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### Does Long-Term Proton Pump Inhibitor Use Pump Up Your Risk of Adverse Effects?

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## Does Long-Term Proton Pump Inhibitor Use Pump Up Your Risk of Adverse Effects?

### Comments

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# Does Long-Term Proton Pump Inhibitor Use Pump Up Your Risk of Adverse Effects?

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## The Problem

Many studies have linked proton pump inhibitor (PPI) use to several adverse effects including *Clostridium difficile*-associated diarrhea, community-acquired pneumonia, bone fractures, and nutritional deficiencies.<sup>1</sup> Other reports have linked PPI use with chronic kidney disease, cognitive decline, myocardial infarction (MI), stroke, and even death.<sup>1,2,3</sup> Many patients take PPIs chronically and may be concerned about the risk of these side effects. This poses a challenge for healthcare providers as safety data has been primarily based on retrospective and observational studies. Thus, the fears associated with long term PPI therapy can create confusion, result in extended patient visits, and lead to under-prescribing PPIs in circumstances when their use is appropriate.

## What's Known

PPIs are among the most widely prescribed and used medications.<sup>1</sup> Although they are most often taken for the management of gastroesophageal reflux disease (GERD) symptoms, PPIs are also the gold standard for the prevention of nonsteroidal anti-inflammatory drug (NSAID) induced ulcers, upper gastrointestinal bleeding, and eradication of *H. pylori* infections. While some studies have suggested that PPIs are generally safe, others have reported some very concerning adverse effects with long-term PPI use. Most safety studies have been retrospective and observational.<sup>4</sup> While we can generate hypotheses from these types of studies, confounding is a significant problem and does not allow us to ascribe a cause and effect relationship.<sup>4</sup>

One population-based cohort study found that acid suppression medications were associated with increased rates of *Clostridium difficile* and Campylobacter positive gastroenteritis in both the community and hospital settings.<sup>5</sup> Another study using case-control analysis found that the use of gastric acid-suppressive therapy was associated with an increased risk of community-acquired pneumonia.<sup>6</sup>

In 2018, an updated systematic review and meta-analysis suggested that PPI use might increase fracture risk but had no effect on bone mineral density (BMD).<sup>7</sup> In a large North European healthcare system, cumulative PPI exposure was associated with an accelerated progression of CKD. However, this association was modest in magnitude and there may have been residual confounders.<sup>8</sup> Similarly, data on PPI use and cognitive decline has been inconclusive. Reassuringly, a prospective population-based cohort study of 3,484 individuals aged 65 and older without dementia at baseline found that presence of PPI use and duration of use were not associated with an increased risk for dementia over a mean follow-up of 7.5 years.<sup>9</sup>

In 2017, the American Gastroenterological Association (AGA) issued a guidance document entitled “Best Practice Advice on Long Term PPI Use.” This document states that PPIs should be used at the lowest effective dose when taken over a long time period and that the need for therapy should be periodically reassessed.<sup>10</sup> Furthermore, the AGA made specific recommendations regarding compelling indications for PPI use and which patients should take them indefinitely, including patients with Barrett’s esophagus and symptomatic GERD (Table 1).<sup>10</sup> Nevertheless, there is still uncertainty about the risks and benefits of long-term PPI use.

**Table 1: 2017 Best Practice Advice From the American Gastroenterological Association (AGA)<sup>10</sup>**

Best Practice Advice for Long-Term PPI Use
1. Patients with GERD and acid-related complications (e.g., erosive esophagitis or peptic stricture) should take a PPI for short-term healing, maintenance of healing, and long-term symptom control
2. Patients with Barrett’s esophagus and symptomatic GERD should take a long-term PPI
3. Asymptomatic patients with Barrett’s esophagus should consider a long-term PPI
4. Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs

### What’s New

A new study published in *Gastroenterology* found that in patients who took PPIs for 3 years, there was no evidence of increased risk for some of the most serious health issues that they have been associated.<sup>12</sup> The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial was a multicenter, double-blind, randomized trial evaluating the prevention of

