

Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture

Yu-Xiao Yang, MD, MSCE

James D. Lewis, MD, MSCE

Solomon Epstein, MD

David C. Metz, MD

MORE THAN 47 000 HIP fractures occur annually in the United Kingdom.¹ Hip fracture is the main manifestation of senile osteoporosis, which results from secondary hyperparathyroidism associated with calcium malabsorption, low calcium intake, and other factors.² Among the various forms of low-trauma fractures, hip fracture leads to the most devastating consequences. The mortality rate during the first year after a hip fracture is 20%.^{3,4} Among those who survived this period, 1 in 5 requires nursing home care.⁵ In addition, hip fractures invariably require an emergency department visit, hospitalization, surgery, and rehabilitation, incurring huge health care costs.

The advent of potent acid suppressive medications such as proton pump inhibitors (PPIs) has revolutionized the management of acid-related diseases such as gastroesophageal reflux disease (GERD). Millions of individuals have been using these medications on a continuous or long-term basis.⁶ Significant hypochlorhydria, particularly among the elderly population who may have decreased PPI clearance and may be more likely to have hypochlorhydria at baseline due to higher prevalence of *Helicobacter pylori* infection,^{7,8} could theoretically result in calcium malabsorption.^{9,10} In fact, limited animal and human studies have shown that PPI therapy may decrease insoluble calcium absorption or bone density.^{11,12} On the other hand, lim-

Context Proton pump inhibitors (PPIs) may interfere with calcium absorption through induction of hypochlorhydria but they also may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps.

Objective To determine the association between PPI therapy and risk of hip fracture.

Design, Setting, and Patients A nested case-control study was conducted using the General Practice Research Database (1987-2003), which contains information on patients in the United Kingdom. The study cohort consisted of users of PPI therapy and nonusers of acid suppression drugs who were older than 50 years. Cases included all patients with an incident hip fracture. Controls were selected using incidence density sampling, matched for sex, index date, year of birth, and both calendar period and duration of up-to-standard follow-up before the index date. For comparison purposes, a similar nested case-control analysis for histamine 2 receptor antagonists was performed.

Main Outcome Measure The risk of hip fractures associated with PPI use.

Results There were 13 556 hip fracture cases and 135 386 controls. The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI therapy was 1.44 (95% confidence interval [CI], 1.30-1.59). The risk of hip fracture was significantly increased among patients prescribed long-term high-dose PPIs (AOR, 2.65; 95% CI, 1.80-3.90; $P < .001$). The strength of the association increased with increasing duration of PPI therapy (AOR for 1 year, 1.22 [95% CI, 1.15-1.30]; 2 years, 1.41 [95% CI, 1.28-1.56]; 3 years, 1.54 [95% CI, 1.37-1.73]; and 4 years, 1.59 [95% CI, 1.39-1.80]; $P < .001$ for all comparisons).

Conclusion Long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture.

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ited in vitro and human data suggest that omeprazole may decrease bone resorption by inhibiting osteoclastic vacuolar $H^+ - K^+ - ATPase$.¹³⁻¹⁶ This study was conducted to determine whether these opposing effects of PPI therapy on bone metabolism translate into clinically important alterations in hip fracture risk in a large cohort representative of the general population.

METHODS

A nested case-control study was conducted using the General Practice Research Database (GPRD), which contains preexisting data. Personal information was removed prior to inclusion in the database. Informed con-

sent was waived by the University of Pennsylvania institutional review board and the GPRD scientific and ethical advising group.

Data Source

The GPRD is a computerized medical record system of a selected group of gen-

Author Affiliations: Division of Gastroenterology (Drs Yang, Lewis, and Metz), Center for Clinical Epidemiology and Biostatistics (Drs Yang and Lewis), Department of Biostatistics and Epidemiology (Drs Yang and Lewis), and Division of Endocrinology (Dr Epstein), University of Pennsylvania School of Medicine, Philadelphia; and Department of Medicine, Doylestown Hospital Research Center, Doylestown, Pa (Dr Epstein).
Corresponding Author: Yu-Xiao Yang, MD, MSCE, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, 722 Blockley Hall, 423 Guardian Dr, Philadelphia, PA 19104 (yangy@mail.med.upenn.edu).

eral practices in the United Kingdom.¹⁷ Under the National Health Services, 98% of the UK population receives all forms of health care through their general practitioners. The database is broadly representative of the UK population in terms of sex, age, and geography.¹⁸

The information prospectively collected in the database includes demographic information, all prescription use, clinical diagnoses, specialty consultation notes, and hospital discharge diagnoses. The Read Clinical Classification¹⁹ and the Oxford Medical Information System²⁰ codes were used to classify medical diagnoses. The Oxford Medical Information System and the Read Clinical Classification system are hierarchical coding systems that are organized based on organ systems and disease types. As such, they allow efficient and systematic identification of relevant diagnostic codes in an exhaustive fashion, leading to extremely high reliability of the codes for individual conditions.

