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PPI therapy: When to worry about fracture risk

High-dose, long-term use of proton pump inhibitors may increase fracture risk, but the evidence is inconclusive. Here's what to keep in mind.

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PRACTICE RECOMMENDATIONS

› *For most patients with chronic heartburn and regurgitation, step-down therapy to the lowest effective dose of proton pump inhibitors (PPIs) or treatment with a histamine-2 receptor antagonist (H2RA) is a reasonable, cost-effective approach.* (A)

› *Advise elderly patients who require long-term, high-dose PPI therapy to increase their dietary and/or supplemental calcium intake.* (C)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE 1 ▶ Damian F,* a 39-year-old construction worker who takes omeprazole for chronic gastroesophageal reflux disease (GERD), comes in to request a refill. He's had several accidents in recent years—he fell off a ladder on one occasion, and went down a flight of stairs on another—but none that resulted in significant trauma. Damian admits that he could better control his GERD symptoms by avoiding spicy and fatty foods, limiting alcohol consumption, and quitting smoking, but takes omeprazole nearly every day instead.

CASE 2 ▶ Estella G,* a 71-year-old retiree, has been on continuous proton pump inhibitor (PPI) therapy for chronic GERD and erosive esophagitis for nearly 20 years. The patient is a frail woman (body mass index=19.8 kg/m^2) and a former smoker (1½ packs a day), both of which increase her risk of osteoporosis. But she has never had a dual energy x-ray absorptiometry (DEXA) scan.

Proton pump inhibitors (PPIs) are one of the most commonly used prescription drug categories in the United States,[1] but they have been associated with an increase in fracture risk. A US Food and Drug Administration (FDA) safety update issued in March 2011 noted that there is little problem with the lower doses and shorter duration for which over-the-counter PPIs are intended, but patients who take higher-dose prescription PPIs or take prescription PPIs for more than a year may be at greater risk.[2]

If Damian and Estella were your patients, would you continue to prescribe PPI therapy or offer them alternatives? How should you treat other patients with chronic upper gastrointestinal (GI) distress? The evidence review that follows can help you answer those questions.

**These cases are based on real patients in my practice, but their names and details have been changed to protect their identity.*

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Patients with concomitant risk factors for fracture—eg, alcohol abuse, smoking, diabetes, neurologic or renal disease—face the highest risk for PPI-associated fracture.

How high is the risk? Evidence is mixed (or lacking)

Several retrospective studies have demonstrated a modest increased risk for hip, spine, and wrist fractures in men and women taking PPIs, with the highest risk in patients who have taken higher than standard doses for >4 years.[3-6] Concomitant risk factors (alcohol abuse, cigarette smoking, diabetes, and neurologic or renal disease) may increase fracture risk.[6] But other retrospective studies, as well as prospective studies, have found no significant increase in fracture risk in patients taking PPIs,[7-9] even after 5 years of therapy.[7] However, some studies that failed to find an increased risk of osteoporosis with PPI use had a small number of subjects,[8,9] resulting in a wide range in confidence intervals.

These findings, based on 6 retrospective case-control, cohort, and cross-sectional studies and 2 prospective cohort studies, are summarized in **TABLE 1**. No prospective randomized, blinded, controlled trials have examined the potential increased fracture risk associated with PPI use.

Do PPIs interfere with calcium metabolism?

Here, too, the findings are mixed. PPIs are known to inhibit the production and secretion of intragastric hydrochloric acid, which mediates small intestinal absorption of calcium,[10] but evidence is conflicting about the role of intragastric hydrochloric acid in calcium absorption. Osteoclasts also have proton pumps, and some researchers have suggested that PPIs have the potential to limit the activity of these proton pumps, leading to reduced bone resorption.[11]

To date, the only studies that have examined the impact of PPIs on intestinal calcium absorption were limited by the health status of the participants—all either had renal failure and were on hemodialysis or had hypo- or achlorhydria, chronic conditions known to adversely affect calcium metabolism.[12] Long-term randomized, double-blinded, placebo-controlled trials are needed to determine whether PPIs adversely affect intestinal calcium absorption and result in bone resorption abnormalities and increased fracture risk.

A closer look at the data

The varying responses associated with PPI dose and duration and the possibility that acid inhibition may decrease calcium absorption support a causal association between PPI use and fracture risk. But the low magnitude of the proposed association (most odds ratios <2) and the lack of data assessing potentially confounding factors limit evidence of causality.[3,5,6,9] One key limitation of the earlier studies is that they were not designed to define the specific mechanism underlying the association between PPI therapy and fracture risk.

Older studies suggest a causal relationship

Two case-control studies[3,4] found a causal association between PPI use and fracture risk, but one of them failed to identify either a dose-response or a duration-response effect.[4] And neither study was designed to define underlying mechanisms to explain the potential association between fracture risk and PPI therapy.

A retrospective matched cohort study[5] found an increase in the overall risk of fracture among patients with ≥7 years of PPI therapy and an increased risk of hip fracture with ≥5 years of therapy, but short-term risk of fracture was not found to be significant. The results of this study suggest that the risk of osteoporotic fracture increases with duration of exposure to PPI therapy, but not in a dose-dependent fashion.

