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Long-term proton pump inhibitor use and effect on risk of fractures

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Abstract

***Objective*:** To conduct an analysis of literature that examined the effects of long-term proton pump inhibitors (PPIs) in adults 50 years and older on fracture risk. ***Methods*:** A literature search of the PubMed database using the terms “long-term use of PPIs” AND “fractures” ***Results*:** All 3 studies reported a statistically significant increased risk of fracture associated with long-term use of PPIs in both men and women over 50. None of the studies showed an increased risk of fracture with short-term PPI use. ***Conclusions*:** Health care providers should be informing their patients of the potential risk associated with long-term PPI use. While there was no increased risk associated with short-term use of PPIs, providers should be sure to only prescribe the medications when they are heavily indicated, especially if they are to be used long-term. We would also recommend that patients who will be on these mediations long-term be assessed for fall risk and have that taken into consideration as well.

Table 1. *Abbreviations and acronyms used in this paper*

Abbreviations and Acronyms:
Body mass index – **BMI**
Confidence interval – **CI**
Gastroesophageal reflux disease – **GERD**
General Practice Research Database – **GPRD**
Hydrochloric acid – **HCl**
H2 Receptor Antagonist - **H2RA**
International Classification of Diseases – **ICD**
Non-steroidal anti-inflammatory drugs - **NSAID**
Odds ration – **OR**
Peptic ulcer disease – **PUD**
Proton pump - **H-K-ATPase**
Proton pump inhibitors – **PPIs**
Randomized control trial - **RCT**

INTRODUCTION

The human stomach contains nearly one billion parietal cells which are responsible for secreting hydrochloric acid (HCl) into the gastric lumen in response to interactions between and fluctuating levels of acetylcholine, histamine, and gastrin[1]. When a meal is ingested, hydrogen ions are actively secreted and exchanged by the H-K-ATPase “proton pump” on the surface of the parietal cell, and HCl is secreted into the gastric lumen to hydrolyze ingested proteins[1].

Due to the recognition that this pump is the final step in acid secretion, proton pump inhibitors (PPIs) were developed to target and inhibit this enzyme. Since their introduction in the late 1980s[2], PPIs have become one of the most widely used classes of drugs[3] and one of the most commonly prescribed medications in geriatric clinical practice[2]. These medications have allowed optimization of medical treatment of acid-related disorders, including peptic ulcer disease (PUD), *H. pylori*, NSAID-use-related ulcers, Zollinger-Ellison syndrome, and gastroesophageal reflux disease (GERD)[1].

All PPIs share a common structure with varying pKa (acid dissociation constant) values specific to each different medication. The pKa of a substance refers to its strength as an acid, and PPIs are weak bases and break down easily in the acidic environment of the stomach. The drugs accumulate selectively in the highly acidic space within the parietal cells and undergo acid-catalyzed conversion into reactive cation species[1]. Each PPI interacts with the surface of the H-K-ATPAse enzymes, forming a disulfide bond with a part of the enzyme that is closely involved in hydrogen ion transport. Inhibition of this enzyme results in specific and long-lasting decrease in gastric acid secretion, thus making PPIs one of the most potent gastric acid secretion inhibitors on the market[1]. The daily dosing for PPIs is usually once daily, with maximal effect on acid secretion within about five days. Thus, PPIs must be taken regularly instead of on an "as needed" basis to optimize its effects.

With chronic use of any medication, it is always important to consider long-term adverse drug effects. Duration of therapy with PPIs varies depending on the clinical indication for its use. For example, in patients with Barrett's esophagus or severe esophagitis, maintenance acid suppression with PPI is required to avoid risk of recurrent symptoms if the drugs are discontinued. Even for patients with nonerosive reflux disease, up to two-thirds relapse when acid suppression is discontinued.[1] Major concerns with PPIs include the effects of hypochlorhydria, hypergastrinemia, and gastric atrophy. Most concerning is hypochlorhydria due to the belief that it can increase the risk of infections and malabsorption[4]. Although the exact mechanism remains unknown, PPI use over a long duration of time has been believed to cause increased risk of fracture, possibly due to a reduction of intestinal absorption of calcium and increasing resorption of bone[2].

Another theory that has been considered was PPI's effects on B12 absorption which leads to a deficiency that causes visual and musculoskeletal disturbances. These disturbances can contribute to falls and subsequent fractures[2]. In the United Kingdom, more than 47,000 hip fractures occur every year, resulting in a mortality rate of 20% for patients in the first year after the injury[5]. With high morbidity and mortality associated with hip fractures, especially in elderly populations, prescribers must make thoughtful decisions when prescribing long-term PPI therapy to their patients. This is especially true when a strong association is found between long-term PPI use with increased incidence of falls and fractures.