The GPRD is fundamentally different from claims-based medical databases; it is essentially an electronic version of the actual patient medical record. A list of diagnoses, documented in GPRD medical codes, is associated with each encounter between the general practitioners and their patients. Participating general practices follow predefined protocols for the recording and transferring of computerized clinical data to the research database.¹⁷ Data reaching predefined quality standards are indicated as "up-to-standard."¹⁷ More than 500 published epidemiological studies have been performed using this database. Previous studies have shown that information on prescription use, diagnoses, and hospitalizations is of excellent quality.^{17,21}

Study Cohort

From the 9.4 million patients who started follow-up in the full version of the GPRD between May 1987 and March 2003, we excluded individuals meeting at least 1 of the following 4 criteria: less than 365 days of total up-to-standard database follow-up (n=2.3

million); younger than 50 years at the time of database enrollment (n=6.9 million); having a documented hip fracture before the start of up-to-standard database follow-up or during the first year of up-to-standard database follow-up (n=15 871); having received a histamine 2 receptor antagonist (H2RA) or PPI therapy exclusively during non-up-to-standard periods of database follow-up (n=21 011). The third exclusion criterion was designed to avoid inclusion of prevalent fracture cases.²² Some individuals met multiple exclusion criteria. All together, approximately 7.6 million patients were excluded based on these 4 exclusion criteria.

The remaining 1.8 million patients made up the eligible study cohort, which consisted of 192 028 users of PPI therapy who received at least 1 prescription for PPIs during their up-to-standard database follow-up, 187 686 users of H2RA who received at least 1 prescription during their up-to-standard database follow-up but no PPI therapy, and 1.4 million acid suppression nonusers who had no documented prescriptions for PPI or H2RA therapy.

The primary nested case-control analysis was conducted within the study cohort consisting of all of the PPI users and the acid suppression drug nonusers. A secondary nested case-control analysis was conducted within the study cohort and included the users of H2RA only and the nonusers of acid suppression. Patients who received both PPI and H2RA therapies were considered in the primary analysis for PPIs only. Cases and controls were sampled from the respective study cohorts using incidence density sampling.²³ Incidence density sampling yields odds ratios (ORs) interpretable as unbiased estimates of the incidence rate ratios.²³

Study Groups

Cases consisted of all individuals in the study cohort with first occurrence of incident hip fracture at least 1 year after the beginning of their up-to-standard follow-up. The diagnosis of hip frac-

ture in the GPRD was found to be highly valid in a previous survey with more than 90% of the cases confirmed by general practitioners.²⁴ Our case definition did not include distal femoral fracture because its association with osteoporosis is uncertain.

Up to 10 controls were selected for each case from the study cohort, using incidence density sampling,²³ matched for sex, index date, year of birth, and both calendar period and duration of up-to-standard follow-up before the index date.

Exposure Ascertainment

The primary exposure of interest was PPI therapy of more than 1 year before the index date. The 1-year duration was chosen because alterations in fracture risk due to the use of other medications, such as bisphosphonates, thiazide diuretics, and corticosteroids were apparent after 1 year of exposure.^{25,26} Calcium absorption decreases with age while urinary calcium excretion increases.²⁷ These changes result in a baseline negative calcium balance in late adulthood.²⁷ Given this background negative calcium balance, any additional calcium deficit due to even short-term acid suppression would persist. Thus, cumulative exposure to acid suppression therapy may be the most clinically relevant measure when considering the risk of osteoporosis and fracture.

Using a continuous variable for cumulative duration of PPI therapy, the effects of increasing durations of exposure were examined. The significance of a quadratic term was tested to assess the linearity of the association between duration of use and the risk of fracture to determine whether to include the quadratic term in the regression model. The ORs associated with durations of up to 4 years of PPI therapy were estimated because there were too few exposed patients beyond 4 years to yield a stable estimate.

