Proton Pump Inhibitors and the Kidney: Implications of Current Evidence for Clinical Practice and When and How to Deprescribe

Ziyad Al-Aly, Geetha Maddukuri, and Yan Xie

Proton pump inhibitors (PPIs), long thought to be safe, are associated with a number of nonkidney adverse health outcomes and several untoward kidney outcomes, including hypomagnesemia, acute kidney injury, acute interstitial nephritis, incident chronic kidney disease, kidney disease progression, kidney failure, and increased risk for all-cause mortality and mortality due to chronic kidney disease. PPIs are abundantly prescribed, rarely deprescribed, and frequently purchased over the counter. They are frequently used without medical indication, and when medically indicated, they are often used for much longer than needed. In this In Practice review, we summarize evidence linking PPI use with adverse events in general and adverse kidney outcomes in particular. We review the literature on the association of PPI use and risk for hypomagnesemia, acute kidney injury, acute interstitial nephritis, incident chronic kidney disease, kidney disease progression, end-stage kidney disease, and death. We provide an assessment of how this evidence should inform clinical practice. We review the impact of this evidence on patients’ perception of risk, synthesize PPI deprescription literature, and provide our recommendations on how to approach PPI use and deprescription.

Clinical Vignette

A patient with a history of hypertension, congestive heart failure, and peptic ulcer disease underwent hospitalization and blood transfusion 6 months ago. He was treated with pantoprazole, 40 mg, once daily and a Helicobacter pylori eradication regimen and continued to be on pantoprazole treatment. He was admitted to the hospital from the primary care clinic following laboratory findings indicating an increase in serum creatinine (Scr) level from 1.4 to 5.4 mg/dL. During his hospital stay, Scr level continued to increase and peaked at 11 mg/dL. Workup revealed proteinuria with protein excretion of 700 mg/dL, and kidney biopsy revealed diffuse acute interstitial nephritis (AIN) and acute tubular injury. Pantoprazole was suspected as the likely culprit and because he had completed more than 6 months of treatment, it was stopped. He was treated with a steroid regimen and his Scr level improved to 1.7 mg/dL.

Six months after the hospitalization with AIN, the patient reported dyspepsia to his primary care physician, and treatment with oral omeprazole, 20 mg, once a day was started. On a follow-up visit, he was noted to have an Scr level of 8.6 mg/dL. He was then admitted to the hospital and underwent kidney biopsy that revealed acute-on-chronic interstitial nephritis. Omeprazole therapy was stopped, and he was treated with steroids. His kidney function partially improved with an Scr level of 3.2 mg/dL. The patient was subsequently managed with ranitidine with satisfactory symptom relief.

Introduction

Proton pump inhibitors (PPIs) are widely used for acid suppression therapy around the globe. They are commonly prescribed for several acid-related disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease, esophagitis, gastritis, Barrett esophagus, and (in addition to antibiotics) Helicobacter pylori eradication. They are also often prescribed for prophylactic indications and as co-prescription with nonsteroidal anti-inflammatory drugs (NSAIDs).

The number of US adults using prescription PPIs is estimated to be around 15 million (estimated prevalence of 7.8% in the US adult population). The true prevalence of PPI use is likely much higher because they are also available for purchase without prescription. Reports from market research groups suggest that in 2017, over-the-counter sales of “heartburn” medications, in which PPIs have a market share of 85%, were 385 million units with an estimated cost of $2.6 billion. The prevalence of PPI use in the chronic kidney disease (CKD) population is likely higher than for patients without CKD because some studies suggest that patients with CKD are prescribed more PPIs and for longer durations than patients without CKD.
PPIs are often used for indications and for lengths of time that were never tested or approved by the US Food and Drug Administration (FDA). They are frequently overprescribed, rarely deprescribed, and often initiated inappropriately during hospitalization, and their use is continued for the long term even in the absence of medical indication. Between 53% and 69% of PPI prescriptions are estimated to be for inappropriate indications for which the benefits of PPI use (or lack thereof) may not justify the risks in many cases.

