



## Side effects of long-term PPI use: Leaving a bad taste in your mouth?

### CLINICAL QUESTION

What are the side effects of long-term proton pump inhibitor (PPI) use?

### BOTTOM LINE

Best evidence from large, randomized, placebo-controlled trials suggest PPIs do not increase the risk of cardiovascular disease, fractures, or pneumonia. Observational studies suggest PPIs may be associated with vitamin B12 and magnesium deficiency.

### EVIDENCE

- Focusing on large randomized controlled trials (RCTs) and systematic reviews of observational studies where RCT outcomes not unavailable.
- RCTs:
  - 17,598 patients with cardiovascular disease, randomized to pantoprazole or placebo.<sup>1</sup> At ~3 years, no statistical difference between PPI or placebo, including:
    - All-cause mortality, cardiovascular disease, fractures, pneumonia, *clostridium difficile* infection, chronic kidney disease, dementia, or gastrointestinal malignancies.
  - 3761 patients with cardiovascular disease on aspirin, randomized to clopidogrel plus omeprazole or clopidogrel plus placebo.<sup>2</sup> Trial ended prematurely when sponsor declared bankruptcy. Outcomes at 180 days:

- All-cause mortality, cardiovascular events, fractures and pneumonia: No difference.
  - Upper gastrointestinal events (examples: bleeding, ulcer): 1.1% omeprazole versus 2.9% placebo, statistically different.
- Observational studies:
  - Observational studies of the above outcomes have inconsistent findings.<sup>3-6</sup>
  - Best systematic reviews of observational studies on vitamin B12 and magnesium deficiency (no RCT evidence available):
    - Vitamin B12 deficiency: increased risk in case-controlled and cohorts.<sup>7</sup>
      - Largest, high quality North American case-control study:<sup>8</sup> Vitamin B12 deficient patients more likely to be on PPIs, Odds Ratio (OR): 1.65, statistically different.
    - Hypomagnesiemia: Increased risk, OR: 1.71, statistically different.<sup>9</sup>
  - Limitations: Observational studies cannot determine causation. Other patient factors may explain associations.

## CONTEXT

- Patients on PPIs should have indication reviewed periodically.<sup>10</sup>
  - Many patients with gastroesophageal reflux disease (GERD) use PPIs, including as needed.<sup>11</sup>
  - Lowering dose or discontinuation could be considered for some; tapering may help.<sup>12,13</sup>
- Continuing PPIs may be appropriate in patients with:<sup>14</sup>
  - Barrett's or eosinophilic esophagus,
  - Erosive esophagitis or GERD related complications (example: stricture), or
  - Previous gastrointestinal bleed or ulcer where gastroprotection is needed.
- All PPIs have similar efficacy: Cost and individual response should guide prescribing.<sup>15</sup>
- Overall, vitamin B12 deficiency occurs in ~5% of patients >60 years.<sup>16</sup>
  - If PPI association is true, the new risk of vitamin B12 deficiency would be ~8%.

## REFERENCES

1. Moayyedi P, Eikelboom JW, Bosch J, *et al.* Gastroenterology. 2019 Sep;157(3):682-691.e2.
2. Bhatt DL, Cryer BL, Contant CF, *et al.* N Engl J Med. 2010 Nov 11;363(20):1909-17.
3. Islam MM, Poly TN, Walther BA, *et al.* Eur J Gastroenterol Hepatol. 2018 Dec;30(12):1395-1405.
4. Shin GY, Myung Park J, Hong J, *et al.* Am J Gastroenterol. 2021 Jun 1;116:1211-1219.
5. Abrahami D, McDonald E, Schnitzer ME, *et al.* Gut. 2022;71:16-24.
6. Friesen KJ, Falk J, Chateau D *et al.* Clinical Pharm Ther. 2023; Jan;113 (1):152-159.
7. Choudhury A, Jena A, Jearth V, *et al.* Expert Rev Gastroenterol Hepatol. 2023 May;17(5):479-487.
8. Lam JR, Schneider JL, Zhao W *et al.* JAMA. 2013 Dec

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- 11;310(22):2435-2442.
9. Srinutta T, Chewcharat A, Takkavatakarn K, *et al.* *Medicine* (Baltimore). 2019 Nov;98(44):e17788.
  10. Katz PO, Dunbar KB, Schnoll-Sussman FS, *et al.* *Am J Gastroenterol.* 2022 Jan 1;117:27-56.
  11. Nocon M, Labenz J, Jaspersen D, *et al.* *Ailment Pharmacol Ther.* 2007 Mar 15;25:715-722.
  12. Kolber MR, Nickonchuk T. *Tools for Practice #190.* Available at: <https://cfpclearn.ca/tfp190/> Accessed July 15, 2024.
  13. RxFiles "Stopping your Proton Pump Inhibitor" Available at: <https://www.rxfiles.ca/RxFiles/uploads/documents/Deprescribing-PPI-Patient-Tool.pdf>. Accessed Dec 1, 2024.
  14. Targownik LE, Fisher DA, Saini SD. *Gastroenterology.* 2022 Apr;162(4):1334-1342.
  15. Alberta College of Family Physicians/PEER team: Price Comparison of Commonly Prescribed Pharmaceuticals in Alberta. Available at: <https://pricingdoc.acfp.ca/>. Accessed July 30, 2024.
  16. Silverstein WK, Cheung MC. *CMAJ.* 2022;194(24):E843.

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