Newer data are less worrisome

The results of a retrospective cross-sectional trial, published last year, are more reassuring. The researchers determined via univariate analysis that PPI use was associated with a *lower* risk of osteoporosis, both at the lumbar spine (for all levels of PPI use) and the hip (in patients who had taken more than 1500 standard PPI doses over the previous 5 years).[7]

This finding—that increasing intensity (both longer duration and higher dosage) of PPI exposure is not associated with an increased risk of osteoporosis—contrasts with results of the authors' earlier study.[5] This may be because they monitored annualized changes in BMD and were able to detect significant

TABLE 1

How PPI use affects fracture risk

Study/year (N)	Study design	Outcomes	OR (95% CI)
Yang/2006[3] (13,556)	Nested case-control	Hip fracture:	
		1 y	1.22 (1.15-1.30)
		>1 y (>1.75 x average daily dose)	2.65 (1.80-3.90)
		4 y	1.59 (1.39-1.80)
Vestergaard 2006[4] (124,655)	Case-control	Any fracture (PPI use within year)	1.18 (1.12-1.43)
		Hip fracture (PPI use within year)	1.45 (1.28-1.65)
		Spine fracture (PPI use within year)	1.60 (1.25-2.04)
Targownik/2008[5] (15,792)	Retrospective matched cohort	Hip fracture:	
		5 y	1.62 (1.02-2.58)
		7 y	4.55 (1.68-12.3)
		Any osteoporosis-related fracture >7 y	1.92 (1.16-3.18)
Kaye/2008[8] (1098)	Matched case-control	Hip fracture*	0.9 (0.7-1.1)
Corley/2010[6] (33,752)	Case-control	Any fracture >2 y + 1 risk factor	1.30 (1.21-1.39)
Targownik/2010[7] (5789)	Retrospective cross-sectional	Osteoporosis of the hip (>5 y)	0.84 (0.55-1.34)
		Osteoporosis of the lumbar spine (>5 y)	0.79 (0.59-1.06)
Yu/2008[9] (10,215)†	Prospective cohort	Hip fracture (current use):	
		Men	0.62 (0.26-1.44)‡
		Women	1.16 (0.80-1.67)‡
		Non-spine fracture (current use):	
		Men	1.21 (0.91-1.62)‡
		Women	1.34 (1.10-1.64)‡
Gray/2010[13] (2831)	Prospective cohort	Hip fracture (current use)	1.00 (0.71-1.40)‡
		Spine fracture (current use)	1.47 (1.18-1.82)‡
		Wrist fracture (current use)	1.26 (1.05-1.51)‡
		Total fracture (current use)	1.25 (1.15-1.36)‡

*In patients who received PPI prescription.

†9494 non-PPI users, 721 PPI users.

‡Adjusted hazard ratio.

CI, confidence interval; OR, odds ratio; PPI, proton pump inhibitor.

PPIs are known to inhibit intragastric hydrochloric acid, which mediates small intestinal absorption of calcium, but there is conflicting evidence about the acid's role in calcium absorption.

changes in other medications participants were taking that might affect bone loss or gain. That allowed them to validate their findings regarding a lack of true association between bone loss and PPI use, the authors reported.

A matched, nested case-control trial[8] determined that the use of PPIs does not increase the risk of hip fracture in patients without associated major risk factors (ie, alcohol dependence, underlying neurologic disease, accidental falls, and senility). The researchers suggested that the difference between their findings and those of an earlier nested case-control study[3] could mean that the increased

TABLE 2

GERD and diet: Foods that worsen symptoms[16]

Alcohol
Caffeine-containing beverages
Citrus fruits
Chocolate
Fried and fatty foods
Garlic and onions
Mint flavorings
Spicy foods
Tomato-based foods (eg, chili, pizza, spaghetti sauce, salsa)

The Women's Health Initiative found PPI use to be associated with a modest increase in spine, forearm, wrist, and total fractures in postmenopausal women.

risk of hip fracture found in the older study occurred only among PPI users with definable risk factors for hip fracture.

Recent results from the Women's Health Initiative (WHI) suggest that in postmenopausal women, PPI use is not associated with hip fractures. The WHI did, however, find a modest association between PPI use and clinical spine, forearm, or wrist fracture, as well as total fractures.[13] Compared with previous trials, this large cohort study had a large number of fracture events and assessed confounding factors that had not been addressed, including calcium intake. It also was the first trial to assess associations between BMD and fracture risk relative to PPI dosing. Although no specific conclusion was reported, the researchers did not find evidence of dose dependence.

A reasonable approach to PPI use

A consensus statement from the FDA[2] and the authors of 2 meta-analyses[14,15] recommend that PPIs be used only for appropriate indications—GERD, peptic ulcer disease, dyspepsia, and treatment of *Helicobacter pylori*—and not in higher doses or for longer periods than are necessary to achieve the desired results.

Whenever possible, implement step-down therapy to the lowest effective dose or prescribe an H2RA rather than a PPI. Both are cost-effective ways to treat most patients with upper GI symptoms.[2] It is important, too, to advise elderly patients who require long-term, high-dose PPI therapy to increase their dietary and/or supplemental calcium intake, to recommend DEXA scans for individuals at risk for osteoporosis, and to counsel patients who suffer from GI distress to avoid foods that are known to exacerbate symptoms (**TABLE 2**).[16]

CASE 1 ▶ Damian

You talk to Damian about the association between prolonged PPI therapy and fracture risk and stress the need for dietary changes and lifestyle modifications, particularly smoking cessation. On a return visit several months later, he reports that he has stopped smoking and cut way back on alcohol consumption, and eats fast food less frequently. As a result, he no longer requires chronic use of PPI therapy, and now takes omeprazole only when he has symptoms of GERD—usually, after indulging in fried or fatty foods.

CASE 2 ▶ Estella

Estella has severe GERD and erosive esophagitis and will probably need lifelong PPI therapy to adequately control her symptoms. After a detailed discussion of potential risks vs benefits of PPIs, she agrees to a DEXA scan to evaluate for osteoporosis. Her test results show osteopenia in the lumbar spine and femoral neck, but no evidence of osteoporosis. You advise her to increase her consumption of calcium and to undergo DEXA scanning in another 2 years. **JFP**

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