**Adverse Effects of PPIs**

**Overview**

Until recently, PPIs were perceived to be safe. This perception was challenged with the emergence of evidence from multiple observational studies and some mechanistic studies suggesting increased risk for serious adverse health outcomes and death. Evidence from these studies suggests that PPI use is associated with increased risk for cardiovascular disease, gastric cancer, dementia, pneumonia, osteoporotic fractures, *Clostridioides difficile* infections, and others.

Recent evidence from studies using a causal inference approach to evaluate the comparative effect of PPIs and histamine H2-receptor antagonists (H2 blockers) on risk for all-cause and cause-specific mortality suggests that PPI use is associated with an increased burden of all-cause mortality and increased burden of death due to cardiovascular disease, CKD, and upper gastrointestinal cancer.

A number of studies have provided evidence linking PPI use and increased risk for hypomagnesemia, acute kidney injury (AKI), and AIN. More recently, several large epidemiologic studies have suggested a strong and consistent association between PPI use and increased risk for incident CKD, CKD progression, and kidney failure. These findings are particularly alarming because these outcomes are associated with increased risk for morbidity, mortality, and substantial economic cost. These studies generated widespread concern among stakeholders, including patients, physicians, regulatory agencies, and the public at large.

In this In Practice review, we summarize the studies linking PPIs with adverse kidney outcomes, evaluate the implications of these studies for clinical practice, and discuss potential strategies of addressing safety concerns, including implementation of deprescription mechanisms.

**PPIs and Hypomagnesemia**

Between 2006 and 2008, several anecdotal reports suggested that hypomagnesemia may be a previously unrecognized adverse event associated with PPI use. These initial observations were followed by several case series, cross-sectional analyses, and a few cohort studies representing various populations (including the general population, hospitalized patients, and critically ill patients in the intensive care unit). Evidence from all these studies suggests that PPI use is associated with increased risk for hypomagnesemia, the risk is amplified in patients concomitantly using diuretics, and the risk is increased with prolonged duration of PPI exposure.

PPI use is also associated with increased risk for hypomagnesemia in patients with CKD, including those receiving maintenance hemodialysis, but evidence in kidney transplant recipients remains scarce.

Several systematic reviews and meta-analyses have since echoed these findings of a significant association between PPI use and risk for hypomagnesemia and suggested that the risk is further increased in patients taking diuretics (either thiazide or loop diuretics) and was more pronounced in those taking PPIs for extended durations (≥1 year). In March 2011, the FDA issued a drug safety announcement to inform the public that prescription PPIs may “cause low serum magnesium levels (hypomagnesemia) if taken for prolonged periods of time (in most cases, longer than one year)” and that “magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued.”

**PPIs and AKI**

A sentinel case report by Ruffenach et al in 1992 was followed by several anecdotal reports and multiple cross-sectional and cohort studies reporting a consistent
association between PPI use and risk for AIN. A study suggested that owing to the high prevalence of PPI use, this class of acid suppressants may be the leading cause of drug-induced AIN. 45,54 Elegant studies by Blank et al29 are noteworthy in that the investigators developed a nested case-control analysis and provided evidence for increased risk for AIN among current PPI users versus an active comparator control of past PPI users, to some extent lessening concerns about confounding by indication (because both groups received PPIs) and providing evidence for temporality between exposure to PPI and occurrence of AIN that may enhance the case for causality. Other large studies reported increased risk for hospital admission with AIN for PPI exposure. 28 The associations between PPI use and risk for AIN and AKI have since been consistently reproduced in multiple other studies. 29,31-34,67-70 Taken together, the constellation of evidence strongly suggests that PPI use should be considered as a putative culprit in the evaluation of AIN and AKI, especially in the hospitalized setting.