CLINICAL SCENERIO

AZ is a 75-year-old female with no history of fractures. She is currently prescribed a once daily dose of the PPI omeprazole for her occasional GERD symptoms. Her primary care physician put her on the PPI 5 years ago, and she has been taking it daily ever since. She heard from a friend that long-term PPI use can cause an increased risk of fractures in elderly individuals and asks whether or not she should take the medication.

CLINICAL QUESITION

P*opulation*: Individuals over age 50 years old
I*ntervention*: Long-term use of proton pump inhibitors (PPIs)
C*omparison*: Similar populations (matched for certain characteristics) without the use of long-term PPI treatment
O*utcome*: Occurrence of bone fracture

Among individuals 50 years and older, does the long-term use of proton pump inhibitor therapy increase the incidence of fractures as compared to similar populations who do not use long-term PPIs?

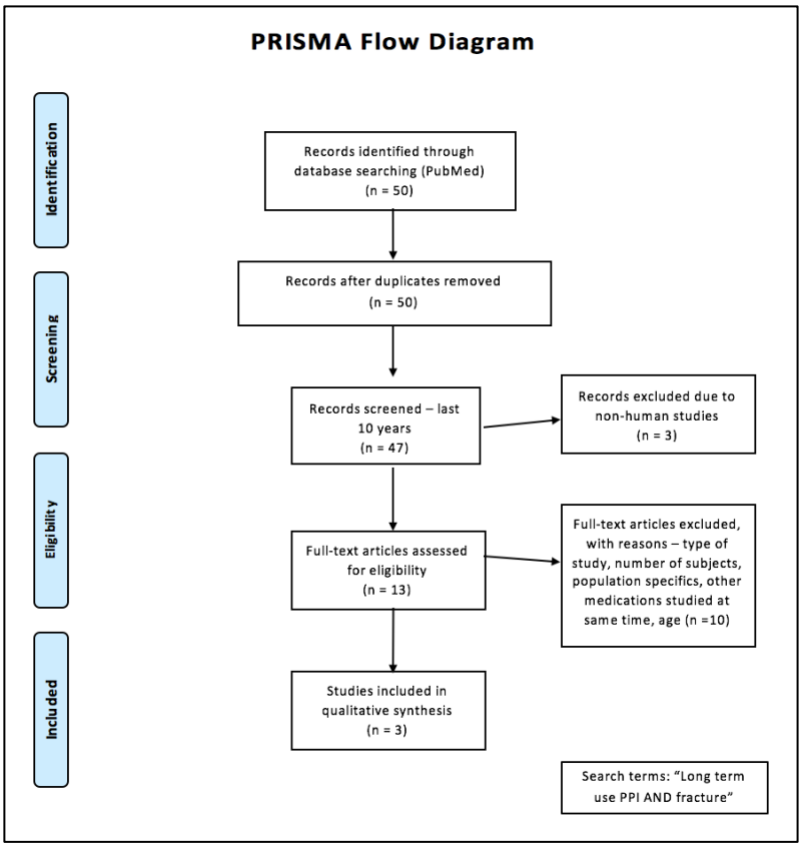

Figure 1. PRISMA Flow diagram

METHODS

In October 2017, a literature review search was conducted on PubMed and Google Scholar databases to find studies that investigated the association between long-term use of proton pump inhibitors (PPIs) with fracture risk and incidence. Search terms used included “long-term use”, “PPI”, and “fracture”. All items returned on the Google Scholar search were simultaneously found on the PubMed search, so PubMed was used as our primary search engine. The search terms yielded 50 articles on PubMed, with zero duplicates. The records were filtered to exclude articles that were not published within the last ten years, and three records were eliminated. Next, a total of three non-human studies were removed from the search. Thirteen full-text articles were assessed for eligibility, and all but three were ruled out due to type of study, a small number of subjects, age of subjects, specifics about the populations being studied, and studies that were analyzing effects of other medications at the same time. This can all be seen in Figure 1.

RESULTS

Study #1

Use of Proton Pump Inhibitors and Risk of Osteoporosis-Related Fractures. Targownik et al.[3]

Study Objective:

To examine the relation between duration of exposure to proton pump inhibitors and osteoporosis-related fractures.

