Review

Proton Pump Inhibitors: More Indigestion than Relief?

Abstract

Proton pump inhibitors (PPIs) are widely prescribed to treat a number of gastrointestinal (GI) disorders due to excessive acid production. While effective and safe, adverse renal effects have been increasingly described in epidemiological literature. The most well-documented adverse renal outcome is acute interstitial nephritis; however, association with overall acute kidney injury has also been recently reported. Recently, two observational studies have linked PPI use with chronic kidney disease. Finally, hypomagnesemia is another reported complication and is thought to be resulting from GI loss of magnesium. This study will critically review literature on the effect of PPIs on the kidney.

Keywords: *Acute interstitial nephritis, acute kidney injury, chronic kidney disease, hypomagnesemia, proton pump inhibitors, transplant rejection*

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Introduction

Now, peptic ulcer disease only infrequently requires surgery although it was once the most common indication for gastric surgery. Over the past several decades, the development of potent antisecretory agents (initially histamine-2 [H2] blockers and then proton pump inhibitors [PPI]) and the recognition that eradication of *Helicobacter pylori* infection (medical equivalent of vagotomy) can eliminate most ulcer recurrences have relegated definitive surgery to the chapters of surgical textbooks.[1] Combinations of multiple antibiotics, coupled with acid-reducing agents, usually PPIs, have been the mainstay of these regimens. With these regimens, cure rates >80% (intent to treat) have been reported.[2] First introduced in the late 1980s (introduction of omeprazole in 1989), PPIs have demonstrated gastric acid suppression superior to that of histamine H2-receptor blockers and, hence, are currently the main therapy for gastroesophageal reflux disease, peptic ulcer disease, nonulcer dyspepsia, and prevention of gastropathy while using nonsteroidal anti-inflammatory drugs (NSAIDs).[3] The broad spectrum of indications, high efficacy, and a favorable safety profile have made them one of the most frequently used pharmaceuticals worldwide. In fact, the favorable safety profile has led to some of these agents becoming available over the counter. However, as the use of PPIs has expanded, there have been concerns about safety and are being looked at more critically. The most common unwanted effects reported are headaches, abdominal pain, and diarrhea;[4] however, other more serious, though uncommon, adverse effects are now being reported. Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) often have gastrointestinal (GI) complications, such as chronic bleeds, gastritis, ulcers, nausea, vomiting, gastroesophageal reflux disease, and stasis.[5-8] Given their predominantly hepatic metabolism, PPIs are also easy to use in patients with reduced kidney function.

Estimate of Use

According to a review of the use of medicines in the United States in 2013, more than 15 million Americans used prescription PPIs in 2013, costing more than $10 billion US dollars,[9] with an additional unknown quantity of users of over-the-counter (OTC) PPIs. Specifically, in patients with kidney disease, a small study suggested a high consumption of acid-suppressing therapy (AST), 93%

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of which were PPIs in patients on dialysis (compared to other chronic diseases and hospitalized patients). The use of AST had, in the majority (63%) of cases, no adequate indication. Majority of patients with a chronic illness—CKD, pulmonary disease, or rheumatic disease—were on long-term AST (>8 weeks). Empiric PPI treatment of uninvestigated dyspepsia in patients younger than 45 years old without alarming symptoms may be a cost-effective and safe approach. However, the mean age in this study population was 65 years, suggesting possible underuse of diagnostic endoscopy and overuse of PPIs.[10]

In the dialysis literature,[11] the Dialysis Outcomes and Practice Patterns Study data (8628 prevalent patients in 308 dialysis facilities) showed a relatively consistent overall prescription rate of about 36% to 38% of AST, suggesting that prescription rates in this population are several times greater than in the general population. The prescription of H2-blockers has experienced an overall decline, mirrored by an increase of a similar magnitude in the prescription of PPIs. There was a large variation in the extent of prescription of the different ASTs, both between countries and within different facilities. Facility use of H2-blockers and PPIs ranged from 0% to 94% of patients, suggesting that there is no standard approach in treatment practices. There were strong associations between GI medication prescription and several comorbidities and concomitant medications. It has been speculated that the overuse in patients with CKD may be related to polypharmacy, comorbidities, hypergastrinemia,[12] or the involvement of many physicians in their care.

