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## Adverse Effects Associated With Proton Pump Inhibitors

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**Proton pump inhibitors (PPIs)** have been among the most widely prescribed medications in the United States for decades. This is largely due to 2 very common uses of PPIs: treatment of dyspepsia and prevention of gastrointestinal bleeding among patients prescribed antiplatelet therapy, coupled with the belief that PPIs have few adverse effects.

However, mounting evidence demonstrates that PPIs are associated with a number of adverse effects and are overprescribed. This issue was highlighted in *JAMA Internal Medicine's* launch of the Less Is More series in 2010.<sup>1,2</sup> Since then, additional evidence of adverse effects of PPIs has accumulated. In this issue of *JAMA Internal Medicine*, Lazarus et al<sup>3</sup> add chronic kidney disease to the list of possible harms of PPIs.

To collate data on the adverse effects of PPIs, we surveyed recent studies focusing on systematic reviews. Most of the evidence supporting the adverse effects of PPIs is observational. Thus, it is possible that PPI users are sicker than nonusers, or that adverse effects are caused by other drugs or conditions associated with PPI use. However, some adverse effects have been documented by multiple high-quality observational studies and are likely causal (Table). Herein, we summarize recent data on the adverse effects of PPI use.

### Kidney Disease

Among 10 439 patients followed for 13.9 years in the Atherosclerosis Risk in Communities study,<sup>3</sup> the risk of

chronic kidney disease was 50% higher in PPI users compared with nonusers. The findings of this study are strengthened by a thorough assessment of potential confounding using both multivariable and propensity score adjusted analyses, by a dose response with higher risk among patients using twice daily compared with once daily PPI dosing, and by higher risk among PPI users compared with patients using histamine H<sub>2</sub> antagonists—a comparison group that should control for potential bias and confounding. Finally, the findings were replicated in a second large cohort using administrative data from patients in the Geisinger Health System.<sup>3</sup> Use of PPIs may lead to chronic kidney disease through recurrent acute kidney injury or hypomagnesemia. Although this is a large, high-quality observational study, additional confirmation would be helpful, especially since chronic kidney disease is a common condition.

Use of PPIs is also associated with increased risk of acute kidney injury, possibly mediated through acute interstitial nephritis. In a population-based study<sup>4</sup> of 290 592 people 66 or older, rates of acute kidney injury and acute interstitial nephritis were 2.5- and 3-fold higher in PPI users compared with nonusers. In a nested case-control study<sup>10</sup> of 184 480 patients 18 years or older, renal disease was 2-fold more common in patients who had used PPIs compared with those who had not after controlling for multiple potential confounding variables.

## Hypomagnesemia

Hypomagnesemia has been associated with increased risk of kidney disease and nonrecovery of renal function after acute kidney injury. When severe, hypomagnesemia can lead to muscle weakness, tetany, convulsions, cardiac arrhythmias, and hypotension. Based on case reports, the US Food and Drug Administration (FDA) issued a warning in 2011 that use of PPIs may cause low serum magnesium levels if taken for prolonged periods of time, and noted that magnesium supplementation alone may not correct low serum magnesium levels unless the PPI is discontinued.<sup>11</sup> Subsequently, a meta-analysis<sup>5</sup> of 9 observational studies including 109 798 participants found that PPI users had a 40% higher risk of hypomagnesemia compared with nonusers.

## Infections

### *Clostridium difficile* Infection

Proton pump inhibitors reduce gastric acidity, which may promote bacterial colonization in the gastrointestinal tract, increasing the risk of infection. A meta-analysis<sup>6</sup> that included 39 studies showed a 74% higher risk of developing *C difficile* infection, as well as 2.5-fold higher risk of recurrent *C difficile* infection among PPI users compared with nonusers. Based on these data, the FDA published a safety alert in 2015 warning of the association of PPIs and *C difficile* infection.<sup>11</sup>

### Pneumonia

Reduced gastric acidity and increased bacterial colonization in the stomach related to PPI use may also lead to increased rates of pneumonia. A meta-analysis<sup>7</sup> of 5 observational studies showed that the risk of community-acquired pneumonia was 34% higher among patients using PPIs compared with nonusers, and that the risk was higher with increasing doses of PPIs. Risk for hospital-acquired pneumonia was not increased. A retrospective cohort study using administrative data evaluated the risk of hospitalization for community-acquired pneumonia among more than 4 million patients newly prescribed nonsteroidal anti-inflammatory drugs from 8 regions in Canada, the United States, and the United Kingdom. Among patients who were also started on therapy with a PPI (presumably for prevention of dyspepsia, ulceration, and bleeding), there was no increased risk of hospitalization for community-acquired pneumonia compared with nonusers.<sup>8</sup> The results of this study may be more reliable than other observational studies because the study population was restricted to patients without known gastric or esophageal disease, and analyses were adjusted using high-dimensional propensity scores to control for potential confounding.