PPIs and CKD

During the past several years, substantial evidence has accumulated from multiple large cohort studies suggesting that PPI use is associated with increased risk for CKD outcomes (incident CKD, CKD progression, and kidney failure). 9,41,71-75 (Table 1). Studies have consistently described a graded increase in risk with higher doses and more prolonged duration of PPI therapy. 9,71,75,76 The question of whether the occurrence of AKI or AIN is driving the increased risk for CKD outcomes associated with PPI use was investigated in a study by Xie et al. 41 The investigators found that a significant proportion (nearly 50%) of the association between PPI use and risk for CKD outcomes is not mediated by the occurrence of intervening AKI or AIN, suggesting a direct pathway of indolent chronic kidney injury. 41 The clinical importance of this study lies with the conclusion that relying on antecedent AKI to warn of the risk of incident CKD and its progression among PPI users is not, on its own, sufficient as a mitigation strategy. 41

Several other observational studies have since reported consistent associations between PPI use and CKD outcomes in multiple other cohorts. 67-72,75-77 Several meta-analyses have also supported the association between PPI use and increased risks for incident CKD, CKD progression, and kidney failure. 67-69,74 The sum of evidence woven together suggests that prevention strategies and efforts aimed at reducing the risk for CKD progression should address PPI use as a likely contributor to risk for the development and progression of CKD.

Table 1. Selected Studies on the Association of PPIs and Risk for Incident CKD, CKD Progression, or ESKD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Characteristics</th>
<th>Outcome(s)</th>
</tr>
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<tbody>
<tr>
<td>Arora et al 73</td>
<td>Population: 99,269 patients who were seen in primary care Study: case-control Exposure: PPI use during a quarter</td>
<td>PPI vs no PPI: OR of 1.15 (95% CI, 1.06-1.23) for development of CKD</td>
</tr>
<tr>
<td>Lazarus et al 71</td>
<td>Population: ARIC cohort with 10,482 participants and Geisinger cohort with 248,751 participants Study: cohort study Exposure: self-reported PPI use in the ARIC or outpatient PPI prescription in Geisinger</td>
<td>PPI vs H2 blocker use: HR of 1.39 (95% CI, 1.01-1.91) in ARIC cohort and 1.39 (95% CI, 1.01-1.91) in Geisinger cohort for incident CKD</td>
</tr>
<tr>
<td>Xie et al 9</td>
<td>Population: Department of Veterans Affairs 173,321 new users of PPIs and 20,270 new users of H2 blockers Study: cohort study Exposure: new use of PPI</td>
<td>PPI vs H2 blocker use: HRs of 1.28 (95% CI, 1.23-1.34) for incident CKD; 1.53 (95% CI, 1.42-1.65) for Scr doubling; 1.32 (95% CI, 1.29-1.37) for &gt;30% decline in eGFR; and 1.96 (95% CI, 1.21-3.18) for ESKD</td>
</tr>
<tr>
<td>Klatte et al 75</td>
<td>Population: Stockholm Creatinine Measurements health care utilization cohort with 105,305 new PPI users and 9,578 new H2 blocker users Study: cohort study Exposure: new use of PPI</td>
<td>PPI vs H2 blocker use: HRs of 1.28 (95% CI, 1.05-1.51) for Scr doubling and 1.26 (95% CI, 1.16-1.36) for &gt;30% eGFR decline</td>
</tr>
<tr>
<td>Xie et al 41</td>
<td>Population: Department of Veterans Affairs with 125,596 new users of PPIs and 18,436 new users of H2 blockers with no AKI Study: cohort study Exposure: new use of PPI</td>
<td>PPI vs H2 blocker use: HRs of 1.26 (95% CI, 1.20-1.33) for incident CKD; 1.22 (95% CI, 1.16-1.28) for &gt;30% eGFR decline, 1.30 (95% CI, 1.15-1.48) for ESKD or &gt;50% eGFR decline</td>
</tr>
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Note: Studies ordered by year of publication, then by first author’s last name.

