PPI Use Linked to Slight Rise in Hip Fracture Risk

BY SARAH PRESSMAN LOVINGER
Contributing Writer

Hip fracture risk was increased with long-term use of proton pump inhibitors in a study published recently in the Journal of the American Medical Association, and the findings have led to concerns and questions among physicians, as well as among patients who take these frequently prescribed drugs.

Dr. Yu-Xiao Yang of the division of gastroenterology at the University of Pennsylvania and his colleagues analyzed data on 1.8 million patients in the General Practice Research Database, a national database of patients in the United Kingdom, to assess a possible association between proton pump inhibitor (PPI) therapy and the risk of hip fracture (JAMA 2006;296:2947-53).

The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI use was significantly increased at 1.44 (95% confidence interval [CI], 1.30-1.59; *P* less than .001). In addition, patients who were prescribed long-term, high-dose PPI therapy had a markedly increased risk of hip fracture, with an AOR of 2.65 (95% CI, 1.80-3.90; *P* less than .001).

Dr. Colin W. Howden, professor of gastroenterology at Northwestern University, Chicago, said while the study indicates that PPIs increase the risk of hip fracture, physicians and patients should avoid becoming overly concerned about the findings. "The risk needs to be put in context," he said.

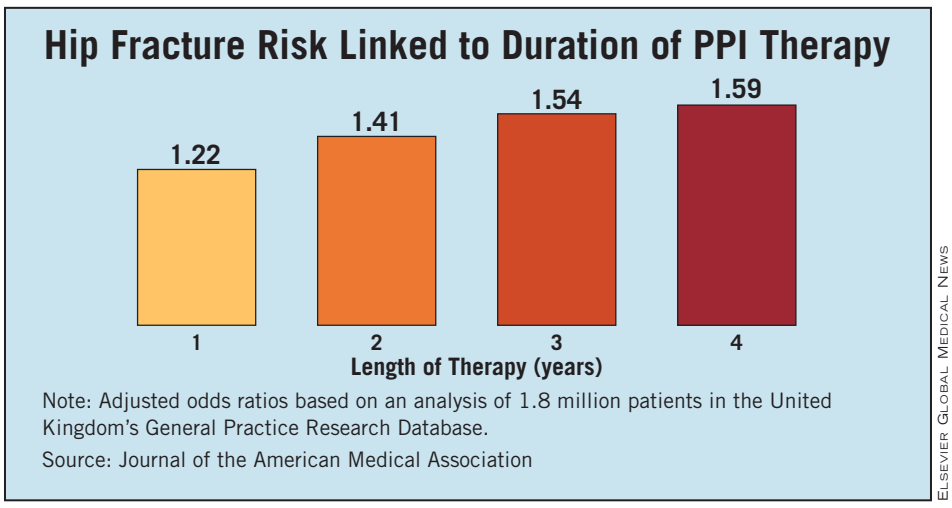
All patients were at least 50 years old and had no documented hip fracture before the study started or during the first year of follow-up; all started follow-up between May 1987 and March 2003. The cohort included 192,028 people who had received at least one prescription for a PPI during the follow-up period; 187,686 people who received at least one prescription for a histamine$_2$ receptor antagonist (H_2RA) during the follow-up period but had not used a PPI; and 1.4 million people who had no documented use of either a PPI or H_2RA, and were thus classified as acid-suppression nonusers.

The authors matched cases of those who had a hip fracture during the study period with controls who did not. Cases and matched controls (up to 10 controls for each case) were similar in terms of sex, age, and both the calendar period and duration of follow-up before the index date.

The results revealed that 13,556 incident hip fractures—10,834 among acid suppression nonusers and 2,722 among PPI users—occurred during the study period. These hip fracture cases were matched with a total of 135,386 controls (at least 1 control per case).

In addition to an increased adjusted odds ratio for hip fracture after more than 1 year of PPI use, the data showed that the strength of the association between hip fracture and PPI use increased with each cumulative year of use. The AOR was 1.22 for 1 year of PPI therapy, 1.41 for 2 years, 1.54 for 3 years, and 1.59 for 4 years, with *P* less than .001 for all comparisons.

Dr. Howden commented that this study should remind physicians to review their patients' medication lists, particularly those of older patients who are at higher risk for hip fractures. "The bottom line is that if [patients need] to be on a PPI for a valid reason, they should be on a PPI," he said. Clinicians who are concerned about the hip fracture risk in patients who may not need to take a PPI continually could discontinue the drug and see how the patient fares.



The study did not determine the mechanism behind the increased risk of hip fracture in PPI users, but the authors noted that these drugs may decrease calcium absorption via induction of hypochlorhydria, and may reduce bone resorption by inhibiting the osteoclastic proton transport system.