Pharmacology of Proton Pump Inhibitors

PPIs are substituted benzimidazole derivatives and are available as enteric-coated tablets or capsules that pass through the stomach intact and get absorbed in the proximal small bowel. Once absorbed, all PPIs have a relatively short plasma half-life (about 1–2 h) but a much longer duration of action because of their unique mechanism of action [Table 1]. PPIs are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus. In this acidic environment, the PPI becomes protonated, producing the activated sulfenamide form of the drug that binds covalently with the H+/K+-ATPase enzyme that results in irreversible inhibition of acid secretion by the proton pump.[13-15] The only way the parietal cell can resume acid secretion is by producing new proton pumps or activating resting pumps.[13,14] In contrast to the other PPIs, rabeprazole forms a partially reversible bond with the proton pump and is activated at a broader range of gastric pH. Therefore, it may have a more sustained acid-suppressing effect than the other PPIs.[13,14,16]

Commonly Reported Adverse Effects of Proton Pump Inhibitors

PPIs are generally well tolerated with a frequency of adverse effects similar to that of placebo, and an overall incidence of <5%. The type and frequency of adverse effects are similar to those observed with H2-receptor blockers. The most common adverse effects are headache, diarrhea, abdominal pain, and nausea. Except for diarrhea, the adverse effects of PPIs do not appear to be related to age, dosage, or duration of treatment. Diarrhea might be related to the profound acid suppression, which has been shown to alter the bacterial content of the gut from colonization by ingested pathogens. Nevertheless, the overall incidence of diarrhea is <5%, and this effect appears to be dose and age related. The short-term safety of all the PPIs has been well established. PPIs are only contraindicated if the patient has a known history of hypersensitivity to them.[17-19] Omeprazole is a pregnancy Category C agent; the others are pregnancy Category B medications. PPIs are not recommended in breast-feeding mothers.[20-24] Unfortunately, for adverse effects which are uncommon, or occur after a longer duration of action, premarketing Phase 3 studies are not helpful. The role of postmarketing surveillance (so-called pharmacovigilance) is hence critical. For PPIs, several recent observational studies have linked their use to hip fracture,[25] community-acquired pneumonia,[26] and clostridium difficile infections[27] and more recently dementia,[28] apart from the kidney problems.

Acute Kidney Injury with Proton Pump Inhibitor Use

In 1992, a sentinel case report identified the PPI omeprazole as a possible cause of acute interstitial nephritis (AIN) in an elderly woman.[29] Overall, the available studies suggest that AIN (of any cause) accounts for about 6%–8% of cases of acute renal failure.[30,31] The diagnosis of AIN is most common in renal failure with an inactive urinary sediment (no hematuria or proteinuria); in this setting, it has been reported to occur in 27% of cases.[32] In contrast, AIN occurs in 1% of renal biopsies performed for the evaluation of hematuria or proteinuria.[33] While AIN is most often induced by medications (this accounts for over two-thirds of cases), it can also be due to infections, tubulointerstitial

Table 1: Pharmacokinetics of orally available proton pump inhibitors

Characteristic	Omeprazole	Lansoprazole	Rabeprazole	Pantoprazole
Bioavailability (%)	30-40	80-85	52	77
Time to peak plasma concentration (h)	0.5-3.5	1.7	1.0-2.0	1.1-3.1
Half-life (h)	0.5-1.0	1.3-1.7	1.0-2.0	1.0-1.9
Protein binding	95	97	96	98
Urinary excretion of oral dose (%)	77	14-23	30-35	71-80

nephritis and uveitis syndrome, sarcoidosis, or it may be idiopathic.[34,35] Among the most commonly implicated medications are antibiotics, especially quinolones, NSAIDs, diuretics, and more recently PPIs.[34]

PPI-induced interstitial nephritis is an idiosyncratic reaction of hypersensitivity to the medication or its metabolites and is not related to the dosage. In a systematic review in 2007,[36] looking at the development of interstitial nephritis and acute renal failure (determined by laboratory tests [creatinine and/or glomerular filtration rate, plus either renal biopsy or recurrence upon reinitiating PPI]), 64 cases (60% females, mean age 78 years, published in the 15 years before this review) of PPI-associated interstitial nephritis were found, of which 60 were included (59 confirmed by renal biopsy, one by recurrence upon reinitiating PPI). The most common symptoms were nonspecific, such as nausea and malaise. All the PPIs available were implicated. The interval between PPI initiation and AIN ranged from 2 to 52 weeks though about two-thirds were within 12 weeks. Three of the 60 cases (5%) required dialysis though only one remained on permanent dialysis. Although renal function recovered in the others, the postrecovery creatinine was higher, suggesting an element of chronic irreversible damage.

