Long term use of proton pump inhibitors : is there an increase in fracture risk?

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Introduction

Background

General Discussion of Osteoporosis

Osteoporosis is generally defined as a skeletal disorder characterized by compromised bone strength, predisposing to an increased risk of fracture. The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) value more than 2.5 standard deviations below the mean for normal young white women. Primary osteoporosis, the most common form, is the result of the cumulative impact of bone loss and deterioration of bone structure as people age. The risk factors for primary osteoporosis include white ethnic background, female gender, increasing age, physical inactivity, poor nutrition, smoking, and low body mass index (BMI), (U.S. Dept of Health and Human Services, 2004).

Secondary osteoporosis is defined as a condition caused by other disease processes or prolonged use of medications that result in bone loss. There are many classes of medications whose long-term use has been linked to higher rates of osteoporosis, including corticosteroids and anti-convulsants. Postmenopausal women are particularly vulnerable to both primary and secondary osteoporosis due to several factors including normal age-related bone loss, multiple comorbidities, and polypharmacy.

Bone strength is determined by several factors, including: the composition and the structure of the bone, the presence of micro-fractures and damage, and its ability to be repaired. Changes in the micro-architecture of trabecular bone are particularly important since osteoporotic fractures most commonly occur at the spine, wrist, and hip, sites where trabecular bone predominates. Fortunately, bone breakdown due to bone loss usually occurs later in life, and it is accelerated for females around the time of menopause. Also, bone formation decreases
with age, failing to keep up with the rate of bone resorption. The imbalance between resorption and formation results in loss of bone mass, leading to structural abnormalities that make the skeleton fragile. Bone breakdown is the first step in the process and blocking bone resorption is one way to decrease bone loss and prevent fractures.

Osteoporosis is the leading cause of bone disease, affecting up to 16% of women and seven percent of men aged 50 years and older. In 2000, the estimated number of people with fractures worldwide was 56 million, and about nine million new osteoporotic fractures occur each year. The case-fatality rate for hip fractures can exceed 20% and all fractures have the potential to leave the individual disabled with altered quality of life, (Targownik, 2008).

**Incidence of Fractures**

The National Osteoporosis Foundation estimates the prevalence of osteoporosis in the United States to increase from ~10 million to 14 million people in 2020, based on 2000 census data. As the U.S. population >50 years old is expected to increase by 60% between 2000 and 2025 (Burge, 2007), there is also an expected increase in the prevalence of osteoporosis. Burge et al. published a study in 2007 that evaluated osteoporosis-related fractures and associated costs across race/ethnicity, age groups, gender, and fracture types in the United States during 2005 and projects costs and fracture incidence to the year 2025.

Burge et al. cites five references that have estimated the direct medical costs of osteoporosis in the United States to be $13.7 – $20.3 billion in 2005. Based on his model for 2005, it was projected that nearly two million fractures occurred that cost more than $16.9 billion. He suggested that in 2005 non-vertebral fractures accounted for 73% of total fractures and 94% of total costs; while hip fractures accounted for 14% of total fractures but 72% of total
costs. Women >65 years had 74% of all fractures and 89% of all costs while Caucasian individuals accounted for 89% of all fractures.

In his study, Burge projected costs and fracture rates from 2006 through 2025. He states that by 2025, fractures and costs are projected to grow by approximately 48% to >3 million fractures, incurring $25.3 billion in costs. The cumulative cost of incident fractures is predicted to rise from $209 billion during 2006-2015 to $228 billion for 2016-2025. He also noted that the most rapid increase is projected to occur in Hispanic and other subpopulations. The annual costs for Hispanics will grow from $754 million in 2005 to over $2 billion per year by 2025, for an increase of 175%. Men will account for 29% of fractures and costs. This startling report makes any increase in fracture risk due to the long-term use of PPIs important for all races and ethnicities; not just Caucasian females.