Abbreviations: AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; OR, odds ratio; PPI, proton pump inhibitor; Scr, serum creatinine.
Table 2. Selected Studies on the Association of PPIs and Risk for All-Cause Mortality and Mortality Due to CKD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Characteristics</th>
<th>Outcome(s)</th>
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<tbody>
<tr>
<td>Xie et al14 (2017)</td>
<td>Population: Department of Veterans Affairs: Cohort 1 with 275,977 new users of PPIs and 73,335 new users of H2 blockers Cohort 2 with 3,288,092 PPI users and non–PPI users Cohort 3 with 2,886,879 PPI users and nonusers of acid suppression therapy Study: cohort study Exposure: new use of PPI</td>
<td>PPI vs H2 blocker use: adjusted HR of 1.25 (95% CI, 1.23-1.28), high-dimensional propensity score–adjusted HR of 1.16 (95% CI, 1.13-1.18), and instrumental variable–adjusted HR of 1.21 (95% CI, 1.16-1.26) for all-cause mortality PPI use vs no PPI use: HR of 1.19 (95% CI, 1.18-1.20) for all-cause mortality PPI use vs no PPI or H2 blocker use: HR of 1.22 (95% CI, 1.21-1.23) for all-cause mortality Graded association between cumulative duration of exposure to PPI and risk for death</td>
</tr>
<tr>
<td>Xie et al27 (2019)</td>
<td>Population: Department of Veterans Affairs with 157,825 new users of PPI and 56,842 new users of H2 blockers Study: cohort study designed to emulate a randomized trial Exposure: new use of PPI &gt; 90 d</td>
<td>PPI vs H2 blocker use: all-cause mortality: HR of 1.17 (95% CI, 1.10-1.24); excess burden of 45.20 (95% CI, 28.20-61.40) per 1,000 PPI users PPI vs H2 blocker use: death due to CKD: HR of 1.95 (95% CI, 1.26-2.89); excess burden of 4.19 (95% CI, 1.56-6.58) per 1,000 PPI users History of CKD does not modify the relationship between PPI and death due to CKD</td>
</tr>
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Note: Studies ordered by year of publication, then by first author’s last name.
Abbreviation: CI, confidence interval; CKD, chronic kidney disease; GI, gastrointestinal; HR, hazard ratio; PPI, proton pump inhibitor.

disease, CKD, and upper gastrointestinal cancer27 (Table 2). Of relevance to this review, excess death due to CKD that was attributable to PPIs was estimated at around 4.19 (95% CI, 1.56-6.58) deaths per 1,000 PPI users27 (Table 2). This excess burden of death was evident in patients without a documented indication for acid suppression drugs (4.74 [95% CI, 1.53-8.05] deaths per 1,000 PPI users) and was not modified by the presence of underlying CKD at baseline27 (Table 2). The findings are significant in that they provide evidence from causal inference studies linking PPI use to death due to CKD.

Implications for Prescribing and Deprescribing PPIs

Considering Evidence of Potential Benefits and Risks of PPIs

Studies of adverse kidney outcomes associated with PPI use are observational in nature.15 These associations have not been validated in randomized controlled trials (RCTs). However, RCTs may not represent the most practical approach to examine serious but infrequent adverse events associated with long-term use of a medication because they require large number of enrollees to be followed up for an extended duration. None of the published RCTs involving PPIs were sufficiently powered in terms of both number of participants and duration of follow-up to detect adverse kidney outcomes (and other adverse outcomes).15

In a narrative review on using alternatives to RCTs to inform health care decision making, Frieden remarked that for much modern clinical practice, RCT-based data are lacking; however, this “dark matter” should not be used as a reason “not to act, or to act on the basis of past practice rather than on the best available evidence”, arguing that “[g]lorifying RCTs above other approaches, even when these other approaches may be either superior or the only practical way to get an answer, relegates patients to receiving treatments that aren’t based on the best available evidence.”79,80 When real-world evidence suggests potential harm, both the precautionary principle and the Hippocratic principle of primum non nocere support use of a careful decision-making strategy, involving both patients and providers, that encourages careful weighing and balancing of potential benefit but also the realism of potential risks81,82 This approach will likely result in minimizing harm and maximizing benefit.81

Patients’ Perceptions of Risk

Because PPIs are one of the most commonly prescribed drug classes in the United States,83 studies reporting adverse events have been featured prominently in mainstream media84-93 and social media. This wide coverage may have influenced patients’ perception about risks. Using an online survey of US adults who use PPIs for GERD, Kurlander et al94 evaluated patients’ perceptions of PPI risks and attempts at treatment discontinuation. The investigators reported that 20% of patients were able to name at least 1 reported adverse effect and 46% indicated awareness of at least 1 adverse effect when presented with a list. Interestingly, CKD was the most common adverse event recalled both passively and actively.94 The investigators reported that 39% of patients had tried to stop PPI use without a provider recommendation, and patients with high risk for upper gastrointestinal bleed were as likely as other patients to have attempted to stop PPI use. This study highlighted the need for provider engagement in discussing benefits and risks of PPI use and providing
clear recommendations on whether and how PPI therapy should be stopped.

