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Proton Pump Inhibitors Linked to Fracture Risk

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Reviewed by Zalman S. Agus, MD; Emeritus Professor at the University of Pennsylvania School of Medicine.
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MedPage Today Action Points

- Explain to interested patients that while long-term use of proton pump inhibitors for acid reflux suppression was associated in this study with higher risk of hip fracture, short-term use is unlikely to have an effect.

Review

PHILADELPHIA, Dec. 26 -- Proton pump inhibitors appear to increase hip fracture risk among older patients, particularly long-duration or high-dose use, according to a large study of British patients.

Taking acid suppressive proton pump inhibitors for more than a year was associated with increased fracture risk by 44% while long-term, high-dose users had 2.6 times greater risk than nonusers, reported Yu-Xiao Yang, M.D., M.S.C.E., of the University of Pennsylvania here, and colleagues, in the Dec. 27 issue of the *Journal of the American Medical Association*.

The study included 13,556 hip fractures and 135,386 controls from the United Kingdom General Practice Research Database, which contains electronic medical records. The researchers looked only at patients ages 50 and older who used acid suppression drugs and controls matched for sex, age, duration of follow-up in the database and other factors.

Dr. Yang and colleagues said the findings are important because millions of people have been using acid suppressive medication on a continual or long-term basis. Hip fracture leads to 20% one-year mortality as well as emergency department visits, hospitalization, surgery, and rehabilitation.

However, "short-term PPI use is unlikely to have a significant impact on fracture risk regardless of how high the daily dosage," they wrote.

Further study is needed to confirm and explain the findings, Dr. Yang and colleagues said, but meanwhile physicians should be cautious.

"At this point, physicians should be aware of this potential association when considering proton pump inhibitor therapy," the authors wrote, "and should use the lowest effective dose for patients with appropriate indications."

"For elderly patients who require long-term and particularly high-dose proton pump inhibitor therapy," they added, "it may be prudent to reemphasize increased calcium intake, preferably from a dairy source, and coingestion of a meal when taking insoluble calcium supplements."

Previous studies have suggested that proton pump inhibitors may interfere with calcium absorption by inducing hypochlorhydria but have an opposite effect in reducing bone resorption by inhibiting osteoclastic vacuolar proton pumps. So, to determine which of these opposing effects would "translate into

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Learning Objectives
Upon successful completion of this educational program, the reader should be able to:
1. Discuss the results of this study
2. Review the relevance and significance of the study in the broader context of clinical care

Disclosures
Crystal Phend and **Zalman S. Agus, MD; Emeritus Professor at the University of Pennsylvania School of Medicine**, have disclosed that

clinically important alterations in hip fracture risk," the researchers looked at risk in a large, general population cohort.

Patients younger than 50 at the time of database enrollment and those with a previous documented hip fracture were excluded. The average age at database enrollment was 77 and about 79% of patients were female.

In the cohort, the crude incidence of hip fracture was about 4.0 per 1,000 person-years among patients with more than one year of proton pump inhibitor therapy and 1.8 per 1,000 person-years among acid suppression nonusers. The average proton pump inhibitor dose was 1.75 doses per day, and prescriptions usually lasted one month. High dose proton pump inhibitor use was therefore defined as more than 1.75 doses a day. The researchers found that the adjusted odds ratio for hip fracture with more than a year of proton pump inhibitor therapy was 1.44 (95% confidence interval 1.30 to 1.59). Among these patients on long-term proton pump inhibitors, high-dose users were much more likely to experience a hip fracture (adjusted OR 2.65, 95% CI 1.80 to 3.90, *P*<0.001). Longer duration proton pump inhibitor therapy was associated with even higher fracture risk. The adjusted odds ratio findings were (all *P*<0.001):

- For one year, 1.22 (95% CI 1.15 to 1.30),
- For two years, 1.41 (95% CI 1.28 to 1.56),
- For three years, 1.54 (95% CI 1.37 to 1.73), and
- For four years, 1.59 (95% CI 1.39 to 1.80).

A similar analysis was done for histamine 2 receptor antagonists, which have a weaker acid suppressive effect compared with proton pump inhibitors and do not interfere with osteoclastic proton pumps to reduce bone resorption. Histamine 2 receptor antagonist use for more than one year was associated with elevated hip fracture (adjusted OR 1.23 compared with nonuse, 95% CI 1.14 to 1.39, *P*<0.001), but a lower risk than long-term proton pump inhibitor therapy (proton pump inhibitor versus H2RA 1.34, 95% CI 1.14 to 1.38, *P*<0.001).

Likewise, in an analysis of proton pump inhibitor users excluding those with overlapping histamine 2 receptor antagonist use, the association with fracture risk was stronger than before (adjusted OR 1.62, 95% CI 1.41 to 1.89, *P*<0.001).

Observational studies always have the potential to be affected by unidentified residual confounding factors. Although fracture risk may have been affected by confounding factors that were not adjusted for in the study, the researchers said that they controlled for a comprehensive list of comorbidities which they felt made this possibility unlikely. Also, the database used in the study did not include information on over-the-counter calcium supplement use.

An analysis restricted to patients with documented chronic gastroesophageal reflux disease (GERD) showed negligible change in the fracture risk point estimate, suggesting little bias from residual confounding by indication and little possibility that GERD itself was responsible for the increased risk.

In addition, because the study was not designed to assess mechanisms, the authors pointed out that "we cannot be certain that there are no alternative explanations for the different effects associated with regular-dose and high-dose proton pump inhibitor therapy."

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