It is clear that the overwhelming majority of fractures and costs incurred will burden those Americans >65 years of age; otherwise known as the Medicare population; making the treatment of osteoporosis and osteoporosis-related fractures a large national expenditure. With the prediction of a 2.7 fold increase in fracture incidence and costs for non-white populations, osteoporosis should no longer be considered a Caucasian phenomenon. The rapidly increasing share of the disease burden amongst non-whites and the overwhelming cost of the outcome of the disease process, underscores the need for targeted disease intervention and risk reduction.

**Bone Mineral Density (BMD)**

Bone mineral density testing is the gold standard assessment tool in osteoporosis. This is because bone strength is strongly related to bone mineral density. BMD has been shown to be a strong independent predictor of fracture. “In fact, there is a clear relationship between BMD and fracture risk in older women. For each standard deviation decrease in BMD (in the spine, a one-
standard deviation drop represents a loss of 10-12 percent of BMD), the risk of fracture increases by 1.5–2.5 times.” (U.S. Department of Health and Human Services, 2004). BMD measurement is used to assess fracture risk, to establish the diagnosis and severity of osteoporosis, and to measure overall bone changes over time.

An individual’s bone mineral density is determined by the interplay of many biological markers. There are many systemic factors at play, including parathyroid hormone, thyroid hormones, growth hormones, sex hormones, and vitamin D. Local factors include prostaglandins, interleukins, and growth factors. Together these hormones and other substances stimulate or inhibit the bone remodeling process through regulation of osteoclasts.

**DXA Scanning**

DXA (dual x-ray absorptiometry) represents the most widely accepted tool for measuring bone mineral density (BMD). It is not possible to measure bone strength directly, or to detect changes in the micro-architecture of bone. Radiographs and absorptiometry therefore determine the mass of bone, its density, and general shape. DXA measures BMD primarily in the spine and hip, two areas affected early in people with osteoporosis. These central sites are also appropriate for monitoring the effectiveness of therapy, as they are more likely than peripheral sites to show increases in BMD in response to treatment.

“An individual’s BMD is compared to the mean value in a reference population, such as young healthy women. The difference between an individual’s BMD and the mean BMD for the reference population can be expressed in standard deviation (SD) units; a score of 0 indicates BMD equal to the mean; a score of +1 indicates one standard deviation above the mean, and -1 is one standard deviation below. When an individual’s BMD is compared to the mean BMD score in a young healthy population, this standard deviation measurement is referred to as a T-score,”
In 1994, the World Health Organization (WHO) developed a classification system for osteoporosis based on BMD. Normal was defined as hip BMD that is no more than one standard deviation below the young adult female reference mean (T-score greater than -1). Low bone mass (osteopenia) was defined as hip BMD between 1–2.5 standard deviations below the young adult female mean (T-score less than -1 and greater than -2.5). Osteoporosis was defined as hip BMD 2.5 standard deviations or more below the young adult female mean (T-score less than -2.5). Finally, severe osteoporosis (established osteoporosis) was defined as hip BMD that is 2.5 standard deviations or more below the young adult mean in the presence of one or more fragility fractures.

It is of importance to note that the WHO classification was derived only from studies of white postmenopausal women. It is a stretch to say that it holds true for men, premenopausal women, or non-white postmenopausal women. Generally speaking, men have a higher bone mass than do women, and Black individuals have higher bone mass than do White men and women of the same age. (U.S. Department of Health and Human Services, 2004).

**Physiologic and Pathophysiologic Gastric Acid Secretion**

The stomach produces acid via parietal cells. These cells are epithelial in nature and primarily secrete hydrochloric acid and intrinsic factor. Parietal cells contain an extensive secretory network, called canaliculi, from which the HCl is released into the stomach. The enzyme hydrogen potassium ATPase (H⁺/K⁺-ATPase), otherwise known as the proton pump, is unique to the gastric parietal cell. The proton pump is the terminal step in acid production. Under normal conditions, acid secretion is appropriately stimulated by histamine, gastrin, and acetylcholine in response to food entering the esophagus and the stomach. The role of gastric
acid is to lower the pH of the stomach contents so that intrinsically secreted enzymes can begin digestion.