Study Design:

This study was a retrospective, matched cohort study using the Population Health Research Data Repository for the residents of Manitoba, Canada. Manitoba Health provides healthcare for all its residents, and records several factors such as demographics, all dispersions of prescription medications, and date and type of service for all inpatient and outpatient contacts.

Cases chosen for this study were defined as people ages 50 years and older who were seen by a physician or admitted to the hospital with a diagnosis of vertebral fracture

(ICD-9-CM code 805), wrist fracture (ICD-9-CM code 813), or hip fracture (ICD-9-CM codes 820-821) between April 1996 and March 2004. To be included in this particular study patients needed to be continuous residents of Manitoba between the years 1988 and 2004. Patients who used osteoprotective medications in the year before their fracture occurred, and patients who were residents of long-term care facilities, were excluded from the study. This information is shown in Table 2.

Table 2: Inclusion and exclusion criteria[3]

Inclusion Criteria	Exclusion criteria

• >50 years
• Diagnosis or hospital admission for:
  ○ Vertebral fracture
  ○ Wrist fracture
  ○ Hip fracture
• Continuous residents of Manitoba between 1988 and 2004
	• Use of osteoprotective medications in the year before fracture
	• Resident of long-term care facility

Each case in this study was linked to 3 controls who had no history of vertebral, wrist or hip fractures. The age of each control was within 5 years of the age of their matched case at the time of fracture. Controls were also matched to cases by sex, degree of comorbidity, and ethnic background. The John Hopkins Aggregated Diagnosis Groups (AGD), diagnostic clusters of ICD codes, were used to determine degree of comorbidity. The degree of comorbidity was grouped into 4 categories based on the total number of aggregated diagnosis groups (0, 1-2, 3-5, >6).

The exposure to PPIs was determined using information in the Drug Program Information Network database. The total exposure time for each case and their controls was separated into either periods of exposure to PPIs or no exposure. A patient in the study was considered exposed to PPIs if the ratio of standard doses dispensed to the number of days between dispensations exceeded 0.70 standard doses per day.

Cases and their controls were further categorized based on their total duration of exposure. Patients were classified as either having continuous exposure, non-continuous exposure, histamine-2-receptor antagonist exposure or no exposure. This was done to try to determine if there was a relationship between the rate of osteoporotic fractures and continuous PPI use. The strength of association between continuous

exposure to PPIs and either combined hip and spine fractures or hip fractures alone was also measured.

Differences between categorical baseline measures for cases and controls were compared using the $\chi 2$ test. A p-value of less than 0.05 was considered statistically significant. Chi-square tests were also used to compare the use of PPIs between cases and controls. A Chi-square test assesses the goodness of fit, also known as the strength of relationship, between observed values and expected values. Conditional logistic regression models were defined, which took case-control matching into consideration for each of the seven exposure intervals (≥ 1 to ≥ 7 years at 1-year intervals). Conditional logistic regression is a specialized type of logistic regression which is used when case subjects with a particular condition are each matched with control subjects without the condition. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were generated using these models. An odds ratio was considered to be statistically significant if the range of the 95% confidence interval did not include 1.0.

Study Results:

A total of 15,719 patients met the inclusion criteria for this study, and those cases were matched with 47,289 well-matched controls. The study found that there was no significant association between use of proton pump inhibitors in the development of any osteoporosis-related fractures in patients with 1 to 6 years of continuous PPI exposure. The study also found that the use of PPIs is associated with increased risk of hip fracture after 5 or more years of exposure (adjusted OR 1.62, 95% CI 1.02-2.58). However, the study found that the use of PPIs is associated with an increased risk of any osteoporosis-related fracture (adjusted OR 1.92, 95% CI 1.16-3.18) after 7 years of continuous exposure. Increasing durations of exposure to PPIs was also found to increase the magnitude of risk for hip fracture (adjusted OR after ≥ 6 years 2.49, 95% CI 1.33-4.67; adjusted OR after ≥ 7 years 4.55, 95% CI 1.68-12.29).

Overall, the study found that the use of PPIs was associated with an increased risk of hip fracture after 5 or more years of continuous exposure, and the risk of any osteoporotic fracture was increased after the 7 years of continuous exposure to PPIs. Although several of the odds ratios in this study are between 1 and 2, which suggests a slight increase in the relative odds of a fracture, osteoporotic fractures are very common

occurrences in elderly populations that are associated with substantial morbidity and mortality. This means that relatively small increases in the relative risk of fracture may have permanent effects on the absolute risk of events. This may lead to an increase in their associated cost to an individual and society. In populations with other established osteoporotic-fracture risk factors, such as smoking, low body mass index, and excessive alcohol intake, the calculated odds ratios for exposure to PPIs were found to be similar.