A large, retrospective, nested case–control study[37] sought to determine whether an association exists between renal injury and PPI use and, in turn, estimate an effect size for this association using data from an insurance database of a single midwestern state (Nebraska, USA). Patients included in the study were 18 years or older, diagnosed with renal disease for at least 12 months, and continuously enrolled with the insurer for at least 24 months between September 2002 and November 2005. PPI exposure status was obtained through prescription claims. Renal disease was defined on the basis of the International Classification of Diseases, Ninth Revision codes, and included codes for both acute and CKD. PPI use was positively associated with renal disease (odds ratio [OR]: 1.72, 95% confidence interval [CI]: 1.27–2.32, $P < 0.001$) even after controlling for potential confounding conditions, providing the first estimate of an effect size for this association. After excluding patients with potential confounding disease states from the study population, the relationship between renal disease and PPI use remained consistent (OR: 2.25, CI: 1.09–4.62, $P < 0.001$). The inclusion of a propensity score in the model did not change the relationship between PPI use and renal disease (OR: 2.05, CI: 1.52–2.72). Analyses of H2-blockers showed that a statistically significant relationship between H2-blocker use and renal disease was not present (OR: 1.37, CI: 0.46–4.13).

A subsequent population-based cohort study, in Ontario, Canada,[38] involving nearly 600,000 patients used propensity score matching to establish a highly comparable reference group of control patients. Apart from excluding patients with other concomitant potentially contributing illnesses, individuals newly prescribed other medications associated with AIN, including NSAIDs, loop and thiazide diuretics, anticonvulsants, and H2-receptor antagonists, were also excluded from the study. Those who commenced treatment with PPIs had a more than two-fold increase in rates of acute kidney injury (AKI) (13.49 vs. 5.46 per 1000 person-years, respectively; hazard ratio [HR]: 2.52, 95% CI: 2.27–2.79) and AIN (0.32 vs. 0.11 per 1000 person-years; HR: 3.00, 95% CI: 1.47–6.14) in hospital admission diagnoses. With sensitivity analyses, a similar increase in the risk of AKI was seen among patients receiving PPIs when censoring patients on admission to hospital for infection (HR: 2.52, 95% CI: 2.27–2.79) or on receipt of other drugs (e.g., antibiotics) classically associated with AIN (HR: 4.03, 95% CI: 3.29–4.92). The respective HRs for AIN were 3.22 (95% CI: 1.53–6.81) and 3.25 (95% CI: 1.06–9.97). Similar results were found in an analysis stratified by individual PPIs, substantiating the class effect. There was no meaningful association between PPI use and cataract surgery (HR: 0.97, 95% CI: 0.93–1.00) – the null association enhancing the causal inference. In addition, more than half (59%) of the patients in this study, on discharge from the hospital, received another prescription for a PPI in the ensuing 100 days. Of these patients, 7.5% were readmitted to hospital with AKI in the ensuing 120 days, consistent with a causal role of PPIs in some instances, providing the first estimate of the risk of drug rechallenge. This also highlights the lack of awareness among clinicians of the potential association between these drugs and renal disease.