However, millions of people across the globe suffer from generalized dyspepsia involving the need to suppress gastric acid secretion. In fact gastroesophageal reflux disease (GERD) alone represents greater than five million outpatient clinic visits in the United States annually (Shaheen, 2006). Dyspepsia, erosive esophagitis, GERD, and peptic ulcer disease (PUD) are the primary indications for use of a proton pump inhibitors and H₂RAs. The definitions of each disease process can be found in the appendix.

**Proton Pump Inhibitor and H₂RA Mechanisms of Action**

Proton pump inhibitors (PPI) act by accumulating in the secretory canaliculus of the acid-secreting parietal cells. The active protonated form irreversibly binds to the proton pump and therefore prevents secretion of H⁺ ions into the gastric lumen (Ali, 2009). Because the mechanism of action is irreversible, acid secretion can only resume after the lumen synthesizes new pump molecules. Therefore proton pump inhibitors are typically effective for 24 to 48 hours and are the most potent suppressors of acid secretion. PPIs undergo rapid first-pass and systemic hepatic metabolism but have negligible renal clearance. It is estimated that elderly patients may have a decreased rate of clearance and are more likely to maintain higher levels of these drugs for longer periods of time. In 1992 Landahl et al. suggested that Omeprazole’s clearance is reduced by 50% and bioavailability is 1.4 fold greater in healthy elderly subjects than healthy younger subjects.

H₂-receptor antagonists (H₂RA) are another class of drugs that work to decrease acid production in the stomach. H₂RAs are competitive antagonists that block only selective pathways
involved in the activation of the parietal cell. The class suppresses normal acid secretion and meal-induced acid secretion. H2RAs are effective acid reducers but are not as potent as PPIs.

Osteoclast ATPase vs. Gastric H\(^+\), K\(^+\)-ATPase

Bone resorption is very complicated and occurs through a multi-step process. An important step in the resorption process is degradation of bone matrix by osteoclasts in the presence of an extracellular acidic environment. In order to achieve an acidic environment, protons need to be pumped across the gradient into the extracellular space. The primary proton transport of osteoclasts is mediated by a vacuolar-type H\(^+\)-ATPase (for a definition of this see the appendix).

Omeprazole and other PPIs are inhibitors of gastric H\(^+\), K\(^+\)-ATPase. This ATPase is different from the vacuolar ATPase found in osteoclasts. In the past it was believed that PPIs only affected parietal cell ATPase. However, there is some \textit{in vitro} research to suggest that the PPIs may have some effect on the osteoclast ATPase; possibly inhibiting bone resorption. In 1993, Mizunashi concluded that Omeprazole inhibits a vacuolar-type H\(^+\)-ATPase-mediated proton transport from osteoclast-containing medullary bone at high concentrations.

Inhibition of bone resorption may either protect against fracture or preclude a bone to fracture. Yang, in 2006, postulated that it is possible that the potentially protective effect of osteoclastic proton pump inhibition may cancel out some of the negative effects of gastric acid suppression by PPIs. Therefore patients taking PPIs should see a “decrease” in fracture rate if bone resorption is inhibited. However, if bone resorption is limited for long periods of time, not allowing minuscule bone architectural fractures to be repaired, fracture risk may increase. Black et al. conducted a meta-analysis that evaluated the association between the long-term use of bisphosphonates and the increased risk in atypical femur fractures. In that study there did appear
to be some connection. Nevertheless, is clear is that large, well-designed randomized studies need to be conducted and analyzed for a causal relationship.

**History of PPI Use**

Proton pump inhibitors were introduced in the late 1980s and their use has grown exponentially. They are available by prescription and have been available over the counter since 2002. “They are now amongst the most widely prescribed drugs worldwide primarily because of their outstanding efficacy and supposed safety. In 2006 worldwide expenditure was estimated to be $24 billion,” (Ali 2009). In 2008, Omeprazole was the 16th most prescribed drug in the United States. There were over 29,174,000 prescriptions written, up nearly 42% from 2007. The annual cost of Omeprazole in 2008 was $1.14 billion. There were approximately 92,849,000 prescriptions written for all proton pump inhibitors combined, costing $11.8 billion in the U.S. alone (Top 200 Generic and Brand Drugs, 2008).