Study Critique:

One strength of this study was that it included patients from over a very large time period (1996-2004). As a result, they were able to compare both short-term and long-term use of continuous PPIs. They were also able to break down the cases into number of years of continuous PPI use, which allowed them to pinpoint which year they started seeing an association with increased fractures. Another strength of the study was that they used 3 matched controls for every case they included in the study. The controls were well matched and used several factors such as sex, degree of comorbidity, and ethnic background to help prevent confounding factors.

One weakness of the study is that they were not able to obtain information about the use of over-the-counter medications such as calcium and vitamin D supplements. If participants were taking these over-the-counter medications, they could have reduced their risk of fracture and potentially countered the negative effects of the PPIs. Another weakness was that they were unable to determine whether increased fracture risk from PPIs were related to reduced bone density or increased risk for falls. They were able to determine that there was an association between an increased risk for fracture and long-term continuous PPI use, but they did not have the data to determine why.

In addition, because of the design of the study, there was no way to randomize the groups or blind patients to the type of treatment they were getting. All of the patients were assumedly aware that they were taking the medications, and because the study was retrospective, all events occurred in the past. There is no way to know or control for any types of counseling that the patients received from their medical providers or personal research about perceived risks of taking the drugs or if patient groups were treated differently in any way.

Study #2

Long-Term Proton Pump Inhibitor therapy and Falls and Fractures in Elderly Women: A Prospective Cohort Study. Lewis et al.[2]

Study Objective:

The study investigated the effects of PPI therapy over one year in duration with fracture risk factors in populations of elderly postmenopausal women.

Study Design:

The original study, referred to as "Study 1", was designed as an *a priori* analysis of data from a long-term Calcium Intake Fracture Outcome Study (CIFOS) in Australia that investigated bone quality and fracture hospitalizations in those who used long-term PPI therapy. Study 1 was a CIFOS extension study; 1,025 subjects were re-enrolled in a 5-year follow-up study where they underwent bone structure assessment during a clinic visit in 2003 to establish baseline data on bone structure.

The primary item that investigators were analyzing was long-term PPI exposure. The researchers defined "exposure" to PPIs as "continuous PPI therapy" of omeprazole, esomeprazole, pantoprazole, lansoprazole, or rabeprazole for at least one year prior to the 2003 baseline clinic visit assessment (see Table 3). The investigators collected medication history using a patient diary approach every 4 months for a time period of 1998 to 2003. Collected information included medication names, dates of use, stop dates, dosages of the medication, and how frequent each medication was consumed by the subject. When possible, the data collected was reviewed with the subjects' primary care physicians. Subjects were excluded if they used PPI therapy only for short periods of time or intermittently, to avoid using subjects who did not in fact have long-term exposure to PPIs. Patients were defined to be on "high dose" PPI therapy if they exceeded the standard daily PPI therapy doses for long-term therapy, as defined in Table 3.

Next, the study analyzed multiple outcomes to help analyze the affect of PPIs on fracture risk. To begin, investigators recorded information in 2003 to obtain a baseline picture of each subject's overall fracture risk (summarized in Table 4).

Table 3: "High Dose" PPI Exposure Ascertainment in Participants on Long-Term PPI Therapy[2]

Medication	Dose of PPI Exposure
omeprazole	Exceeding 20 mg/day
esopmeprazole	Exceeding 20 mg/day
pantoprazole	Exceeding 20 mg/day
lansoprazole	Exceeding 15 mg/day
rabeprazole	Exceeding 10 mg/day

Table 4. Baseline information collected on each subject in 2003[2]

• **Bone mineral density** at hip and whole body • **Quantitative heel ultrasound** • **Mobility**: time it takes patient to stand up from chair, walk 3 meters, turn around, walk back to chair, and sit down • **Grip strength** of dominant hand: three attempts using handheld dynamometer • **Balance**: sharpened Romberg test • **Fear of falling**: questionnaire; 1. "Do you limit any household activities because you are frightened you may fall?", 2. "Do you limit any outside activities because you are frightened you may fall?" • **Falls metrics**: questionnaire (including numbness of feet, dizziness) ranking on a scale of 1 (never) to 5 (once per day or more)	Baseline medical history: • **Smoking history** • **Medication history**: central nervous system (CNS) medications including antidepressants, antipsychotics, anxiolytics/hypnotics; anticonvulsants; opiates • **Weight**: using digital scales; participants wore light clothes and no shoes • **Body mass index** (BMI): kg/m^2 • **Physical activity level**: questionnaire; activity levels calculated in kcal/day • **Dietary vitamin B12 intake**: semi-quantitative food frequency questionnaire (FFQ) • **Serum vitamin B12 levels**: morning venous blood samples after overnight fast from 10pm