Proton Pump Inhibitors Use and Chronic Kidney Disease

A recently published article in *JAMA*[39] looked at PPI use and the risk of CKD in two large cohorts, 10,482 participants in the Atherosclerosis Risk in Communities (ARIC) study group and 248,751 patients in the Geisinger Health System. In the ARIC study, PPI use was associated with incident CKD in unadjusted analysis (HR: 1.45; 95% CI: 1.11–1.90); in the analysis adjusted for demographic, socioeconomic, and clinical variables (HR: 1.50; 95% CI: 1.14–1.96); and in the analysis with PPI ever use modeled as a time-varying variable (adjusted HR: 1.35; 95% CI: 1.17–1.55). The association persisted when baseline PPI users were compared directly with H2-receptor antagonist users (adjusted HR: 1.39; 95% CI: 1.01–1.91) and with propensity score-matched nonusers (HR: 1.76; 95% CI: 1.13–2.74). The 10-year estimated absolute risk of CKD among the baseline PPI users was 11.8% while the expected risk had they not used PPIs was 8.5% (absolute risk difference, 3.3%, which would correspond to a number needed to harm of only 30).

In the Geisinger Health System replication cohort, PPI use was significantly associated with incident CKD in

unadjusted analyses (HR: 1.20; 95% CI: 1.15–1.26; $P < 0.001$), in adjusted analyses (adjusted HR: 1.17; 95% CI: 1.12–1.23; $P < 0.001$), and when estimated using a time-varying ever-use model (adjusted HR: 1.22; 95% CI: 1.19–1.25; $P < 0.001$). Twice-daily PPI dosing (adjusted HR: 1.46; 95% CI: 1.28–1.67; $P < 0.001$) was associated with a higher risk of CKD than once-daily dosing (adjusted HR: 1.15; 95% CI: 1.09–1.21; $P < 0.001$). The 10-year absolute risk of CKD among the baseline PPI users was 15.6%, and the expected risk had they not used PPIs was 13.9% (absolute risk difference, 1.7%, corresponding to a number needed to harm of 59). The use of H2-receptor antagonists was not associated with increased risk of incident CKD in either cohort (adjusted HR: 1.15; 95% CI: 0.98–1.36; $P = 0.10$ in the ARIC study and adjusted HR: 0.93; 95% CI: 0.88–0.99, $P = 0.03$ in the replication cohort). This study provides a first possible association between use and incident CKD.

In the same study, PPI use also resulted in a higher risk of incident AKI. Twice-daily PPI dosing (adjusted HR: 1.62; 95% CI: 1.32–1.98; $P < 0.001$) was associated with a higher risk of AKI than once-daily dosing (adjusted HR: 1.28; 95% CI: 1.18–1.39; $P < 0.001$) showing a biological gradient.

The finding of the link between PPI and incident CKD was corroborated in a study of about 200,000 veterans. In adjusted Cox survival models, users of PPIs compared with H2-blocker users[40] had an increased risk of incident estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 and of incident CKD (HR: 1.22; 95% CI: 1.18–1.26; and HR: 1.28; 95% CI: 1.23–1.34, respectively). Patients treated with PPI also had a significantly elevated risk of doubling of serum creatinine level (HR: 1.53; 95% CI: 1.42–1.65), of eGFR decline >30% (HR: 1.32; 95% CI: 1.28–1.37), and of ESRD (HR: 1.96; 95% CI: 1.21–3.18). Furthermore, they detected a graded association between duration of PPI exposure and risk of renal outcomes among those exposed to PPI for 31–90, 91–180, 181–360, and 361–720 days compared with those exposed for ≤30 days.

Finally, a small, single-center retrospective study published this year (2016) also linked PPI use to a higher risk of biopsy-proven acute rejection in kidney transplant recipients (16/171, 9.4% vs. 3/113, 2.6%; $P = 0.03$).[41]

Proton Pump Inhibitors use and Hypomagnesemia

Magnesium (Mg), one of the most abundant elements on the Earth and the fourth most abundant cation in the human body, is an integral part of ATP, nucleic acids, and a cofactor to hundreds of enzymes. As it is excreted by the kidneys, its level rises with declining kidney function, and in dialysis patients, dialysate Mg plays a critical role in Mg homeostasis. Of interest to the renal community has been the association between PPIs and hypomagnesemia, which was again substantiated in a population-based cohort study in the general population (involving 9,818 individuals),[42] which showed PPI use was associated with increased risk of hypomagnesemia (OR: 2.00; 95% CI: 1.36–2.93) compared to no use. Effect modification was found between the use of PPIs and loop diuretics; in participants using loop diuretics, PPI use was associated with a further increased risk of hypomagnesemia (OR: 7.22; 95% CI: 1.69–30.83) compared to no use. The increased risk with PPIs was only seen after prolonged use (range, 182–2618 days; OR: 2.99; 95% CI: 1.73–5.15). To analyze whether PPI-induced hypomagnesemia could be explained by confounding by indication, sensitivity analyses were performed with serum phosphate level, dietary Mg intake, and use of vitamin and mineral supplementation. No significant association was found between PPI use and serum phosphate level (0.006 [95% CI: 0.028–0.040] mg/dl) compared to no use, suggesting that the indication for PPIs did not result in poor dietary intake and, therefore, lower serum Mg and phosphate levels. Including dietary Mg intake into the model also did not alter results.