Ali sites three references that have measured the PPI use in hospitalized patients. From these sources “it is estimated that 50-60% of prescriptions of acid-suppressive medications in hospitalized patients are without appropriate indications”. Many of these patients will go home using the PPIs and will continue on them for an indefinite amount of time; without a true indication.

**Normal and Pathophysiology of Calcium Absorption in the Gut**

Many older adults have inadequate calcium intake. In fact, calcium intake has been shown to decrease by 0.2% per year in women after the age of 40, (Ensrud, 2000 and Heaney, 1989). Low fractional calcium absorption has been shown to increase the risk of hip fracture. Other age-related changes in the gastrointestinal tract take place, including an increased incidence of prolonged gastric-emptying, hypochlorhydria, and achlorhydria. But the question
remains: does achlorhydria or hypochlorhydria reduce calcium absorption in the gastrointestinal tract?

Absorption of calcium is the result of either active transport across duodenal and upper jejunal cells or passive diffusion throughout the small intestine but primarily the ileum. The active transport system is saturable and regulated by dietary intake, the needs of the body, and vitamin D concentrations. Absorption through passive diffusion is not saturable, increases with dietary intake, and is independent of vitamin D and age. However, this is all provided that the calcium in the intestines is in an absorbable form. (Gueguen, 2000)

Calcium salts are relatively insoluble in water and require dissolution in the gut. This process is thought to be highly dependent on acidic pH. It is generally accepted that calcium carbonate (one of the most common calcium salts) reacts with HCL, the primary acid in the stomach, to become a soluble complex of calcium chloride. Calcium chloride is then taken up by the small intestine for use in the body. Age associated atrophic gastritis, gastric resection, and medication with potent H2-receptor blockers or PPI for PUD are conditions associated with hypo and achlorhydria that may significantly modulate the bioavailability of many dietary minerals including calcium, (Wood, 1992). As many as 30% of women 60 years and older have reduced basal gastric acid secretion, (Kassarjian, 1989).

Ivanovich in 1964 showed, via measurement of CaCO3 isotopes, that patients with achlorhydria were physically unable to breakdown the CaCO3, rendering the supplement useless in these patient’s GI tracts. In 1984 Bo-Linn published his article refuting Ivanovich. Bo-Linn revealed that patients with pernicious anemia-induced achlorhydria were able to adequately absorb CaCO3 and that changing the gastric pH from 3.0 to 7.4 did not alter the rate of calcium
absorption. Recker, in 1985, concluded: “calcium absorption from carbonate is impaired in achlorhydria under fasting conditions and therefore may not be the ideal dietary supplement.”

Wood and Serfaty-Lacrosniere conducted a meta-analyses of the sentinel articles that investigated gastric acidity, atrophic gastritis, and calcium absorption from 1967 through 1992. The three primary papers listed above were included in this meta-analysis. In their 1992 study, Wood and Lacrosniere concluded: “calcium absorption from calcium carbonate can be shown to be very different in achlorhydic subjects in the fasting and the fed state. This may explain why some studies indicate a detrimental effect of low gastric acid production on calcium absorption and others indicate no apparent effect of achlorhydria.” Research only shows a calcium malabsorption cause and effect relationship in those patients who were fasting; not in those who were studied after being fed.