MI, stroke, or cardiovascular death in participants with stable cardiovascular disease and peripheral artery disease. Participants were given either rivaroxaban alone, aspirin alone, or rivaroxaban in combination with aspirin.<sup>11</sup> A substudy of this study evaluated the safety outcomes from concurrent pantoprazole use.<sup>12</sup>

A total of 17,598 (64%) of the COMPASS study participants who did not have a compelling indication for continuous PPI therapy at the time of study enrollment were *randomly assigned* in a 1:1 ratio to receive either pantoprazole 40 mg daily (n = 8,791) or placebo daily (n = 8,807). Exclusions included a high risk of bleeding from any site, severe heart failure, significant renal impairment, need for dual antiplatelet therapy, dementia, severe COPD, eGFR < 15 mL/min, or known hypersensitivity to any of the study drugs. The baseline characteristics of the two groups in this substudy were similar, including similar age, estimated eGFR breakdown, and incidence of previous peptic ulcers, liver disease, diabetes, and concurrent NSAID use.

When comparing the pantoprazole and placebo groups in terms of efficacy, there was no significant difference in the composite outcome of MI, stroke, or cardiovascular death (MACE) or any of the individual outcomes.

The safety outcomes reported in the substudy included the development of pneumonia, *Clostridium difficile* infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, and dementia. Diabetes and chronic obstructive lung disease were also assessed but were not the primary focus. Data were collected by patient interviews every 6 months without adjudication. More than 96% of patients in both groups took their assigned medication more than 80% of the time as assessed by tablet count.

Ultimately, there were no statistically significant differences between the two groups for any of the safety outcomes (see Table 2), except for enteric infections in the pantoprazole group (OR = 1.33; 95% CI, 1.01-1.75) with a number needed to harm (NNH) of 301.

**Table 2: Safety Outcomes in Intention-to-Treat Population<sup>12</sup>**

Safety Outcome	Pantoprazole (n=8791)	Placebo (n=8807)	OR (95% CI)
<b>Pneumonia</b>	318 (3.6)	313 (3.6)	1.02 (0.87-1.19)
<b><i>Clostridium difficile</i> infection</b>	9 (0.1)	4 (< 0.1)	2.26 (0.70-7.34)
<b>Other enteric infections</b>	119 (1.4)	90 (1.0)	1.33 (1.01-1.75)
<b>Gastric atrophy</b>	19 (0.2)	26 (0.3)	0.73 (0.40-1.32)
<b>Fracture</b>	203 (2.3)	211 (2.4)	0.96 (0.79-1.17)
<b>Chronic kidney disease</b>	184 (2.1)	158 (1.8)	1.17 (0.94-1.45)

<b>Dementia</b>	55 (0.6)	46 (0.5)	1.20 (0.81-1.78)
<b>Diabetes mellitus</b>	513 (5.8)	532 (6.0)	0.96 (0.85-1.09)
<b>COPD</b>	146 (1.7)	124 (1.4)	1.18 (0.93-1.51)

## Our Critical Appraisal

The COMPASS trial is the first randomized placebo-controlled trial to evaluate some of the critical adverse effects that have been linked to long-term PPI use over the past decade. The researchers were able to confirm a high rate of medication adherence through tablet counts, thus minimizing differences in medication use as a potential confounding factor.

Although this trial provides us with robust, data-driven insights into the risks of long-term PPI use, it has some limitations. Previous reports have claimed that adverse effects of PPIs may not be evident until after 5 years of continuous use — this study only followed patients for a median of 3 years.<sup>13</sup> A longer study duration would be necessary to appropriately evaluate the potential risk of bone fractures and the development of dementia. A small percentage of participants, 56 (0.6%) in the pantoprazole group and 78 (0.9%) in the placebo group, were already taking a PPI at the start of the trial. Although a small percentage of the total, these patients raise a question of the duration and frequency of their existing PPI therapy and its effect on the outcomes.

The rate of adverse effects in the two groups may be underreported. The safety outcomes were obtained through patient interviews and self-reporting is not the most accurate method of capturing outcomes like CKD and dementia as opposed to well-defined events such as pneumonia and fractures.

