

Proton Pump Inhibitors Raise Hip Fracture Risk Over Time

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January 31, 2012 — A new study strengthens the association of long-term use of proton pump inhibitors (PPIs) with increased risk for hip fracture in postmenopausal women, particularly those who smoke.

PPIs can affect fracture risk by increasing secretion of gastrin, inhibiting calcium absorption, and altering osteoclast function. Use of these drugs to treat indigestion increased when they became available over the counter in the United States in 2003. In May 2010, the US Food and Drug Administration issued a warning about the possible link between extended PPI use and hip fracture and requested further information.

The new study, published online January 31 in the *British Medical Journal*, adds information from nearly 80,000 women to the body of data. Hamed Khalili, MD, from Massachusetts General Hospital, Boston, Massachusetts, and colleagues examined data from the prospective cohort Nurses' Health Study, which provided information on lifestyle and dietary risk factors. The study, which began in 1982, assesses participants by questionnaire every 2 years.

Use of PPIs increased nearly 3-fold from 2000 to 2008 among the 79,899 women in the study, from 6.7% to 18.9%. The researchers documented 893 hip fractures over 565,786 person-years of follow-up. Absolute risk for hip fracture among the women who regularly used the drugs for at least 2 years was 2.02 events per 1000 person years compared with 1.51 events per 1000 person years among women who did not take the drugs.

The risk for hip fracture among women who used PPIs for 2 or more years was 35% higher (age-adjusted hazard ratio, 1.35; 95% confidence interval [CI], 1.13 - 1.62). The association held up after adjusting for body mass index, physical activity level, calcium intake, and use of other drugs that can affect fracture risk, such as bisphosphonates, thiazide diuretics, corticosteroids, and hormone replacement.

Hip fracture risk correlated with PPI use over time. "Compared with non-users, the fully adjusted hazard ratios of fracture were 1.36 (1.12 - 1.65) for women with two years' use of PPIs, 1.42 (1.05 - 1.93) for four years' use, and 1.55 (1.03 - 2.32) for six to eight years' use," the researchers report. However, the risk returns to normal for women who have ceased taking the drugs for at least 2 years.

Smoking history stood out among the risk factors considered. Fracture risk rose by more than 50% for women who currently smoke or did so previously (fully-adjusted hazard ratio 1.51 [95% CI, 1.20 - 1.91]). By contrast, the authors found no association between PPI use and fracture risk in never smokers (fully-adjusted hazard ratio 1.06 [95% CI, 0.77 - 1.46]). The researchers suggest that the inhibition of calcium absorption from smoking may act synergistically with PPIs to increase fracture risk. The reason for PPI use did not affect fracture risk.

Strengths of the study, according to the investigators, include its prospective design, large sample, and analysis of several putative confounding risk factors. A limitation is that the study did not include brands and dosages of the PPIs. The researchers conclude that "regular use of PPI was associated with increased risk of hip fracture among postmenopausal women, with the strongest risk observed in individuals with the longest duration of use or with a history of smoking."

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