut microbiome

It is conceivable that PPIs, by producing hypochlorhydria, may allow survival of certain ingested microbes and, thus, alter the composition of the gastrointestinal microbiome. Prior studies have reported an overexpression of oral bacteria in the faeces of individuals taking PPIs as well as an increased ratio of *Firmicutes* to *Bacteroidetes* at the phylum level and an increase in *Holdemania filiformis* and decrease in *Pseudoflavonifractor capillosus* at the species level [10]. Ten healthy adult volunteers on no medications were enrolled in a study in which salivary, periodontal pocket and faecal samples were analysed for bacterial composition using 16S rRNA before and after 4 weeks of once daily 20 mg esomeprazole [11]. The genus *Streptococcus* was increased after PPI administration in all three samples but reached statistical significance only in stool. The degree of change in the gut microbiome associated with PPIs is comparable to that induced by antibiotics. The clinical significance of these and other changes in the microbiome induced by PPIs remains to be elucidated.

Infection

As gastric acid kills ingested microorganisms, it is biologically plausible that PPIs, by reducing gastric acid secretion, may increase enteric infection, particularly of acid-sensitive organisms such as *Vibrio cholera*, *Salmonella*, *Campylobacter* and, perhaps, norovirus [12]. Other mechanisms may include increased intestinal permeability and altered microbiome. In mice, a PPI (lansoprazole) increased host susceptibility to colitis after oral gavage with *Citrobacter rodentium*, an enteropathogen used experimentally as a model of human enterohemorrhagic *Escherichia coli* [13]. The ileal microbiota were altered as a result of the increased gastric pH. The decrease in

Clostridiales may have compromised colonization resistance to *C. rodentium*. It should be noted that rodents practice coprophagy and reduced killing of orally ingested faecal bacteria could have been responsible for the altered microbiome. Studies in humans indicate that PPIs alter the faecal microbiome with increased abundance of oral bacteria [14].

Numerous observational studies, all with OR less than 3, report an association between PPIs and *C. difficile* infection (CDI) [14,15]. It should be noted that vegetative cells of *C. difficile* are susceptible to gastric acid, but spores are resistant. Thus, if PPIs are eventually proven to cause CDI, the effect is more likely related to dysbiosis than to an acid antisecretory effect *per se*.

Although PPIs have been associated with an increased risk of infection, a retrospective cohort study of 24 774 ICU patients failed to show an association between PPIs, used for stress ulcer prophylaxis, and bloodstream infections [16].

Cancer

Gastrin is not only a secretagogue but also a growth hormone capable of stimulating proliferation, cell migration and angiogenesis as well as inhibiting apoptosis and activating autophagy [17]. Gastrin receptors (termed gastrin/CCK2, CCK2 or CCK-B receptors) have been identified in various human cancers including adenocarcinomas of the stomach and oesophagus [18]. Gastric hypoacidity, induced by PPIs, interferes with the feedback pathway whereby luminal acid stimulates somatostatin secretion, which, in turn, inhibits gastrin secretion. Patients on high-dose PPIs manifest hypergastrinaemia and hypergastrinaemia has been associated with an increased risk of gastric adenocarcinoma, neuroendocrine tumours (i.e. enterochromaffin-like cell carcinoids) and possibly oesophageal adenocarcinoma [19].

A total of 1 563 860 individuals in the Danish Prescription Drug Registry taking acid-suppressive medications were matched to unexposed population-based controls [20]. Those with five or more prescriptions for PPIs were six-fold and 10-fold more likely to develop proximal and distal gastric cancer, respectively. In a Hong Kong health database, PPI use, after eradication of *H. pylori*, was associated with an increased gastric cancer risk (hazard ratio, 2.4) [21]. In mice, omeprazole promotes carcinogenesis of the fore-stomach following treatment with the nitrosamine, N-methyl-N'-nitro-N-nitrosoguanidine [22]. Dose-response effects were reported in both the epidemiological and experimental studies.

A study from China reported significant microbiome dysbiosis in gastric biopsies from patients

with progressive stages of gastric carcinogenesis starting from superficial gastritis and progressing through atrophy, intestinal metaplasia and cancer [23]. Gastric cancer patients harboured increased numbers of oral bacteria, including *P. micra*, *P. stomatis* and *F. nucleatum*. It is not known what percentage of patients were taking PPIs.