**Deprescribing of PPIs: When Less Is More**

Deprescribing is defined as the planned and supervised process stopping a medication or reducing its dose to improve the person’s health or reduce the risk of adverse side effects or when the medication no longer providing benefit to a patient.95,96 Deprescribing is rooted in the fact that while medications have beneficial effects, they may also be causing harm12; when the scale tilts toward more harm than benefit, deprescribing is the pathway that will result in reduced suffering and improved well-being of patients.12

Overuse of PPIs is not harmless; it is associated with significant risk for adverse events and substantial economic cost.97 Overuse of PPIs is likely driven by the misperception that this class of therapeutics is safe (or free of side effects), the reality that clinicians often underestimate harms and overestimate benefits,98 and to some extent by the general tendency in American medicine “to do something” and that “despite our oath to do no harm, we fear missing a diagnosis more than the possibility of therapeutic… misadventure.”81,99 Although deprescribing strategies may be applied to all drugs, owing to the high prevalence of overuse, PPIs are a prime target for deprescription programs. Deprescribing PPIs can include stopping, stepping down by converting to H2 blockers, or reducing doses to intermittent use or on-demand use or lowering the dose. Serious consideration should be given to addressing this in clinical encounters.

**Deprescribing Is Challenging but Achievable**

While advocating for deprescribing, it is very important to acknowledge that deprescribing is difficult, as evidenced by the frequent observation that ineffective or potentially harmful treatments are often not stopped, even years after they have been started.100,101 In a short essay about the “perils of deprescribing,” Helen Salisbury, a general practitioner, remarked that “Many of my patients are taking too much medicine, but it’s so much easier to start something than to stop it.”100 Deprescription is resource intensive in that it requires that providers reassess use of medications, particularly those that are not clearly related to the focus of a given patient encounter.101

Often deprescription is avoided by health care providers and patients on the basis of uncertainty about what would happen when a medication is stopped or anxiety that stopping may worsen symptoms. Providers may also be uncertain of when and how best to deprescribe a medication. A patient-centered deprescription framework that considers the clinical context (disease-related factors, patient goals of care, treatment targets, treatment duration, patient life expectancy, patient preferences, and prescriber-related factors) and also psychological, social, financial, and physical deprescribing determinants may serve to optimize the design, implementation, and ultimate success of deprescription programs.102,103 A potentially valuable approach could include empowering stakeholders, including patients and providers, with more knowledge about deprescription, developing decision support systems and tools to assist in deprescription, and implementing broader health system level changes to promote a more robust culture of drug safety that might at times entail deprescription.

**Deprescription Guidelines**

Clinical practice guidelines for deprescribing PPIs are emerging; a Canadian report104 that systematically evaluated evidence from prior Cochrane reviews105 and deprescription studies and sought input from key stakeholders suggested that evidence failed to demonstrate important clinical harms in deprescribing PPIs in adults. There are broadly 5 categories of patients: (1) those who have no indication for PPI use, (2) those for whom the indication is unknown, (3) those with mild or moderate esophagitis or GERD, (4) those who were treated with PPIs for a well-defined indication (eg, peptic ulcer disease due to NSAID use, or H pylori infection, intensive care unit prophylaxis, or upper gastrointestinal symptoms) but remained on PPI treatment beyond the indicated period and well after resolution of symptoms, or (5) those with conditions that require long-term use of PPIs, including Barrett esophagus, bleeding ulcers, severe esophagitis, and long-term NSAID users with bleeding risk (Fig 1).