Bone mineral density tests, whole body, and quantitative heel ultrasounds were performed in the 2003 baseline visit. For falls, several factors including metrics, mobility, grip strength, balance, fear of falling, foot numbness, and dizziness were all assessed. The Timed Up and Go (TUAG) test was used to measure mobility, as predictors of falling and fracture in subjects. Dominant hand grip strength was measured using a handheld grip dynamometer. Romberg tests was performed to assess balance, and participants were placed into five categories: unable to perform, side by side sway, semi-tandem position, tandem position for less than 9 seconds, and tandem position for more than 9 seconds. A questionnaire was used to assess fear of falling, which included questions about whether the subject limited their participation in certain activities due to a fear of falling. The other fall metrics were assessed by using a questionnaire about how often

each subject experienced certain relevant symptoms, such as feet numbness and dizziness.

Medical history was also collected at the 2003 baseline visit. Items included smoking and medication history, weight on a digital scale, and body mass index (BMI). A questionnaire was used to assess physical activity level. In addition, another questionnaire was used to assess dietary intake to include in the baseline 2003 analysis. Using the Anti-cancer Council of Victoria semi-quantitative food frequency questionnaire (FFQ), intake of Vitamin B12 was assessed for each subject. Following an overnight fast from 10pm until morning, venous blood samples for serum Vitamin B12 were collected and measured in a two-step 12 assay. Subjects were defined as having low vitamin B12 if their serum levels were less than 350 pg/mL.

To collect data on the incidence of falls in the subjects during the study period of 2003 to 2008, the Western Australian Data Linkage Service (WADLS) was used to retrieve patient information from seven different databases. To define falls, the investigators looked for subjects "unintentionally coming to rest on the ground, floor, or other lower level". Data was retrieved for each of the study participants from 2003-2008 using international classification of external causes of injury (E) codes ad international classification of diseases (ICD) codes from public and private hospital admissions. These included ICD-10 E codes W01, W05-W08, W10, W18, and W19. ICD-10 codes used were S02, S12, S22, S32, S43, S52, S62, S72, S82, and S92. The investigators defined "major fractures" as any fracture occurring in the hip, pelvis, spine, shoulder, or forearm.

A post hoc prospective analysis was performed of falls metrics and falling as fracture risk factors. Next, the findings were confirmed in the second study, the "Replication Study". The "Replication Study" subjects included 686 women over age 70 who were enrolled in a 2009 9-month randomized controlled trial measuring effects of vitamin D supplementation in prevention of falls. The investigators analyzed medication history that was collected at baseline (2009), and at 3, 6 and 9-month intervals. They collected data on medications, dates of use, dosages, and frequency. The participants were categorized for their PPI therapy use similar to how they were in Study 1. To assess falls, the subjects kept a diary to record nature, timing, and other features each time they

had a fall, and this diary was checked every 3 months by study staff. Study participant baseline characteristics are summarized in Table 5.

Table 5. Baseline characteristics of study subjects[2]

Variable	Study 1	Replication Study
Total number of subjects	No long-term use: 905 Long-term use ≥ 1 year: 120	No long-term use: 554 Long-term use ≥ 1 year: 132
Mean age	No long-term use: 79.9 +/- 2.6 Long-term use ≥ 1 year: 80.1 +/- 2.5	No long-term use: 76.5 +/- 3.9 Long-term use ≥ 1 year: 77.5 +/- 4.5
Low BMI <22 kg/m^2	No long-term use: 120 Long-term use ≥ 1 year: 7	No long-term use: 61 Long-term use ≥ 1 year: 10
Median physical activity (kcal/day)	No long-term use: 104 Long-term use ≥ 1 year: 83	No long-term use: 100 Long-term use ≥ 1 year: 122
Ever smoked	No long-term use: 332 Long-term use ≥ 1 year: 43	No long-term use: 168 Long-term use ≥ 1 year: 49
Diabetes	No long-term use: 69 Long-term use ≥ 1 year: 15	No long-term use: 44 Long-term use ≥ 1 year: 9
CNS medication use	No long-term use: 174 Long-term use ≥ 1 year: 33	No long-term use: 125 Long-term use ≥ 1 year: 41
Bisphosphonate use	No long-term use: 72 Long-term use ≥ 1 year: 8	No long-term use: n/a Long-term use ≥ 1 year: n/a
Corticosteroid use	No long-term use: 25 Long-term use ≥ 1 year: 4	No long-term use: n/a Long-term use ≥ 1 year: n/a
Vitamin D treatment	No long-term use: n/a Long-term use ≥ 1 year: n/a	No long-term use: 277 Long-term use ≥ 1 year: 76