The impact of PPIs on development and progression of oesophageal adenocarcinoma is unclear. However, the gastrin/CCK2 receptor is upregulated in Barrett's oesophagus and L2-IL-1 β transgenic mice manifest increased proliferation and expansion of Barrett's-like oesophagus when rendered hypergastrinemic by treatment with PPIs [24²²]. Furthermore, in cultures of gastric cardia, gastrin stimulates organoid growth while CCK2R inhibition prevents Barrett's-like oesophagus and dysplasia. The data suggest a progression of Barrett's oesophagus to adenocarcinoma in which CCK2R+ progenitor cells, stimulated by hypergastrinaemia, proliferate to give rise to dysplasia [24²²]. In a Swedish population-based cohort study of 796 492 adults exposed to maintenance therapy with PPIs, an increased risk for development of oesophageal cancer, in particular adenocarcinoma, was reported among individuals using maintenance PPI therapy overall (hazard ratio, 3.9) as well as among those who used PPIs for indications not associated with an increased risk of oesophageal adenocarcinoma (hazard ratio, 2.0–2.7) [25]. These findings herald a warning regarding the use of high-dose PPIs, especially in patients with asymptomatic Barrett's oesophagus.

Chronic kidney disease

Data purporting an association between PPIs and chronic kidney disease (CKD) have been weak. Two additional studies, one of which is a meta-analysis, were published this past year; both show a weak association and cannot exclude residual confounding [26,27]. A Stockholm administrative database of creatinine measurements of all the region's citizens from 2007 to 2010 was analysed to examine the association between new users of antisecretory medications and progression of CKD, defined as a doubling of creatinine levels or a decline in estimated glomerular filtration rate of at least 30% [26]. Patients using PPIs were more likely to experience progression when compared with those using histamine H₂-receptor antagonists (H₂As), but the association was relatively weak (hazard ratio, 1.26). Those taking PPIs, were older, had more comorbidities and took more medications, including NSAIDs.

A systematic review and meta-analysis identified five studies with 536 902 participants that investigated that association between antisecretory

medications and CKD [27]. When compared with non-PPI users, the pooled risk ratio of CKD with PPI use was only 1.22. When compared with the use of H₂RAs, the pooled relative risk of CKD in patients using PPIs was 1.29. Unaccounted biases and confounding variables were most likely responsible for the weak associations reported by these observational studies. For example, PPI users had increased comorbidities, including diabetes, hypertension and ischemic heart disease and dose and frequency of PPI use is not documented.

Cognitive decline

Inconsistent and conflicting results have been reported regarding the association of PPIs with cognitive decline. Several studies found no association and when an association was present, it was weak (hazard ratio, ~1.4). This past year, four additional studies were published, each of which showed no association between PPIs and cognitive decline [28–31]. A large study of 13 864 participants in the Nurses' Health Study II, who had data on medication use prospectively collected and had completed a self-administered computerized battery of neuropsychological tests, found no convincing association between PPI use and cognitive dysfunction [28]. Data from two large population-based studies of middle-aged and older twins in Denmark, who underwent cognitive assessments over a 2 to 10-year period, also found no association between PPI and cognitive decline [29]. A United States population-based cohort study of individuals aged 65 years and older without dementia at study entry ($N=3484$) who were screened for dementia every 2 years for a mean of 7.5 years, also found no association between PPI use and dementia, even for people with high cumulative exposure [30]. Finally, a very large Finnish nested case–control study (70 718 cases of Alzheimer's disease and 282 862 controls) reported no significant association between PPI use and Alzheimer's disease [31]. Thus, patients and providers should be reassured that accumulative data indicate a lack of a causal relationship between PPI use and changes in cognitive function.

Myocardial infarction and stroke

The evidence linking PPIs to an increased risk of major adverse cardiac events has been weak. A 2017 meta-analysis of 17 GERD trials reported a hazard ratio of only 1.7 for patients taking PPIs [32]. The quality of evidence, however, was moderate or low, cardiovascular outcomes were not study endpoints and confounding variables such as obesity, smoking, alcohol and family history were not assessed.

Three studies were subsequently published, in 2018, that support the cardiovascular safety of PPIs. A Danish registry study of 214 998 individuals, without prior history of MI or stroke who underwent an elective upper endoscopy between 1997 and 2012, reported only a minimal increase in ischaemic stroke and MI for current PPI users (hazard ratio, 1.13 and 1.31, respectively) [33]. Although obesity, smoking and exercise status were addressed, a major limitation of this and all such observational studies is the inability to correct for unmeasured confounding variables and medication adherence.

A United States study, using a large administrative database of 80 million individuals covered by commercial and Medicare supplemental plans, reported no evidence that prescription PPIs increased risk of MI compared with prescription H2RAs [34]. Patients diagnosed with an MI within 1 year of the first prescription claim were excluded.

Another United States study of 68 514 women (mean age, 65 ± 7 years) enrolled in the Nurses' Health Study and 28 989 men (mean age, 69 ± 8 years) enrolled in the Health Professionals Follow-up Study report no increased risk of stroke in regular PPI users [35]. The individuals were followed biennially with detailed questionnaires and follow-up rates exceeded 90%.