In those who are receiving PPIs but have no indication for PPI use, the answer is simply to deprescribe PPIs because the risk for side effects will not likely be counterbalanced by any benefit. Several deprescription strategies have been proposed to reduce the chance of rebound hypersecretion; these include abrupt discontinuation and a tapering approach with gradual dose reduction followed by stopping or using on-demand dosing for symptomatic relief.

The guideline suggested that in patients with heartburn, mild or moderate GERD, or esophagitis whose symptoms have resolved following a 4- to 8-week course of PPIs, the medication should be deprescribed by either decreasing it to a lower dose or discontinuation and use on demand. A follow-up assessment may be needed to evaluate the need for continued PPI use.

In patients for whom the indication is unknown, a cautious approach to lower the dose, or stop and use an “on-demand” approach with follow-up to monitor continued need for PPIs, may be an appropriate avenue for deprescription.

Another set of patients comprises those with peptic ulcer disease due to either NSAIDs or H pylori infection who have been treated for 2 to 12 weeks, those with upper gastrointestinal symptoms who were treated with PPIs and now are asymptomatic, those who have been started on PPI treatment for intensive care unit stress ulcer
prophylaxis, and those with uncomplicated and asymptomatic *H pylori* infection treated for 2 weeks. In these patients, the general recommendation is to deprescribe PPIs by stopping their use.

Patients with severe esophagitis, Barrett esophagus, and history of bleeding gastrointestinal ulcers and long-term NSAID users with bleeding risk will need long-term PPI treatment. In case of adverse events related to PPI use (such as the occurrence of AIN, hypomagnesemia, etc), a deprescription trial in consultation with a gastroenterologist may be considered.104

PPIs are abundantly prescribed in patients with CKD, including those with kidney failure treated by dialysis or kidney transplantation and patients with glomerulonephritis or vasculitis treated with high-dose steroids. Evidence on who to target for deprescription and how best to deprescribe PPIs in these patient groups is still lacking. Generally, the benefit of PPI use should be balanced against potential risk. Dose and duration of use should be limited to the extent possible; alternatives including use of H₂ blockers may also be considered.

**System-Level Interventions Needed to Reduce Overuse**

Although deprescription of PPIs may be meritorious in some instances, it may be challenging to achieve without substantial changes at the health-system level. Deprescription initiatives from several large health care systems are beginning to emerge; for example, the US Department of Veterans Affairs is pioneering a deimplementation program to deprescribe PPIs. Ongoing Veterans Affairs studies aim to identify system-, provider-, and patient-level barriers and facilitators to PPI deprescribing; assess the impact of the deprescribing program on important clinical outcomes; understand how and why these outcomes were achieved or not achieved; and assess the economic effects of the deprescribing program.106

The hallmark of successful deprescription models is the engagement of all relevant stakeholders, including provider, pharmacist, and patient. A recent study from Quebec suggested that a pharmacist-led educational intervention that engaged both patients and their physicians resulted in greater discontinuation of prescriptions for inappropriate medication compared to usual care.107 The Choosing Wisely Canada campaign and the Toronto Western Hospital Family Health Team jointly developed the Bye-Bye PPI toolkit, which could be integrated into electronic medical record systems, to help providers deprescribe PPIs.108 The initial report on this toolkit suggested that implementation of this program in a primary care setting led to PPI need being reassessed in 93% of patients, which resulted in a 26% deprescription rate.109

Health care systems should develop and implement PPI stewardship programs and monitor frequency of use (and overuse) of PPIs. Decision support systems, automatic prompts or algorithms, and ongoing education of both

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**Figure 1.** A deprescribing algorithm for proton pump inhibitors (PPIs). Abbreviations: GERD, gastroesophageal reflux disease; *H pylori*, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drug. Based on information in Farrell et al.104
health professionals and patients may need to be developed to facilitate wider deprescription. Accurate estimation of rates of overprescription may serve as a tool to evaluate and track the performance of deprescription interventions and may serve as quality metrics for health care systems. We view PPI overuse and its attendant consequences in terms of both health and economic loss as significant, and we posit that investment in and development of policies and technologies to aid in curbing overuse will contribute to the greater public good.

