

ALTERNATIVE VIEWPOINTS

Conflicting Data: Association of Proton Pump Inhibitors and Risk of Osteoporotic Fractures

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Proton pump inhibitors (PPI) are widely used in treatment of gastroesophageal reflux disease and peptic ulcer disease, among others. They account for eight of the top 200 medications dispensed in 2007.¹ Therefore, it is of considerable importance to know if long-term use of these medications has any negative implications for common diseases such as osteoporosis. In a recent issue of *Pharmacotherapy*, evidence is presented that suggests that the use of proton pump inhibitors is not associated with an increased risk of osteoporotic fracture.²

Using patient information from a large, automated, medical record database, Kaye and colleagues report that the use of PPIs does not increase the risk of hip fracture in patients without major risk fractures (Relative Risk (RR) 0.9, 95% confidence interval (CI) 0.7–1.1). Additionally, they report that there was no increased risk of hip fracture with longer duration of PPI use, defined as patients receiving more than 30 prescriptions for a PPI.² The report by Kaye and colleagues stands in stark contradiction to two previously published large administrative database studies^{3,4} and a third, just recently published report by Targownik and colleagues.⁵

The two previously published trials have demonstrated an association between the use of PPIs and increased risk of osteoporotic fracture, which appears to be both dose- and duration-dependent.^{3,4} Of particular interest is the study

by Yang and colleagues which found that the risk of hip fracture increased with the duration of exposure.⁴ Coincidentally, this study analyzed patient data from the same medical record database used in the publication by Kaye and colleagues, known as the United Kingdom General Practice Research Database.

The Targownik report, which was not available to the authors at the time they conducted the study or results available before publication, showed an increased risk in hip fracture in patients that received PPIs for at least five years (Adjusted OR 1.62, 95% CI 1.02–2.58). Furthermore, they found an association of an increased risk in overall fractures in patients that received at least seven years of PPI therapy (Adjusted OR 4.55, 95% CI 1.68–12.29).

Proton pump inhibitors, which are potent acid-suppressing drugs, work by inhibiting the final step in gastric production in the stomach to produce a more basic environment. Calcium absorption in the stomach and small intestine is dependent on solubility in an acidic environment.^{4,6} Therefore, calcium malabsorption secondary to acid suppressive therapy may explain the positive association between use of PPIs and increased risk for osteoporotic fractures.

It is understood that bone mineralization and calcium resorption occurs over many years. This process would lead one to believe that clinical outcomes of a medication that may have an effect on this process would not be seen for several years. This theory is supported by the findings of Targownik and colleagues, in which an increased risk was not seen until at least five years of exposure. In the study by Kaye and colleagues, the maximum duration of exposure

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to PPIs was in patients that received at least 30 prescriptions for PPIs, or 2.5 years of therapy. The duration of exposure occurring past 30 prescriptions or 2.5 years is not reported. Therefore, it is possible that this study would not detect a significant association between the extent of PPI use and risk for osteoporotic fracture.

We commend the authors on the work and contribution to the medical community's understanding in this area but caution against over-interpretation of findings in this report. With the report by Targownik, further examination of the effects of acid inhibition on bone mineralization and calcium absorption is warranted. More definitive findings of risk from long-term exposure may change prescribing patterns and necessitate that studies be conducted to evaluate the use of osteoprotective medications, such as bisphosphonates, calcium supplements, and estrogen analogues in patients who require long-term treatment with PPIs.

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Authors' Reply

Drs. Kaye and Jick declined the opportunity to reply.