In conclusion, research that has been conducted over the last 45 years regarding the role of acid production on calcium absorption remains controversial. The 2009 Insogna and 2005 O’Connell studies were conducted after the Wood, Serfaty-Lacrosniere meta-analysis and were also limited by several factors, including: small number of study participants, inconsistent and indirect measurement of calcium absorption and inclusion of patients with disease states that alter mineral metabolism such as renal failure. To date, there are no randomized placebo-controlled studies on the effects of PPIs on calcium absorption. With every study published that supports the role of gastric acid secretion in calcium absorption there is a contrary study published. The studies and their methods have been inconsistent and are limited by many factors.
**Problem Statement**

In the last few years there have been several studies that looked at the safety concerns of long-term PPI use. Some of the major concerns include carcinogenesis, enteric infections including *Clostridium difficile* colitis, respiratory infections, malabsorption of calcium, Vitamin B₁₂, and iron, and most recently bone fractures. Long-term use of proton pump inhibitors may cause decreased calcium absorption may alter the parathyroid axis, and may act on the osteoclast vacuolar ATP-ase. All have the propensity to alter bone mineralization and remodeling, at worst causing osteoporosis-related fractures and at best altering bone quality. At this time, however, the mechanism for each is poorly understood. Nevertheless, with the widespread use of PPIs and the recent revelation of possible long-term safety issues, a thorough review is mandated.

**Purpose**

To become familiar with available literature regarding the use of proton pump inhibitors and their relationship to overall fracture risk. It remains pertinent to fully investigate all adverse side effects of the medications health care providers prescribe. The end point will be to determine if changes in prescribing habits are needed in order to protect patients who are at an increased risk for developing osteoporotic-related fractures.

**Research Question**

Does the long-term use of proton pump inhibitors increase the risk for osteoporotic-related fractures?
Methodology

Search Terms

All search terms were searched independently and also paired as appropriate. Terms included “proton pump inhibitor,” “omeprazole,” “acid-suppressive medications,” “osteoporosis,” “bone mineral density,” “osteoporosis-related fractures,” “gastric calcium absorption,” “achlorhydria,” “hypochlorhydria,” “vacuolar ATP-ase,” and “H-K ATP-ase.”

Databases

All articles and other texts used to prepare this document were found using MEDLINE and PubMed via the MESH database.

Inclusion and Exclusion Criteria for Articles

Within the MEDLINE and PubMed databases all searches were limited by “human subjects,” “adults,” and “English language,” thereby excluding all articles that were focused on children, animal models, or written in another language. Articles were not excluded, however, if the primary population studied were persons from countries other than America. Articles were excluded if published before the year 2000 unless found to be sentinel to the appropriate field of research and cited by several recent articles. Articles were also excluded if the patients in question were receiving or had received hemodialysis or peritoneal dialysis to treat chronic renal insufficiency and/or acute renal failure. The well recognized disturbances in the PTH axis as well as in the skeletal metabolism that occur with end-stage renal disease make it difficult, if not impossible, to interpret any data that emerges from studies on PPI use in patients with renal disease, (Wright, 2008). It is also postulated that PPIs themselves may induce the PTH axis and papers with that focus were also excluded. Articles that studied the changes in bone mineral density but did not correlate the measure to overall fracture risk were also excluded.
Inclusion into this body of research was not dependent on research design, as the primary goal of this paper was to look at recent human studies published that measure outcomes of proton pump inhibitor use on overall or specific site fracture risk. Unfortunately, to date there are no randomized, double-blinded, placebo-controlled clinical trials detailing the complications of long-term PPI use on fracture risk.
Literature Review

Vestergaard Study

In 2006 Peter Vestergaard et al. published the first large-scale population-based case controlled study that detailed the risk of fracture when taking proton pump inhibitors, H₂ receptor antagonists, and other antacids. It was their belief that these drugs may interfere with bone metabolism and thus may affect the risk of fracture. The study population was limited to any citizen of Denmark who sustained a fracture in the year 2000. Each case was then randomly matched with three controls of the same birth year and gender. Total number of cases was 124,655 and total number of controls was 373,962.

“The source population is the Danish people, which comprise about 5.3 million individuals” (Vestergaard, 2006). The population is considered fairly homogenous in that it is primarily Caucasian. The authors employed national data registers managed by the Danish National Board of Health, the Danish Medicines Agency, and the National Bureau of Statistics. Information on fracture occurrence was retrieved between 1977 and December 31, 2000. Information on prescribed drugs was obtained from 1996 through 2000. It is important to note that this database does not capture medications sold over the counter, nor those that are prescribed in the hospital. However, from 1996 through the study period, proton pump inhibitors were not labeled for over the counter use.