**New Prescriptions of PPIs**
New prescriptions for PPIs should be provided only when there is a clear indication. Providers should develop a written plan for treatment that includes therapeutic goals, dose, duration, and plan for discontinuation. The plan should be discussed with the patient, along with a conversation about potential adverse events. We urge providers to not prescribe (or renew) PPIs without a well-documented indication. Providers should also routinely ask and counsel patients about proper use of over-the-counter PPIs.

**Monitoring of Kidney Function and Serum Magnesium Concentrations**
There is no clear evidence suggesting improved outcomes associated with monitoring of kidney function and serum magnesium levels among PPI users. Generally, and for most indications, PPI use should be limited to short-term treatment (4–8 weeks), for which the risk for adverse events is likely low and may not warrant monitoring of kidney function or magnesium levels.

In those who require more prolonged therapy, and in the absence of evidence, we think a once-yearly monitoring of estimated glomerular filtration rate (eGFR) may be appropriate. The FDA warning specifically suggests that for patients expected to be using PPIs for a prolonged duration (≥1 year), serum magnesium levels should be assessed at baseline before PPI treatment initiation and periodically. In patients at risk for hypomagnesemia (history of hypomagnesemia or other predisposing conditions) and those taking concomitant diuretics or other drugs that may increase the risk for hypomagnesemia or digoxin (for which hypomagnesemia may be associated with serious side effects), more than once-a-year periodic evaluation of serum magnesium levels may also be needed. The frequency of this also remains unclear but should be based on the clinical history and risk-factor profile of each individual patient.

**Strategies for Addressing PPI Use in Patients Who Develop PPI-Related Adverse Kidney Outcomes**

**Hypomagnesemia**
Several studies suggested that magnesium replacement alone is not sufficient to ensure restoration of magnesium levels. Patients with hypomagnesemia may also require PPI treatment discontinuation. In patients who must remain on acid suppression therapy, consideration should be given to H₂ blockers or if absolutely needed, continued use of PPIs with careful monitoring of magnesium levels.

**AKI, AIN, and CKD**
In patients who experience an AKI event or decline in eGFR that may be plausibly attributed to the use of PPIs, consideration should be given to stopping PPI therapy. In those with a need for continued use of acid suppression therapy, H₂ blockers should be considered. Anecdotal evidence suggests that PPI rechallenge in patients with AIN can lead to recurrence of the kidney disease and may not be advised.

**Alternatives to PPIs**
A stepping-down approach that involves either abrupt discontinuation or tapering of PPI dosage followed by prescription of H₂ blockers may be considered. Some nonpharmacologic interventions may be used because they have also been shown to ameliorate (reduce) symptoms, and these include attention to dietary or other triggers, weight loss, avoiding meals within 2 to 3 hours of bedtime, and raising the head of the bed.

**Review of Clinical Vignette and Conclusions**
The clinical vignette illustrates the challenges of addressing PPI deprescription in patients who may need them. In this patient, PPI use was stopped following the first episode of AIN. It was resumed by his primary care physician to address concern about dyspepsia, and this rechallenge with PPIs led to another episode of AIN with only partial recovery, leaving him with advanced CKD. He was subsequently switched to treatment with H₂ blockers, which provided symptomatic relief.

PPI use is associated with increased risk for hypomagnesemia, AKI, AIN, incident CKD, CKD progression, kidney failure, all-cause mortality, and death due to kidney disease. PPI use should be considered as a potential culprit in the evaluation of hypomagnesemia, AKI, and AIN. Reducing un-indicated exposure to PPIs may also be used in strategies aimed at prevention of CKD development and reducing its risk for progression. Given their ubiquitous availability and abundant overuse, PPIs should be viewed as a public health risk. We urge all providers to consider reviewing the need for PPIs in every patient and to deprescribe when not necessary. In those for whom a PPI is clinically indicated, providers should limit dose and duration to minimum necessary, and consideration should be given to monitoring eGFR and serum magnesium levels; the latter is especially important in patients using concomitant diuretics. Implementation of deprescription programs to curb overuse of PPIs will require engagement...
of all relevant stakeholders and will likely require a shift in attitude at the provider level and changes at the health-system level.

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