For analysis, Study 1 participants were categorized into those with no long-term PPI therapy at baseline (2003) and those who were exposed to long-term PPI therapy at baseline. A Student's *t*-test or χ^2 test was used to analyze baseline values between these two groups. Log regression, a model to estimate probability of an event happening based on a predictor variable, was conducted to analyze association between the predictor value of long-term PPI exposure and the event of fall-related hospitalizations. Models used were either unadjusted or adjusted to include falls-related variables as defined in Table 5. In the Replication Study analysis, one additional variable of Vitamin D intake was used in the adjusted model due to the design of that

particular study. The investigators also analyzed medication to test the actual mechanism by which PPI exposure could affect fractures and falls. P-values of <0.05 in two-tailed testing were statistically significant. A two-tailed test shows results both greater or less than a certain value, while a one tailed test can only show one or the other.

Study Results:

Falls - In Study 1, 28/120 (23.3%) long-term PPI users sustained fall-related hospital admissions with injury, as compared to 124/905 (13.7%) in those who did not use long-term PPI therapy. The risk for hospitalizations due to falls was significantly higher in the long-term PPI therapy users, even after adjustment for pre-existing falls risk factors (AOR, 1.95; 95% CI, 1.2-3.16; p=0.007). Further, those subjects defined as using higher doses and longer terms of therapy were found to have an even greater increase in risk (AOR, 2.31; 95% CI, 1.14-4.70; p=0.021). In the Replication Study, 47/132 (35.6%) long-term PPI users sustained self-reported falls, as compared to 144/554 (26%) in those who did not use long-term PPI therapy. The unadjusted OR was 1.57, 95% CI, 1.05-2.36, p=0.028, and the adjusted OR was 1.51, 95% CI, 1.00-2.27, p=0.049. An unadjusted OR, also known as a crude OR, is calculated from the chi-squared test and only accounts for one variable. The adjusted OR is calculated using the log regression and takes into account other variables such as confounding factors.

Fracture-related hospitalizations - In study 1, there were fracture-related hospitalizations in 21/120 (17.5%) of subjects on long-term PPI therapy, as compared with 89/905 (9.8%) in those without long-term PPI use. Even after adjustment for use of corticosteroid drugs, bisphosphonates, and total hip bone density, these numbers remained significant (AOR, 2.17; 95% CI, 1.25-3.77; p=0.006). Regarding major osteoporotic fractures, 17/120 (14.2%) of those on long-term PPI use were hospitalized compared with 77/905 (8.5%) of those who did not have long-term PPI exposure. Even after adjustment for multiple other variables, the association remained significant (AOR, 2.07; 95% CI, 1.14-3.77; p=0.017).

Mechanistic data – There was no difference between Study 1 category groups of PPI exposure in total hip bone mineral density (BMD), whole body BMD, or quantitative heel ultrasound (QUS). In both groups, clinical and self-reported incidents of falls were

impaired. In the Replication Study, the study group who had long-term PPI exposure had a significantly higher amount of feet numbness. The percentage of Replication Study participants reporting dizziness and fear of falling were lower than the older Study 1 subjects. Mediation analyses (a hypothesis of a chain of events in which one variable has an effect on a second variable which then causes a third variable) of long-term PPI use and fracture risk using the mediator of the listed falls metrics demonstrated that they partially accounted for the determined association between PPI use and risk of fractures via the PPI use to fall risk to fracture chain of events.

Study Critique:

Notable strengths of the Study 1 include the timely collection at regular 4-month intervals over a 5-year period after collecting baseline data. Due to this method, the dates, duration, dose, frequency, and type of PPI exposure could be determined. The Replication Study added strength to the overall investigation due to use of falls as a primary outcome and the comprehensive assessment of falls and risk of fractures while accounting for many variables. In addition, the use of actual medical records from hospitalizations instead of patient reporting removed any recall bias or patient reporting errors.