The basis for the Mg-lowering effect of PPIs has yet to be fully elucidated; the finding of low urinary Mg levels suggests that Mg depletion occurs in the GI tract. While passive absorption accounts for most of the GI Mg uptake, carrier-mediated pathways involving TRPM-6 (transient receptor potential cation channels) and TRPM-7 are also known to be critical to GI Mg homeostasis.[43] While it has been suggested that the major mechanism by which PPIs induce Mg wasting is through TRPM-6 and TRPM-7 inhibition[44] (caused by changes in intestinal pH), there is also some evidence that interference with the passive absorption mechanism may underlie this phenomenon.[45] To support this, a recent cross-sectional study[46] conducted in hemodialysis patients with minimal residual renal function revealed that PPI use was associated with lower serum Mg levels as compared with nonusers (even after stratifying for dialysate Mg concentration).

Severe hypomagnesemia may result in tetany, convulsions, or cardiac arrhythmias.[47] Mild hypomagnesemia is often asymptomatic, but it may still be relevant as population studies have shown that even mild hypomagnesemia is associated with increased risk of diabetes mellitus,[48] osteoporosis,[49] cardiovascular disease,[50,51] and mortality.[52] In addition, in another report from the ARIC study,[53] low serum Mg levels (0.7 mmol/L or less) had significant associations with incident CKD and ESRD compared with the highest quartile with adjusted HR of 1.58 (95% CI: 1.35–1.87) for CKD and 2.39 (95% CI: 1.61–3.56) for ESRD. These associations remained significant after excluding users of diuretics and across subgroups stratified by hypertension, diabetes, and self-reported race.

Previous studies have suggested that serum Mg may influence kidney function through the regulation of vascular and endothelial function.[54] The rate of circulating Mg transport into a cell varies depending on tissue and cell type.[55] The endothelial cell, which expresses the Mg transporter TRPM7,[56] may be more readily influenced by circulating Mg. *In vitro* studies have shown that low extracellular Mg levels inhibit endothelial cell proliferation[57] and promote the expression of inflammatory biomarkers. Low Mg levels have also been shown to promote vascular calcification in both *in vitro*[58] and *in vivo* studies. Further, serum Mg levels may affect the endothelium through a thrombotic process since low circulating Mg levels increase platelet aggregation[59] and have a prothrombotic effect in animal studies.[60] Chronic inflammation and hemostatic biomarkers have also been linked to kidney function decline.[61] Overall, some of these effects may underlie the adverse clinical outcomes reported with hypomagnesemia, including the renal effects.

Finally, PPI-induced hypomagnesemia is also relevant to ESRD patients. Three large observational studies[62-64] have reported a strong association between hypomagnesemia and mortality in hemodialysis patients despite controlling for a swath of confounders. Although not all the hypomagnesemia seen in ESRD patients is definitively from PPI, PPI overuse could certainly be playing a role in some patients.

Association or Causation?

Most of the studies discussed are observational, cohort, or cross-sectional studies [Table 2] which can only show an association and, hence, cannot prove causality between PPI use and AKI/CKD or hypomagnesemia. Participants who are prescribed PPIs may be at a higher risk of CKD/AKI for reasons unrelated to their PPI use. For example, PPI users in both ARIC study and replication cohort in the JAMA study were more likely to be obese, have a diagnosis of hypertension, and carry a greater burden of prescribed medications. The use of adjustment with regression, and even more so with propensity score matching, attenuates the effect of confounding; however, some elements of residual confounding may still be present [Figure 1]. Indeed, the associations of PPI use with multiple clinical outcomes, apart from the renal issues, such as fractures, diarrhea, and dementia, may only be representative of the PPI use being a marker for a patient phenotype at high risk for adverse outcomes. Even with AIN, cause and effect is not always easy to prove, given that most patients are on multiple drugs. The effect of rechallenge, reported in one of the studies, with 7.5% developing AKI again, is a more specific measure. Conversely, baseline users may represent a special group of PPI users who tolerate the medication without the development of CKD leading to selection bias.