Individual periods of PPI or H2RA exposure were determined according to the intended duration of each prescription recorded in the database. In addition, the risks associated with medica-

tion doses above and below the average of 1.75 per day were compared for the treatment period (ie, calculated by dividing sum of the number of daily doses prescribed by the total number of prescriptions). Dosages greater than twice daily were rarely prescribed, and prescriptions commonly lasted 1 month. As such, the group with an average daily dose greater than 1.75 contained patients who had received at least 75% of their prescriptions at a dose of twice daily. In the group with an average daily dose of less than 1.75, 90% had an average daily dose of less than 1.1.

Statistical Analysis

Conditional logistic regression was used to estimate the unadjusted and adjusted ORs (AORs) and 95% confidence intervals (CIs). In addition to the matching factors of age and sex, a comprehensive list of potential confounders that are risk factors for falling, had known associations with osteoporosis, and/or determined comorbidity status were examined. These included body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), smoking history, alcoholism, congestive heart failure, cerebral vascular accident, dementia, impaired mobility, myocardial infarction, chronic obstructive pulmonary disease or asthma, peptic ulcer disease, peripheral vascular disease, rheumatoid arthritis, vision loss, celiac sprue, Paget disease, osteomalacia, chronic renal failure, Cushing disease, inflammatory bowel disease, and prior history of fracture (ie, >3 months before the index date), or seizure disorder.

Exposures to the following classes of medications also were considered: anxiolytics, antidepressants, antiparkinsonian drugs, thiazide diuretics, statins, corticosteroids, hormone therapy, bisphosphonates, calcitonin, nonsteroidal anti-inflammatory drugs, anticonvulsants, thyroxine, and calcium and vitamin D supplementation. Patients with medication-related variables were defined dichotomously as users (ie, ≥ 12 months of cumulative use before index date and last prescrip-

tion ≤ 6 months before the index date) and nonusers. The presence of comorbidities was determined based on identification of GPRD medical diagnostic codes (ie, Oxford Medical Information System and Read codes) documented on at least 1 date prior to the index date.

All of the potential confounders listed above that had a prevalence of 1% in at least 1 of the comparison groups were simultaneously included in the multivariable logistic regression model

(TABLE 1). For comparison purposes, a separate nested case-control analysis for H2RA therapy was conducted in a similar fashion. The H2RAs have a weaker acid suppressive effect compared with the PPIs and they do not interfere with osteoclastic proton pumps. As a result, examining the risk associated with H2RA therapy can be useful in the interpretation of any observed association between PPI therapy and fracture risk. In addition, a third case-control analysis nested within a cohort

Table 1. Characteristics of Hip Fracture Cases and Controls*

	Cases (n = 13 556)	Controls (n = 135 386)	Crude OR (95% CI)
Female sex	79.90	79.89	NA
Age at database enrollment, mean (SD), y	77 (9.3)	77 (9.3)	NA
Body mass index†			
<20	6.77	3.59	1.95 (1.82-2.10)
>30	4.51	6.71	0.65 (0.60-0.71)
Medication use			
Anxiolytic	14.95	9.20	1.76 (1.67-1.85)
Antidepressant	8.42	4.09	2.17 (2.03-2.32)
NSAID/aspirin	9.16	6.84	1.38 (1.30-1.47)
Thiazide diuretic	5.85	6.05	0.95 (0.89-1.04)
Antipsychotic	4.46	1.39	3.34 (3.03-3.67)
Antiparkinsonian	3.49	0.94	3.83 (3.44-4.26)
Antiseizure	2.26	0.68	3.42 (3.00-3.90)
Hormone therapy	0.74	1.03	0.53 (0.39-0.71)
Corticosteroid	3.15	1.43	2.25 (2.02-2.51)
Thyroxine	5.09	3.69	1.40 (1.29-1.52)
Health condition			
Alcoholism	1.93	0.42	4.70 (4.05-5.44)
Arthritis	29.85	24.56	1.32 (1.27-1.37)
Stroke	13.96	7.23	2.10 (1.99-2.22)
Asthma or COPD	11.67	8.02	1.52 (1.44-1.61)
Dementia	11.07	3.57	3.48 (3.27-3.70)
Diabetes mellitus	4.40	2.94	1.52 (1.39-1.66)
Congestive heart failure	6.72	4.52	1.54 (1.43-1.65)
Impaired mobility	6.14	2.47	2.61 (2.41-2.82)
Myocardial infarction	5.28	4.33	1.23 (1.14-1.34)
Peptic ulcer disease	4.34	2.87	1.54 (1.41-1.69)
Seizure disorder	3.16	1.03	3.15 (2.82-3.51)
Peripheral vascular disease	5.39	3.59	1.54 (1.42-1.66)
Visual impairment	2.16	1.53	1.43 (1.26-1.62)
Current smoker	13.68	9.65	1.53 (1.45-1.62)
Prior fractures			
High trauma	10.08	4.72	2.43 (2.29-2.59)
Low trauma‡	9.51	4.50	2.44 (2.28-2.60)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; NA, data not available; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