### Cardiovascular Events

Patients with coronary disease and those who have undergone coronary procedures are generally prescribed antiplatelet therapy to reduce the risk of coronary events. Proton pump inhibitors are often prescribed along with antiplatelet therapy to prevent gastrointestinal bleeding. The commonly used antiplatelet agent, clopidogrel, is

**Table. Evidence Supporting the Potential Adverse Effects of Proton Pump Inhibitor Drugs**

Source	Adverse Effect	Adjusted OR (95% CI)
Lazarus et al, <sup>3</sup> 2015	Chronic kidney disease	1.50 (1.11-1.90)
Antoniou et al, <sup>4</sup> 2015	Acute kidney disease	2.52 (2.27-2.79)
Antoniou et al, <sup>4</sup> 2015	Acute interstitial nephritis	3.00 (1.47-6.14)
Cheungpasitporn et al, <sup>5</sup> 2015	Hypomagnesemia	1.43 (1.08-1.88)
Kwok et al, <sup>6</sup> 2012	<i>Clostridium difficile</i>	1.74 (1.47-2.85)
Eom et al, <sup>7</sup> 2011	Community-acquired pneumonia	1.34 (1.14-1.57)
Filion et al, <sup>8</sup> 2014	Community-acquired pneumonia	1.05 (0.89-1.25)
Zhou et al, <sup>9</sup> 2015	Bone fracture	1.33 (1.15-1.54)

Abbreviation: OR, odds ratio.

metabolized to the active form by liver enzymes that also metabolize PPIs, suggesting that competitive metabolism by PPIs might lead to reduced activation of clopidogrel, reduced antiplatelet effects, and increased cardiovascular events. In fact, pharmacologic studies demonstrate that adding PPIs to clopidogrel results in reduced platelet inhibition, and this finding led the FDA in 2009 to warn against combining clopidogrel and PPIs.<sup>11,12</sup> A meta-analysis<sup>13</sup> of 31 observational studies found that patients using PPIs with clopidogrel have about a 30% increased risk of cardiovascular events compared with nonusers of PPIs. However, none of the 4 randomized clinical trials identified by this systematic review found an increased risk of coronary events among patients prescribed clopidogrel and treated with omeprazole or esomeprazole.<sup>13</sup> It is not clear how to resolve these conflicting findings. The observational studies are much larger than the randomized trials and provide “real-world” experience. However, the observational studies are prone to selection bias and confounding, which are minimized by randomization. In summary, we do not find clear evidence that PPIs increase risk for coronary events in patients on clopidogrel.

### Fractures

Use of PPIs may decrease bone density and increase fracture risk by reducing intestinal calcium absorption. Many observational studies have shown an association between PPI use and increased risk of fractures, prompting the FDA to publish a safety alert in 2010 noting a possible increased risk of fractures among PPI users.<sup>11</sup> A recent meta-analysis<sup>9</sup> of 18 observational studies that included 244 109 fractures found that compared with nonuse, PPI use was associated with a 26% higher risk of hip fracture, a 58% higher risk of spine fracture, and a 33% higher risk for fracture at any site, even after short-term use of less than 1 year.

### Conclusions

Available evidence suggests that PPI use is associated with an increased risk of both acute and chronic kidney disease,

hypomagnesemia, *C difficile* infection, and osteoporotic fractures. Caution in prescribing PPIs should be used in patients at high risk for any of these conditions. Given the association with kidney disease and low magnesium levels, serum creatinine and magnesium levels should probably be monitored in patients using PPIs, especially those using high doses.

Given the evidence that PPI use is linked with a number of adverse outcomes, we recommend that patients and clinicians discuss the potential benefits and risks of PPI treatment, as well as potential alternative regimens such as his-

tamine H<sub>2</sub> receptor antagonists or lifestyle changes, before PPIs are prescribed. In patients with symptomatic gastrointestinal reflux, ulcer disease, and severe dyspepsia, the benefits of PPI use likely outweigh its potential harms. However, for less serious symptoms and for prevention of bleeding in low-risk patients, potential harms may outweigh the benefits. A large number of patients are taking PPIs for no clear reason—often remote symptoms of dyspepsia or “heartburn” that have since resolved. In these patients, PPIs should be stopped to determine if symptomatic treatment is needed.

#### ARTICLE INFORMATION

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**Published Online:** January 11, 2016.  
doi:10.1001/jamainternmed.2015.7927.

**Conflict of Interest Disclosures:** None reported.

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