In recent years, PPIs have become available over the counter. Therefore, medication exposure may have been misclassified, with an unknown proportion of patients in the nonexposed (or control) group also taking a PPI. This would bias an analysis toward the null, thus strengthening the validity of association reported. Other OTC medication use is also not captured, importantly NSAIDs. It is indeed quite plausible that PPI use also associates with NSAID use, and the increase in risk of AKI/CKD reported with PPI use is partly due to underlying NSAID use.

Surveillance bias (disease ascertainment) may be better in the monitored population than in the general population and could overestimate the impact of PPI exposure, especially with the relatively soft outcome of GFR < 60, as was used in the ARIC study. Many of the studies used hospital diagnosis codes, which have limited sensitivity, particularly for milder forms of the condition (AKI/CKD), which are less sensitive, and may indeed underestimate the true incidence and association. In addition, they relied on administrative data and, hence, had no access to laboratory indices of renal function, renal biopsy results, and treatment indication or medication adherence.

Similarly, with respect to the association of serum Mg, Mg is also closely associated with serum potassium,

Table 2: Summary of studies looking at proton pump inhibitor use and adverse outcomes

Author	Year of publication	Study design	Country	Outcome
Sierra *et al*.[36]	2007	Systematic review	USA	AIN
Klepser *et al*.[37]	2013	Nested case-control study	USA	AKI
Antoniou *et al*.[38]	2015	Population-based cohort study	Canada	AKI/ AIN
Lazarus *et al*.[39]	2016	Prospective cohort study	USA	CKD/ AIN
Xie *et al*.[40]	2016	Retrospective cohort study	USA	CKD
Courson *et al*.[41]	2016	Retrospective cohort study	USA	Acute rejection

CKD: Chronic kidney disease, AKI: Acute kidney injury, AIN: Acute interstitial nephritis