*Values are expressed as percentages unless otherwise indicated. Dichotomous variables with a prevalence of less than 1% in both case and control groups were omitted for both proton pump inhibitor and histamine 2 receptor antagonist analyses due to negligible effect.

†Calculated as weight in kilograms divided by height in meters squared.

‡Defined as individuals with wrist and vertebral fractures.

that included H2RA and PPI users together was performed to calculate the OR directly comparing H2RA therapy with PPI therapy.

In addition, the primary analysis for PPIs was repeated, restricting it to those patients who had chronic GERD (ie, ≥ 3 diagnoses recorded on different dates in the database). The recorded diagnosis of GERD in the GPRD was validated in a previous study.²⁸ This restriction analysis was intended to exclude the possibility that GERD itself may be associated with fracture risk. Furthermore, this restriction analysis could help assess the extent of residual confounding by comorbidity status in the primary analysis. The ORs and 95% CIs were estimated by multivariable logistic regression in this analysis.

Because osteoporosis is more common in women and because women are probably more likely to take calcium supplements, sex-specific risks also were determined and interactions between sex and each form of acid suppressive therapy were tested using the likelihood ratio test.

All analyses were performed with Stata version 8.0 (StataCorp, College Station, Tex). A *P* value of less than .05 was considered statistically significant for all analyses.

RESULTS

Among the acid suppression nonusers, 10 834 incident hip fractures were identified. These fractures were added to 2722 incident hip fractures identified among the PPI users to make up the case group. These cases were matched with 135 386 controls with at least 1 eligible control to each case. The crude incidence rate of hip fracture was estimated to be 4.0/1000 person-years among patients with more than 1 year of PPI therapy and 1.8/1000 person-years among acid suppression nonusers.

The characteristics of the case and control groups appear in Table 1. The hip fracture cases were more likely to have received medications or medical diagnoses that had known associations with either osteoporosis or the risk of falling. High BMI, hormone therapy,

and long-term statin therapy were associated with reduced risk of hip fractures in crude analysis.

Controlling only for the matching variables, the crude OR for hip fracture associated with more than 1 year of PPI therapy was 1.82 (95% CI, 1.67-2.00; *P* < .001), while the multivariable AOR for all the potential confounders was 1.44 (95% CI, 1.30-1.59; *P* < .001). The corresponding AOR associated with more than 1 year of H2RA use was 1.23 (95% CI, 1.14-1.39; *P* < .001). Our PPI user group contained some users of both PPI and H2RA. To determine the effect of PPI taken alone, PPI only users were compared with acid suppression nonusers (AOR, 1.62; 95% CI, 1.41-1.89; *P* < .001). In a separate secondary case-control analysis, long-term PPI therapy was associated with a higher fracture risk (AOR for >1 year of cumulative use, 1.34; 95% CI, 1.14-1.38) compared with long-term H2RA therapy (*P* < .001).

In the regression model in which duration of PPI therapy was included as a continuous variable, the quadratic term was significant (*P* < .001), suggesting that the duration variable was associated with fracture risk in a nonlinear fashion. Therefore, the quadratic term was included in the regression model. The strength of the association with hip fractures increased with increasing duration of PPI therapy (TABLE 2).

Among users of PPI therapy for more than 1 year, a significant dose-response effect with respect to the average daily dose was observed (TABLE 3). The risk of hip fracture was markedly increased among long-term users of high-dose PPI therapy compared with acid suppression nonusers (AOR, 2.65; 95% CI, 1.80-3.90; *P* < .001).

The positive association between long-term PPI therapy and hip fracture was stronger in men (OR, 1.78; 95% CI, 1.42-2.22) than women (OR, 1.36; 95% CI, 1.22-1.53). The test for interaction between PPI therapy and sex was statistically significant (*P* = .04).