The authors calculated exposure to the drugs as cumulated number of defined daily dosages (DDDs); which is equivocal to the sum of drugs used. They also wished to analyze an average daily use by dividing the DDD by day. The incorporation of defined daily dosages is inherent to the validity of this study. This method allowed a better comparison of different drugs with differing dosages. This system has been validated by the World Health Organization Collaborating Center for Drug Statistics Methodology.
At the time of this study Denmark was using the ICD-10 system. Vestergaard therefore modeled the endpoints to reflect any occurrence of fracture; equaling 11 groupings of diagnoses. Denmark has a nationally run healthcare system and the previously validated capture rate of fractures in this country is approximately 97% (Vestergaard ref #14).

The authors identified seven variables including; (1) use of PPIs, (2) use of histamine H₂ antagonists, (3) use of other antacids, (4) use of H₁ antagonists, (5) prior use of non-steroidal anti-inflammatory drugs (NSAIDS), (6) previous stomach or duodenal ulcer, and (7) previous stomach or duodenal resection. They also listed four primary confounders; (1) ever use of other drugs important to fracture risk (steroids, anxiolytics and sedatives, neuroleptics, antidepressants, and anti-epileptics), (2) co-morbidity, (3) number of bed days in year previous to fracture (1999) and (4) number of contacts to general practitioner or practicing specialist, social variables (income, education level, living alone or with someone, working or not), and other important variables associated with fracture risk (prior fracture and alcoholism). Co-morbidity was defined using the Charlson index, which is an index of 19 co-morbid conditions including heart, liver, kidney, and lung disease, cancer, and HIV/AIDS.

Results

After result analysis it was discovered that the cases were more likely to be retired, have a lower income, and were less likely to be married. As with many other well documented studies, Vestergaard et al. showed that patients with multiple comorbidities; previous fracture, alcoholism, any use of antiepileptic drugs, and gastric resection surgery are at an increased overall risk for any type of fracture.

Results were further stratified by looking at patient’s adjusted odds ratios when broken down into “last PPI use ≤ 1 year ago” and “last PPI use >1 year ago.” An association with time since last use was seen. For the subgroup “last use ≤ 1 year ago” PPIs and other antacids were
associated with a small increase in overall fracture risk (OR of 1.18 – 1.33). Vestergaard used adjusted odds ratio to reflect a statistical manipulation of the data for alcoholism, working or not, ever use of anti-epileptics, ever use of anti-anxiolytics or sedatives, ever use of antidepressants, ever use of neuroleptics, ever use of corticosteroids, number of bed days in 1999, number of contacts to general practitioner or specialist in 1999, living with someone or alone, prior fracture, education level, and income in 1999. In the subgroup “last use >1 year ago” the data for users of PPIs and risk of any fracture was not statistically significant.

When Vestergaard looked at the data to stratify by fracture risk at known osteoporotic fracture sites a similar pattern was seen. Patients who used PPIs within the last year had an OR of 1.45 at the hip and 1.60 at the spine. Patients who used PPIs >1 year ago had an OR of 1.08 at the hip and 0.98 at the spine. For patients with forearm fractures the OR was equivocal in both subgroups at 0.95 in group ≤1 year and 0.94 in the group >1 year. In summary the data showed a disappearance of any association after one year since the last use of the proton pump inhibitor.