Currently, there are no guidelines for intensifying osteoporosis screening in patients on long-term PPI therapy. Until guidelines are published, physicians should consider the needs of individual patients and make diagnostic and treatment recommendations accordingly.

Dr. Howden cautioned against taking an alarmist approach to this study. "I think the absolute risk is quite small, but it's not zero," he said.

Dr. George Sachs, professor of medicine and physiology at the University of California, Los Angeles, agreed that the study shows only a small excess risk of hip fracture in the group taking PPIs. These medications have only a small effect on stomach pH levels and hence calcium absorption, according to Dr. Sachs. Increasing calcium supplements or milk intake is the best method of decreasing the risk of hip fracture, he said.

"The findings are not surprising," commented Dr. Steven Petak, president of the American Association of Clinical Endocrinologists. "Vitamin D and calcium insufficiency are very common in the population and it is likely [that] using a PPI only adds to an already significant problem."

He recommends that patients consume 1,200-1,400 mg of calcium and 600-1,000 IU of vitamin D_3 (cholecalciferol) daily; supplements should be taken in divided doses with food to help absorption.

"If PPI drugs are needed, then certainly they should be used, but with additional evaluation of the bone and calcium status," Dr. Petak said. ■

Obese Patients May Not Be Safe From Osteoporosis After All

VERONA, ITALY — Contrary to conventional wisdom, obese patients may not be protected against osteoporosis and could present with significant bone loss, new data show.

In a study of 233 morbidly obese patients, 34% showed a significant decrease in bone mineral density at the lumbar spine with a median T score of –1.98 (range –1.1 to –4.2), Dr. Carlo Lubrano and his colleagues reported in a poster at a joint meeting of the Italian Association of Clinical Endocrinologists and the American Association of Clinical Endocrinologists.

Low bone mass is defined as a bone density at the spine or hip between 1.0 and 2.4 standard deviations below the average for healthy young adults, which translates to a T score of –1 to –2.5, according to the World Health Organization. Bone density 2.5 standard deviations or more below the young adult mean is categorized as osteoporosis.

The 195 women and 38 men in the study had an average body mass index of 37 kg/m^2 and a mean age of 44 years. Bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry.

Overall, 31.5% of the women showed a median BMD of 0.971 g/cm^2 and a median T score of –1.93 (range –1.0 to –4.2). Among the male population, 45% showed a modification in BMD with a median lumbar BMD of 0.93 g/cm^2 and a median T score of –1.85 (range –1.3 to –2.6), wrote the investigators from the University of Rome La Sapienza.

It had been thought that obesity might protect the skeleton against osteoporosis. Recent evidence suggests that obesity may actually weaken the skeleton and increase the risk of fractures. The authors concluded that a "specific and careful characterization of skeletal metabolism might be useful in both female and male obese subjects."

—Patrice Wendling

After 5 Years of Alendronate, 5 More Years Show Little Benefit

BY BARBARA RUTLEDGE
Contributing Writer

Postmenopausal women who discontinue alendronate after 5 years of treatment may experience a moderate decline in bone mineral density but are not at a significantly higher risk for fracture compared with those who continue alendronate for an additional 5 years, reported Dennis M. Black, Ph.D., of the University of California, San Francisco, and his colleagues.

"For many women, discontinuation of alendronate after 5 years for up to 5 more years does not significantly increase fracture risk, but women at high risk of clinical vertebral fractures, such as those with vertebral fracture or very low [bone mineral density], may benefit by continuing beyond 5 years," Dr. Black wrote (JAMA 2006;296:2927-38).

This conclusion was based on findings from a 5-year extension of the Fracture Intervention Trial (FIT), a randomized, placebo-controlled trial designed to evaluate the effect of daily alendronate on bone mineral density (BMD) and fracture risk in postmenopausal women with low BMD.

The FIT Long-Term Extension (FLEX) study was open to women who had been assigned to the alendronate treatment arm in FIT and who had completed at least 3 years of alendronate treatment. Women with a total hip BMD of less than 0.515 g/cm^2 (T score less than –3.5) at baseline were ineligible to participate in FLEX.

Participants were randomly assigned to receive daily treatment with 10 mg alendronate (30%), 5 mg alendronate (30%), or placebo (40%). The primary end point was total hip BMD.

Of 1,099 women participating in FLEX, 437 were assigned to placebo, 329 were assigned to 5 mg alendronate, and 333 were assigned to 10 mg alendronate.

After 5 years, total hip BMD declined 3.38% from baseline in the placebo group and 1.02% in the combination of the two alendronate groups. The combined alendronate group experienced a mean 5.26% increase from FLEX baseline in lumbar spine BMD compared with a mean 1.52% increase in the placebo group.

The treatment groups did not significantly differ in adverse events or other safety parameters during the study.

Notably, mean BMD levels remained at or above FIT baseline levels in all treatment groups after 5 years. ■