When the analysis was restricted to patients with documented chronic GERD, the multivariable OR was 1.41 (95% CI, 1.02-1.94; *P* = .03) for hip fracture asso-

Table 2. Risk of Hip Fracture Associated With Increasing Cumulative Duration of Proton Pump Inhibitor Therapy

	Cumulative Proton Pump Inhibitor Therapy Duration, y			
	1	2	3	4
OR (95% CI)*				
Crude	1.43 (1.35-1.52)	1.84 (1.67-2.01)	2.10 (1.91-2.35)	2.17 (1.93-2.45)
Adjusted†	1.22 (1.15-1.30)	1.41 (1.28-1.56)	1.54 (1.37-1.73)	1.59 (1.39-1.80)

Abbreviations: CI, confidence interval; OR, odds ratio.

*The ORs are from the conditional logistic regression model matched by year of birth, sex, and both calendar period and duration of follow-up before the index date, and included a quadratic term for duration of proton pump inhibitor therapy in years (*P* < .001 for the test of significance for the quadratic term).

†Adjusted for matching variables and all potential confounders in Table 1.

Table 3. Risk of Hip Fracture Associated With Increasing Daily Dosages of Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Therapies

	No. (%) of Participants		OR (95% CI)*	
	Cases	Controls	Crude	Adjusted†
>1 y of H2RA				
≤1.75 average daily dose	345 (2.53)	2189 (1.61)	1.66 (1.48-1.86)	1.23 (1.09-1.40)
>1.75 average daily dose	387 (2.84)	2289 (1.68)	1.78 (1.60-1.99)	1.30 (1.16-1.46)
>1 y of PPI				
≤1.75 average daily dose	534 (3.94)	3228 (2.38)	1.77 (1.61-1.95)	1.40 (1.26-1.54)
>1.75 average daily dose	37 (0.27)	123 (0.09)	3.18 (2.20-4.60)	2.65 (1.80-3.90)

Abbreviations: CI, confidence interval; H2RA, histamine 2 receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor.

*The ORs are from a conditional logistic regression model matched by year of birth, sex, and both calendar period and duration of follow-up before the index date.

†Adjusted for matching variables and all potential confounders in Table 1.

ciated with PPI therapy for at least 1 year, after adjustment for age, sex, duration of follow-up, and all potential confounders listed in Table 1. The corresponding AOR associated with H2RA use was 1.21 (95% CI, 0.67-2.22; $P = .46$). A significant dose-response effect associated with PPI therapy was again observed in this analysis restricted to patients with GERD. The multivariable AOR associated with high-dose long-term PPI therapy was 3.49 (95% CI, 1.24-9.84; $P = .02$).

COMMENT

We found a significantly increased risk of hip fracture associated with long-term PPI therapy, particularly among long-term users of high-dose PPI. The large number of hip fracture cases in our study cohort enhanced the precision of our point estimates, and allowed adequate assessment of the effects of a comprehensive list of potential confounders.

Calcium malabsorption secondary to acid suppressive therapy may potentially explain the positive association. Calcium solubility has been believed to be important for its absorption.²⁷ An acidic environment in the gastrointestinal tract facilitates the release of ionized calcium from insoluble calcium salts.²⁹ In rats, gastrectomy or omeprazole therapy leads to malabsorption of calcium phosphate and impaired bone mineral density.^{11,30} Lowering gastrointestinal pH with dietary lactate reversed the calcium malabsorption in both cases.^{11,30} In humans, both gastrectomy and pernicious anemia are associated with increased risk of osteopenia and fracture,^{31,32} although it is unclear whether achlorhydria is the primary culprit.

Furthermore, there are conflicting data regarding the importance of calcium solubility and the role of gastric acid in intestinal calcium absorption. In individuals with normal acid secretion, insoluble calcium salts taken with or without food are absorbed at similar rates as soluble calcium salts.²⁹ In contrast, in patients with pernicious anemia, the absorption of insoluble calcium salts taken under fasting conditions virtually does

not occur, while soluble calcium salts are still absorbed normally.^{9,10} These data suggest gastric acid may be important for insoluble calcium absorption. Curiously, patients with achlorhydria can absorb calcium carbonate, coingested with a slightly acidic meal, as efficiently as controls.^{10,33} Furthermore, in a study of young healthy individuals given an H2RA, the absorption rates of calcium carbonate coingested with a slightly acidic meal were comparable whether the gastric pH was titrated to 7.4 or 3.0.³³ This experiment casts some doubt on the importance of an acidic gastric milieu in calcium absorption. However, because the *in vivo* intragastric titration used is usually carried out by measuring the pH of small aliquots of gastric content obtained every few minutes, it is uncertain whether the pH of the entire gastric content could be maintained at a neutral level instantaneously throughout the experiment. A study of insoluble calcium absorption in patients with achlorhydria using a pH-neutral meal could further clarify this issue.