Limitations of Study 1 include the fact that since these investigations were only observation, only association, and NOT causation, can be determined. For the Replication Study, there is a stronger argument that there is causation between PPI use and self-reported falls and foot numbness, however, the authors provide no information about how the patients were randomized, if and how groups were similar regarding prognostic factors for the outcome of falls, and whether participants were blinded to the treatment that the researchers were investigating. Besides the analysis of data collected at regular intervals through 9 months of time, there is no information regarding follow-up and further outcomes for these subjects. In addition, the very specific population of women subjects, with a mean age of 80 in Study 1 and 77 in Replication Study, limits the use of the findings to similar populations of postmenopausal, community-dwelling women. Lastly, as the exact mechanism through which use of PPIs can increase fracture risk is yet unknown, more investigation is needed to prove that there is a related underlying mechanism.

Study #3

Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture. Yang et al. [5]

Study Objective:

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

Study Design:

This study was a nested case-control study, with the exposure of interest only being measured among the case subjects and controls. It was conducted using the General Practice Research Database (GPRD), which contains preexisting data of patients in the United Kingdom. Patients in this particular study started follow-up in the full version of the GPRD between May 1987 and March 2003. The study excluded individuals meeting at least 1 of the 4 following criteria: younger than 50 years of age at the time of database enrollment, less than 365 days of total up-to-standard database follow-up, having received a histamine 2 receptor antagonist or PPI therapy exclusively during non-up-to-standard periods of database follow-up, and having a documented hip fracture before the start of up-to-standard database follow-up or during the first year of follow-up.

The authors of the study chose their case subjects from the database if they had a first occurrence of hip fracture at least one year after the beginning of their up-to-standard follow-up period; they included the users of PPIs, users of H2RAs, and non-users of acid suppression. They then chose controls for each case from the study cohort, matching them for sex, year or birth, and duration of follow-up (Table 6). There were 13,556 total individuals who qualified for this study, consisting of 10,834 acid suppressant nonusers and 2,722 PPI users. Density sampling was used to select up to 10 controls for each case from the study cohort, and a total of 135,386 controls were used. The controls were matched for year of birth, sex, index date, and both calendar period and duration of up-to-standard follow-up before the index date.

A continuous variable for cumulative duration of PPI therapy was used, and from that the effects of increasing durations of exposure were examined. In this study, the y of exposures of 4 years or greater were estimated because there were too few patients beyond 4 years to yield a secure estimate. Each individual length of exposure to PPI

therapy was determined by using the intended duration of each prescription recorded in the database. This study also looked at the risks associated with medication doses above and below the average of 1.75 per day for the treatment period. The medication dose was calculated by dividing the sum of the number of daily doses prescribed by the total number of prescriptions.

Table 6. Inclusion and Exclusion criteria[5]

Inclusion Criteria	Exclusion criteria
• Sustained incident hip fracture at least 1 year after starting up-to-standard follow-up • > 50 years old at the time of database enrollment	• < 50 years old at the time of database enrollment • < 365 days of total up-to-standard database follow-up • Having received a histamine 2 receptor antagonist or PPI therapy exclusively during non-up-to-standard periods of database follow-up • Having a documented hip fracture before the start of up-to-standard database follow-up or during the first year of follow-up

Study Results:

For this study, log regression was used to estimate the unadjusted and adjusted ORs and 95% confidence intervals, and a P value of less than .05 was considered statistically significant. The crude (unadjusted) OR for hip fracture associated with more than one year of PPI therapy, controlling for only the matching variables, was 1.82 (95% CI, 1.67-2.00; p <.001). The multivariable adjusted OR for all the potential confounders was 1.44 (CI 95%, 1.30-1.59; p <.001). In a regression model in which duration of PPI treatment was included as a continuous variable, the quadratic term was significant (p <.001). This suggests that the duration variable was associated with risk of fracture in a nonlinear fashion. It was found that there was stronger association between increasing duration of PPI therapy and increased hip fractures.

There was a significant dose-response effect with respect to the average daily dose among users of PPIs for over 1 year. This is shown in Table 7. With high-dose PPIs, the risk of hip fracture among long-term users was markedly increased when compared to acid suppression nonusers. When results were broken down by sex, the positive association between hip fractures and long-term PPI use was stronger in men (OR, 1.78;

95% CI, 1.42-2.22) than women (OR 1.36; CI1.22-1.53). The p value for interaction between PPI therapy and sex was statistically significant at p=.04.