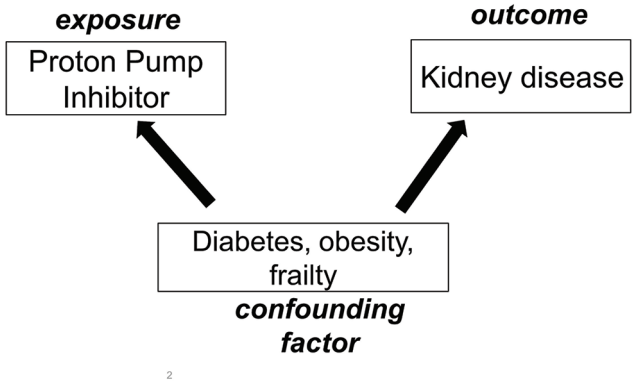
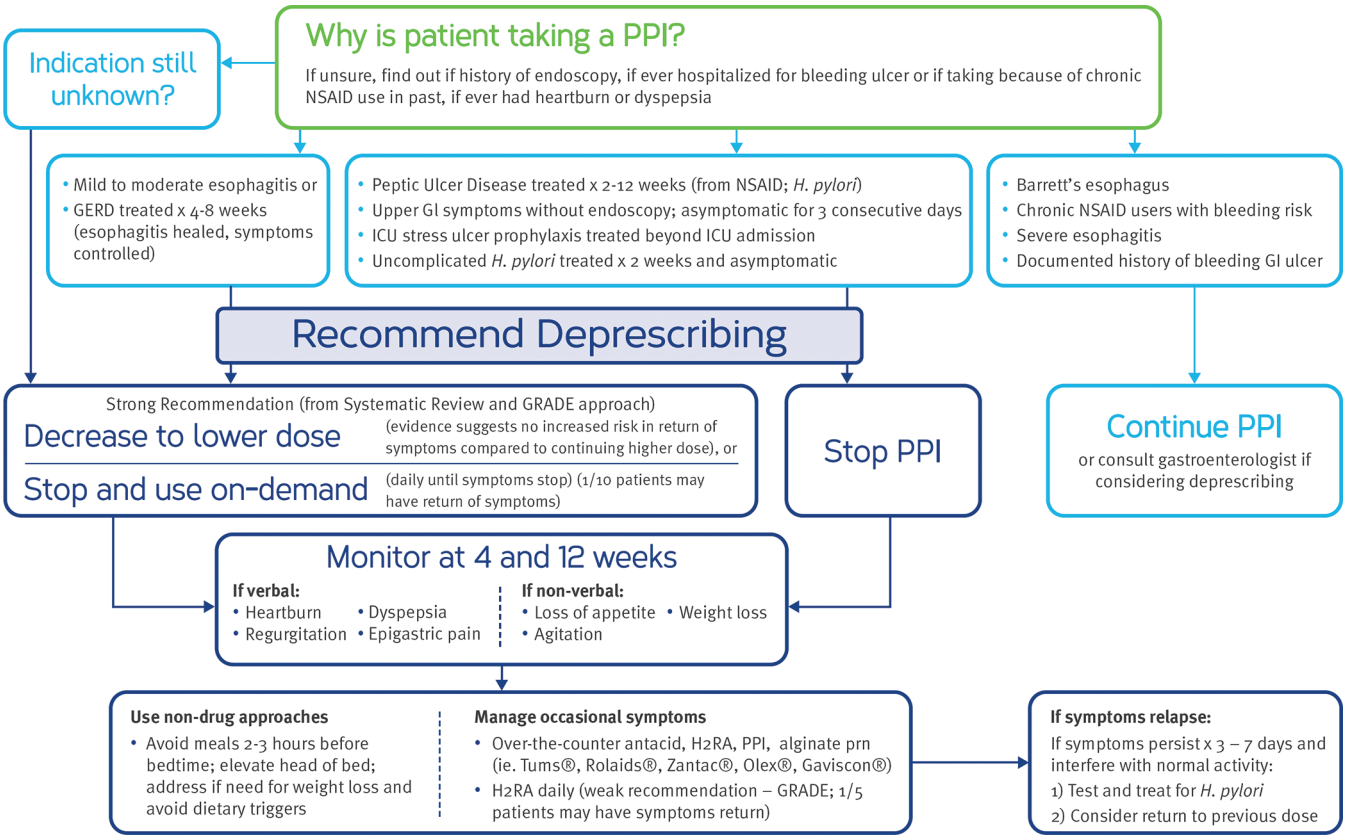


Figure 1: Exposure and outcomes with confounders



PPI Availability

PPI	Standard dose (healing) (once daily)*	Low dose (maintenance) (once daily)
Omeprazole (Losec®) - Capsule	20 mg+	10 mg+
Esomeprazole (Nexium®) - Tablet	20[a] or 40[b] mg	20 mg
Lansoprazole (Prevacid®) - Capsule	30 mg+	15 mg+
Dexlansoprazole (Dexilant®) - Tablet	30[c] or 60[d] mg	30 mg
Pantoprazole (Tecta®, Pantoloc®) - Tablet	40 mg	20 mg
Rabeprazole (Pariet®) - Tablet	20 mg	10 mg

Legend

a Non-erosive reflux disease

b Reflux esophagitis

c Symptomatic non-erosive gastroesophageal reflux disease

d Healing of erosive esophagitis

+ Can be sprinkled on food

***** Standard dose PPI taken BID only indicated in treatment of peptic ulcer caused by *H. pylori*; PPI should generally be stopped once eradication therapy is complete unless risk factors warrant continuing PPI (see guideline for details)

Key

GERD = gastroesophageal reflux disease

NSAID = nonsteroidal anti-inflammatory drugs

H2RA = H2 receptor antagonist

SR = systematic review

GRADE = Grading of Recommendations Assessment, Development and Evaluation

Engaging patients and caregivers

Patients and/or caregivers may be more likely to engage if they understand the rationale for deprescribing (risks of continued PPI use; long-term therapy may not be necessary), and the deprescribing process