Gastrectomy and pernicious anemia are generally associated with much more profound levels of acid suppression than PPI therapy. Therefore, calcium absorption data obtained from these disease models cannot be readily extrapolated to PPI therapy. A few studies have directly examined the effect of PPI therapy on calcium absorption. Among young healthy individuals, full-dose omeprazole therapy did not reduce the absorption of calcium contained in milk and cheese.³⁴ However, in another study involving a more relevant population of women older than 65 years, omeprazole significantly reduced the absorption of calcium carbonate (an insoluble calcium salt) taken under the fasting condition.¹² It is unclear whether such malabsorption is reversible with coingestion of a meal. More studies conducted in the elderly populations using valid absorption assays are needed to better elucidate the effect of antisecretory therapy on calcium absorption.

A considerable amount of insoluble calcium dissolves under even mildly acidic conditions.³³ One would there-

fore expect that profound acid suppression (possible with high-dose PPI therapy) may be necessary to have a significant impact on calcium absorption and bone metabolism. Lower levels of acid suppression, such as those induced by regular-dose PPI therapy or H2RA therapy, may still have a positive effect because of the significant prevalence of *H pylori* gastritis, which may reduce acid production, among the elderly population. However, this effect, whether due to regular-dose PPI therapy or H2RA therapy, is likely much more modest compared with high-dose PPI therapy. This hypothesis is consistent with our observation that the increase in fracture risk surged from a modest level with regular-dose PPI therapy to a much higher magnitude with high-dose PPI therapy.

While PPI therapy may hinder insoluble calcium absorption taken without a meal, limited experimental data indicate that PPIs may inhibit the osteoclastic proton transport system, potentially reducing bone resorption.¹³⁻¹⁶ The irreversible proton pump inhibition by the PPIs requires a specific pH milieu. The PPIs are all prodrugs that require 2 sequential protonation steps for activation with a pK_a for the second step of less than 1.³⁵ As a result, the proton pump inhibition action of the PPIs is extremely site-specific. In addition to the secretory canaliculi of the gastric parietal cells, the osteoclastic resorption vacuole may be the only other place in which proton pump inhibition by PPIs is known to take place. Our results would suggest that it is possible that the potentially protective effect of osteoclastic proton pump inhibition may have canceled out some of the negative effects of gastric acid suppression by PPIs, especially at regular doses, potentially leading to overlap between the effect of low-dose PPIs and H2RAs. However, with high-dose PPI therapy, the effect of gastric acid suppression dominated.

Our findings are consistent to some extent with a recent case-control study conducted in a Danish population by Vestergaard et al,³⁶ which showed that recent PPI therapy was associated with

an increased risk of hip fractures (OR, 1.45; 95% CI, 1.28-1.65). However, in contrast to our study, Vestergaard et al observed neither a duration-response nor a dose-response effect associated with PPI therapy. The discrepancy is probably due to differences in study design. The maximum follow-up and duration of potential PPI exposure in our cohort were close to 15 years (1988-2003) compared with 5 years (1996-2000) in the study by Vestergaard et al.³⁶ As such, our study may be less susceptible to the influence of left censoring and thus better able to capture the effect of long-term PPI therapy. In fact, duration of PPI use was indirectly measured by cumulated number of daily defined doses (ie, a standardized daily dose unit) in the study by Vestergaard et al, and the longest duration category was more than 3 months in their study compared with 4 years in our study. In addition, while we assessed the presence of a dose-response effect associated with PPI therapy among long-term (ie, >1 year) users only, Vestergaard et al³⁶ analyzed the dosage effect among PPI users of any duration, including those with minimal duration of total PPI exposure. Because short-term PPI use is unlikely to have a significant impact on fracture risk regardless of how high the daily dosage, a positive dose-response effect may only be demonstrable among long-term PPI users.