Bone fracture

Although there may be some evidence suggesting an association between PPIs and osteoporosis, the evidence linking PPIs to bone fracture is more tenuous [36,37]. It has been proposed that PPIs may induce bone fracture by reducing calcium absorption and/or increasing falls due to vitamin B12 deficiency. A Finnish nested case-control study using a nationwide database of elderly patients with Alzheimer's disease, half of which used PPIs, found no association between PPIs used for longer than a year and hip fracture [37].

Drug interaction

It is conceivable that PPIs, by increasing gastric pH, could adversely affect the bioavailability and absorption of certain medications. Although the package insert for direct-acting antiviral medications used to treat hepatitis C cautions against concomitant use of PPIs, a recent secondary analysis of data from six phase III trials of ombitasvir, ritonavir and dasabuvir with or without ribavirin reports that PPI use was not a predictor of treatment failure [38]. A subsequent meta-analysis, however, comprising nine cohort studies with 32 684 participants, reports that use of PPIs was associated with a lower odds of

achieving a sustained virologic response (1.4-fold increased risk of failure) [39]. There are some data to suggest that twice-daily PPI, but not once daily, may be associated with a lower OR for treatment success [40].

PPIs might affect the absorption and therefore the effectiveness of certain chemotherapeutic drugs. Preclinical data indicate that a number of tyrosine-kinase inhibitors rely on pH-dependent solubility to dissolve within the stomach and be absorbed. Capecitabine is an oral 5-fluorouracil prodrug used in the adjuvant treatment of gastrointestinal cancer. A secondary analysis of TRIO-013, a phase III randomized trial, comparing capecitabine and oxaliplatin with or without lapatinib in 545 patients with metastatic gastroesophageal cancer, reports that PPI use, identified by medication records, was associated with a poorer progression-free and overall survival [41].

Death

Although PPI associations with cardiac events and dementia have largely been debunked and concerns assuaged, a recent study associating PPI use with a higher risk of death has grabbed attention and rekindled unnecessary angst and alarm [42]. Researchers mined administrative data from the U.S. Department of Veterans Affairs to evaluate the risk for all-cause mortality in mainly white male veterans who began taking PPIs ($n=275\,933$) or H2RAs ($n=73\,355$) between October 2006 and September 2008. Over a median follow-up of 5.7 years, PPIs were associated with a minimal increased risk for death compared with no PPI (hazard ratio, 1.15) and to H2RAs (hazard ratio, 1.25). The cause of death was not collected and there is no clear mechanism to explain the association. As discussed previously for these types of retroactive analyses of large databases, patients using antisecretory medications, especially PPIs, are different from patients not taking these medications, that is confounding by indication; the patients are sicker, have more severe degrees of disease and have increased exposure to the healthcare system itself, including hospitalizations. Thus, this study provides no convincing evidence that PPI use is the cause of the excess deaths.

CONCLUSION

PPIs are well tolerated and effective. Despite the ever-increasing number of associations and the widespread media coverage with accompanying brouhaha, the quality of the evidence linking PPIs to a wide range of serious adverse effects is very low.

When PPIs are prescribed appropriately, the benefits greatly outweigh potential adverse effects. The absolute risk to an individual is extremely low (less than 1 in 500) and fear of these risks should not dictate prescribing habits. PPIs should be prescribed for patients with GERD, especially those with erosive esophagitis and strictures, as well as for patients at an increased risk for ulcer-related bleeding from NSAIDs, aspirin, and dual antiplatelet therapies. In those patients without a valid indication, PPIs should be discontinued.

Not only has the information derived from these observational studies been unhelpful, but also the unattended consequence is that patients who require PPIs to prevent UGI bleeding are not receiving these medications, mainly due to fear on the part of the patient and provider. Gastroenterologists and primary care providers, who already have limited time to spend with their patients, are incessantly spending additional time discussing and reassuring their patients, both when initiating treatment and on every follow-up visit. Established benefits are being obfuscated by potential unproven risks. We, physicians and researchers, are to blame, both as authors for sensationalizing conclusions and as reviewers for accepting the studies for publication. There used to be a time, not long ago in the galaxy, when science sold itself. Now, investigators must 'sell' their research in order to get published and funded, and journals are more than willing to publish controversial less than optimally executed studies in an effort to improve their impact factor. Although one may argue that these studies, with overstated conclusions that imply but cannot demonstrate cause and effect, ought not to be published, perhaps it can be more strongly argued that, if published, authors must be mandated to strongly indicate that such associations are weak and more likely to be caused by confounding variables both in the study itself and media interviews, conclusions should be tempered and derived the data without added hyperbole, articles should not be published, especially in high impact journals, for the sake of publicity for the journal, and editorials should accompany the papers that place the findings in appropriate context and caution about misinterpretation.

There is no question that PPIs are overprescribed. It has been estimated that 30–50% of prescriptions for PPIs may be inappropriate [43]. When PPIs are prescribed long-term, they should be used at the lowest effective doses and the need for their use should be periodically reassessed.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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