Table 7. Risk of Hip Fracture Associated With Increasing Daily Dosages of PPIs[5]

	No. (%) of Participants		OR (95% CI)	
	Cases	**Controls**	**Crude**	**Adjusted**
$\leq$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)

Study Critique:

One strength of this case-control study was that it used a very large population number and that it used up to 10 very well-matched controls for each case. This helped decrease some of the confounding factors and helped make the study population more representative of the general population, especially given the fact that subjects could not be randomized nor were they blinded to the types of therapy they were receiving. The large population size also allowed the researchers to compare different types of patients and the effects of their PPI use, such as men vs women and patients on low dose vs high dose PPIs. Like the other studies, this one also used patients for a very large time period (1987-2003) which made it representative of a much greater population and allowed them to track PPI use over several years, with good follow-up of their outcomes via analysis of their records in the database.

One weakness of this study was the lack of assessment regarding patient compliance. Since the exposure data was collected from the intended duration of each prescription, if an individual was non-compliant with their PPI as prescribed, it could have skewed the results. They also did not have any data on PPI use prior to enrollment in the database so their exposure times could have been off. Another weakness of this study was that they were not able to identify if patients had been taking over the counter vitamin D or calcium supplements, which could have prevented some of the potential hip fractures. This study also excluded the possibility that the hip fractures may have been a result of the GERD itself.

DISCUSSION

Due to the limited number of studies published, the lack of randomized controlled trials, and variety of population risk factor characteristics and outcomes investigated amongst available studies, it is difficult to compare and draw conclusions with such limited data. In addition, without a randomized controlled trial, only associations between PPI use and falls and fracture risk can really be assessed. However, overall, the three studies did find associations between PPI use of variable dosage and duration with incidents and risk of falls and fractures.

Study #1 by Targownick et al. found no significant association between PPI use and the development of osteoporosis-related fractures in patients over age 50 with 1-6 years of continuous PPI exposure, but it found a statistically significant association in those with at least 7 years of continuous PPI exposure. PPI use was also found to show an increased association of the general risk of hip fracture in those with 5 or more years of continuous PPI therapy exposure. Osteoporotic fractures pose a significant increase in morbidity and mortality, especially in populations of increasing age.

Study #2 by Lewis et al. found that there was an increased association in the risk of fall-related hospital admissions due to injury in postmenopausal women who had a mean age of 80 in the first study and 77 in the replication study, and who had a history of long-term (>1 year duration) PPI use, with an even greater risk found in those using higher doses and for longer periods of time. Risk of fracture-related hospitalizations, even when adjusted for a multitude of other risk factor variables, was increased in subjects on long-term therapy as compared to those without long-term PPI exposure.

Study #3 by Yang et al. found an increasing strength of association for risk of hip fracture with increasing durations of PPI therapy. In high-dose PPI therapy users, risk of fractures if PPIs were used long-term was markedly increased in comparison to nonusers of acid suppression. When stratified by sex, there was stronger positive association between long-term PPI use and hip fracture incidence in men than women.

All of the studies that were used in this review had similar weaknesses, most notably the fact that none of them were randomized control trials (RCT), which makes it impossible to draw conclusions about cause and effect. RCTs would not be feasible due to ethical concerns about the high morbidity and mortality associated with diseases such as acid

reflux, esophagitis, and Barrett's esophagus. It would not be appropriate to withhold protections from a study control group from such diseases just to study the long-term effects of a drug. Further, the elderly populations that were being studied already have high risk of sustaining falls and fractures without any additional risk factors being added, so it is difficult to ascertain which risk factor was the predominant cause of the incident of fracture.

CONCLUSION

Due to the high use of long-term PPI therapy in elderly, and their overall risk of falling as a general population, the association between increased fall risk and PPI exposure is an extremely important relationship to investigate. All of the research articles compared in this study found a significantly increased association between long-term PPI use with falls and fractures. Even minor increases in fractures in this population may have permanent effects on the overall absolute risk of events and their associated cost to an individual and society. Low dosage PPI prescriptions and minimal duration use should be recommended when medically appropriate. There are also certain lifestyle changes that can be initiated by the patient to help reduce risk of disease and complications. Further study needs to be done to examine the possible mechanisms for this association including the effect of acid inhibition on calcium absorption and bone mineral density.

In regard to the patient AZ, her physician would have to discuss with her that there is no definitive answer for whether or not she is at an increased risk for fractures due to the lack of research on a cause and effect relationship between long-term PPI use and fractures in the elderly. He can inform her that there may be a potential association of long-term PPI use with fractures, and have a personalized discussion with her based on her individual risk factors for falls and other conditions such as osteoporosis. Her physician can also reassess the severity of her GERD and subsequently weigh the risks and benefits of continuing the PPIs with her to come to a conclusion.

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