In addition, the daily dosage variable in the study by Vestergaard et al³⁶ was defined by dividing the cumulative daily defined doses of PPI used during the last year of follow-up by the number of days from first PPI use in the last year to the index date. Based on this definition, even the highest daily dosage category (>1 defined dose per day) could theoretically include patients receiving once daily PPI exclusively, while the lower dosage categories could include those receiving a double daily dose of PPI therapy exclusively. Therefore, in contrast to our study, this daily dosage variable in the Danish study was not designed to capture the variation in the extent of acid suppression due

to different PPI daily dosages during the periods of active therapy, which may be the crucial factor in this context based on our data. In fact, Vestergaard et al³⁶ indicated that this variable was defined as such to account for the expected intermittency of PPI use.

As with all observational studies of the effects of medications, the potential for confounding by indication should be carefully assessed. Patients with comorbidities may be more likely to be prescribed acid suppressive therapy. These patients also may be more likely to experience hip fracture due to factors such as decreased weight-bearing activities, poor nutrition, increased fall risk, and decreased sunlight exposure. In this study, we controlled for comorbidity status primarily through the inclusion of a comprehensive list of relevant variables in the regression model.

Residual confounding by unmeasured factors is always possible in an observational study. However, such confounding would not only have to be of considerable magnitude but also be substantially independent of the comprehensive list of factors already included to negate the positive association observed in this study in general and the marked risk increase among high-dose PPI users in particular.

Furthermore, we conducted an additional analysis restricted to patients who had documented chronic GERD. What we were interested in learning from this analysis was whether there was a significant change in the point estimate between this analysis and the primary analysis. At the very least, the PPI users in this restricted analysis were much more likely to have received PPI for GERD than a mixed group of PPI users with or without a GERD diagnosis. Therefore, to the extent that confounding by indication is present in the primary analysis, its effect should be less in a comparison between PPI users with GERD and PPI nonusers with GERD than in a comparison between all PPI users and all PPI nonusers. The fact that the point estimate changed negligibly between these 2 analyses suggested that

residual confounding by indication was unlikely to be a major source of bias in our primary analysis. This analysis also largely excluded the possibility that GERD itself may be responsible for the increase in hip fracture risk.

Several other limitations also warrant consideration. Our study was not designed to define the specific mechanism(s) underlying the association between PPI therapy and the risk of fracture. As a result, while the dose-response effect observed could be explained by a mechanism mediated by gastric acid suppression, we cannot be certain that there are no alternative explanations for the different effects associated with regular-dose and high-dose PPI therapy. In addition, in our cohort, the BMI was missing for 33% of the patients. We conducted a restriction analysis limited to those patients with BMI information recorded. The results of this analysis were nearly identical to the analyses in which those with missing BMI information were placed in a separate category of "unknown" (data not shown). Furthermore, inclusion of BMI information in the regression model generally increased strength of the positive association between PPI use and fracture risk in these analyses. Thus, it seems unlikely that the observed association between long-term PPI use and fracture risk is due to incomplete adjustment for BMI.

We could not capture PPI use prior to patient enrollment in the database. Therefore, we could have underestimated the duration of exposure. However, this should have created bias against observing a trend for a stronger association with longer duration of therapy. That we observed such an association argues against this form of bias having led to the wrong conclusions.

Finally, we were unable to fully determine whether receiving calcium supplementation influenced the primary association because we did not have information on over-the-counter calcium supplement use. We observed significant modification of the primary effect by sex among long-term PPI users. While this phenomenon may be due to other sex-related

factors involved in the pathogenesis of osteoporosis, future studies should assess whether a higher prevalence of calcium supplement use among women compared with men played a role.³⁷

In summary, we observed that PPI therapy is associated with a significantly increased risk of hip fractures, with the highest risk seen among those receiving high-dose PPI therapy. Osteoporotic fractures are common among the elderly population, and they entail considerable morbidity and mortality. On the other hand, PPI therapy is widespread and may have an exaggerated effect among those at risk for osteoporosis. Thus, further studies are urgently needed to confirm our findings and clarify the underlying mechanism. At this point, physicians should be aware of this potential association when considering PPI therapy and should use the lowest

effective dose for patients with appropriate indications. For elderly patients who require long-term and particularly high-dose PPI therapy, it may be prudent to reemphasize increased calcium intake, preferably from a dairy source, and coingestion of a meal when taking insoluble calcium supplements.

Author Contributions: Dr Yang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Yang, Lewis, Metz.

Acquisition of data: Yang, Lewis, Epstein.

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