PPI side effects

- When an ongoing indication is unclear, the risk of side effects may outweigh the risk of benefit
- PPIs are associated with higher risk of fractures, *C. difficile* infections and diarrhea, community-acquired pneumonia, vitamin B12 deficiency and hypomagnesemia
- Common side effects include headache, nausea, diarrhea and rash

Tapering doses

- No evidence that one tapering approach is better than another
- Lowering the PPI dose (for example, from twice daily to once daily, or halving the dose, or taking every second day) OR stopping the PPI and using it on-demand are equally recommended strong options
- Choose what is most convenient and acceptable to the patient

On-demand definition

Daily intake of a PPI for a period sufficient to achieve resolution of the individual's reflux-related symptoms; following symptom resolution, the medication is discontinued until the individual's symptoms recur, at which point, medication is again taken daily until the symptoms resolve

Figure 2: Deprescribing proton pump inhibitors

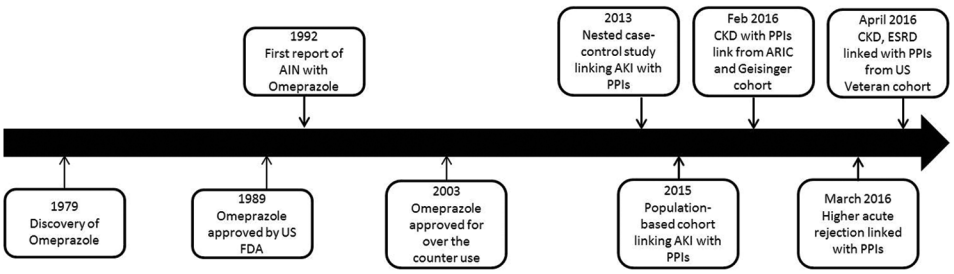


Figure 3: Chronological events of discovery of proton pump inhibitors and events

phosphate, albumin, and poor nutrition. Hence, although the association between Mg and mortality was attenuated and remained significant after adjustment in the studies, there could be residual confounding from other unmeasured factors at play.

Deprescribing Proton Pump Inhibitors

However weak the association between PPI use and kidney disease, it is rational to use PPI only when indicated and only for as long as indicated. Current data indicate that PPIs are often used when unnecessary, for longer than necessary, and on occasion when an H2-blocker might be sufficient. In addition, PPIs do not always need to be prescribed on a continuous basis and could also be sometimes used on an as-needed basis. Pharmacological debridement, in the form of deprescribing, can be a valuable tool in the hands of not only the nephrologist but also the general practitioners. Figure 2 shows an algorithm that could be used to evaluate PPI use and aid in deprescribing.

Conclusion

The favorable safety profile of PPIs is perhaps not so favorable with reports of uncommon adverse outcomes being regularly reported [Figure 3]. Observational cohort studies represent one of the best methods to study adverse effects of medications used in real-world settings. Given the millions of individuals who take PPIs each year and the fact that more than half of such prescriptions may not be clinically indicated, even a small absolute increase in risk of AKI/CKD may outweigh any benefit that might be derived from overuse of these drugs in many patients for whom they are prescribed. AIN is not preventable due to its idiosyncratic nature; therefore, it is important that emphasis is placed on timely recognition. Although it should not deter clinicians from prescribing PPIs for patients with well-defined indications and durations, the current evidence underscores the importance of ongoing efforts to curtail the indiscriminate use of these drugs. Discontinuation of inappropriately prescribed PPIs would have great economic implications leading to a reduced economic burden for health-care providers. Given the significant association of hypomagnesemia with mortality in our patients, it would be prudent to avoid any preventable cause, in this case, PPI-induced hypomagnesemia.

Several questions remain unanswered. If PPIs do have a direct causal role in the development of CKD, what could be the exact mechanism of CKD due to PPI use? Is it due to repeated episodes of AKI, or a hitherto unreported "chronic interstitial nephritis," or perhaps related to hypomagnesemia? Studies are needed to determine whether modification of serum Mg levels (and to what targets) might alter subsequent incident kidney disease rates and other hard outcomes such as mortality/hospital admissions.

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Conflicts of interest

There are no conflicts of interest.

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