The incidence of *Clostridium difficile* infection was double in the PPI group compared to the placebo group, but it did not reach statistical significance due to the small number of events. It would have been helpful if the study had also evaluated electrolyte disturbances and vitamin B12 deficiency, both of which have been reported in previous observational studies.

Pantoprazole was the only PPI used in this study. While it is likely that these findings can be extrapolated to other PPIs, there may be important differences among the PPIs in terms of their safety.

## The Bottom Line

The COMPASS substudy analysis of long-term pantoprazole use is the most robust safety study conducted to date and provides reassuring data. While the risk of enteric infections was higher in the pantoprazole group, the number-needed-to-harm (NNH=301) was reasonably high. Given the lack of differences in most safety outcomes, the benefits of PPI therapy for up to 3 years likely outweigh these risks in patients with a clear indication for therapy.

## The Key Points

- The COMPASS trial was the first randomized placebo-controlled trial investigating the emerging safety concerns of long-term PPI use.
- PPI therapy taken for a median 3 years duration appears to be safe, but the risk of enteric infections was modestly increased in pantoprazole users (NNH=301).
- There was no significant difference in efficacy outcomes (including MACE) when patients used rivaroxaban or aspirin with pantoprazole compared to placebo, suggesting there is no clinically important drug interaction.

**FINAL NOTE:** This program will be available for recertification credit through the American Pharmacists Association (APhA) Ambulatory Care Review and Recertification Program. To learn more, visit <https://www.pharmacist.com/ambulatory-care-review-and-recertification-activities>.

1. Batchelor R, Kumar R, Gilmartin-Thomas JFM, et al. Systematic review with meta-analysis: risk of adverse cardiovascular events with proton pump inhibitors independent of clopidogrel. *Aliment Pharmacol Ther* 2018;48:780–796. DOI: 10.1111/apt.14955.
2. Badiola N, Alcalde V, Pujol A, et al. The proton-pump inhibitor lansoprazole enhances amyloid beta production. *PLoS One*. 2013;8(3):e58837. DOI:10.1371/journal.pone.0058837
3. Wijarnpreecha K, Thongprayoon C, Chesdachai S, et al. Associations of proton-pump inhibitors and H2 receptor antagonists and chronic kidney disease: a meta-analysis. *Dig Dis Sci* 2017; 62:2821–2827. DOI:10.1007/s10620-017-4725-5.
4. Vaezi MF, Yang Y-X, Howden CW. Complications of proton pump inhibitor therapy. *Gastroenterology* 2017; 153:35–48. DOI: 10.1053/j.gastro.2017.04.047.
5. Wei L, Ratnayake L, Phillips G, et al. Acid suppression medications and bacterial gastroenteritis: a population-based cohort study. *Br J Clin Pharmacol* 2017; 83:1298–1308. DOI: 10.1111/bcp.13205.
6. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292(16):1955-60.
7. Nassar Y, Richter S. Proton-pump inhibitor use and fracture risk: an updated systematic review and meta-analysis. *J Bone Metab* 2018;25:141–151. DOI:10.11005/jbm.2018.25.3.141.
8. Klatte DCF, Gasparini A, Xu H, et al. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. *Gastroenterology* 2017; 153:702–710. DOI:10.1053/j.gastro.2017.05.046.
9. Gray SL, Walker RL, Dublin S, Yu O, Aiello Bowles EJ, Anderson ML, Crane PK, Larson EB. Proton Pump Inhibitor Use and Dementia Risk: Prospective Population-Based Study. *J Am Geriatr Soc*. 2018 Feb;66(2):247-253. DOI:10.1111/jgs.15073.
10. Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. *Gastroenterology*. 2017 Mar;152(4):706-715. DOI:10.1053/j.gastro.2017.01.031.

11. Eikelboom JW et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017. 377(14):1319-1330. DOI: 10.1056/NEJMoa1709118
12. Moayyedi, Paul, et al. Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin. *Gastroenterology* 2019;157(3):682-691. DOI: 10.1053/j.gastro.2019.05.056.
13. Laura E. Targownik, Lisa M. Lix, Colleen J. Metge, Heather J. Prior, Stella Leung and William D. Leslie. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ* 2008 August; 179(4):319-326. DOI: 10.1503/cmaj.071330