**Conclusion**

Vestergaard et al. observed a statistically significant trend toward an increase in relative fracture risk in those patients using proton pump inhibitors. However, this study did not support a dose-response relationship and therefore a causal relationship cannot be propagated. In his discussion Vestergaard ponders a few mechanisms of action for this documented phenomenon but, in the end, lands on one major theme; decreased calcium absorption. He postulates that PPIs may cause a decrease in calcium absorption, which can cause secondary hyperparathyroidism, leading to a negative calcium balance despite a decrease in urine calcium excretion. He references the 1993 Mizunashi article as well as his 2000 article on fractures and primary hyperparathyroidism.
Yang Study

In 2006 Yang et al. published a study out of the United Kingdom that studied the long-term use of proton pump inhibitors and their specific risk of hip fractures. Every year there are greater than 47,000 hip fractures in the United Kingdom. In his paper, Yang postulates that this is the primary manifestation of senile osteoporosis attributed to secondary hyperparathyroidism related to the decreased absorption of calcium.

This was a prospective nested case control study utilizing the General Practice Research Database (GPRD) housed in the United Kingdom. Yang describes the GPRD as a “computerized medical record system of a selected group of general practices in the United Kingdom.” The United Kingdom is a country that has nationwide healthcare for the population and it is estimated that nearly 98% of all residents receive care through the system’s general practitioners. The valid and non-biased use of this database for research purposes is well cited throughout the paper. In fact it is stated that over 500 published epidemiological studies have been performed using the GPRD database. Protocols for recording and transferring information via this database have been predefined and followed for several years.

The original population of the GPRD was nearly 9.4 million people. After exclusion of individuals meeting one of four criteria the cohort population was defined as 1.8 million patients. The four exclusion criteria included: (1) less than 365 days of total follow up, (2) younger than 50 years of age at the time of database enrollment, (3) a documented hip fracture prior to standardization of the database, and (4) use of H2 receptor antagonist or proton pump inhibitor therapy exclusively prior to database enrollment. Of the 1.8 million patients within the cohort, 192,028 received at least one prescription for a PPI, 187,686 received at least one prescription for a H2RA but not a PPI, and 1.4 million were considered “non users” or those never having a documented prescription for either class of drug therapy, “controls.” “Users” in this publication
were defined as any patient with greater than or equal to twelve months of cumulative use of either PPIs or H2RAs before the index date with the last prescription having been less than or equal to six months prior to the index date.

“The primary nested case-control analysis was conducted within the study cohort consisting of all PPI users and the acid suppression nonusers. A secondary nested case-control analysis was conducted within the study cohort and included the users of H2RA only and the non-users of acid suppression therapy. A third case control analysis nested within the cohort that included the H2RA and PPI users together was performed to calculate the OR directly comparing H2RA therapy to PPI therapy (thereby separating users of PPIs from users of H2RAs and comparing the groups). The importance of this third nested case control analysis will be discussed further in the discussion section of this paper. The authors used odds ratios to determine incidence rate ratios in all of the nested case controls.

Out of the cohort, cases were randomly selected using incidence sampling; again, a method for which Yang provided many citations to show non-bias. Cases consisted of all individuals who suffered a hip fracture at least one year after standardization of the GPRD database. The GPRD database has been proven to have >90% validity in confirming hip fractures with the case’s general practitioner. Out of the cohort, controls were selected using incidence sampling, and were matched for gender, index date, birth year, and amount of follow up since database standardization.

The author’s primary variable in this study was “PPI therapy of more than one year before the index date (date of hip fracture).” Yang felt the most clinically relevant aspect to study when considering osteoporosis and fracture risk was the cumulative exposure to acid suppression coupled with an increasing negative calcium balance due to age. Therefore, he used
cumulative PPI therapy as a continuous variable lending the results to reveal a linear relationship between amount of use over time and fracture risk. The odd’s ratios were associated with durations of up to four years, as that seemed to be a natural drop off in the number of patients exposed to PPIs. In addition to cumulative exposure this study also looked at number of doses taken within the treatment periods. There appeared to be small numbers of patients in each group who were prescribed either the PPI or the H2RA twice per day; whereas the overwhelming majority of cases were taking the medications only once per day. In the group taking the medications twice per day the average length of the prescription was only for one month.

Similar to Vestergaard, Yang et al. used conditional logistic regression to estimate the unadjusted and adjusted odds ratios. The authors labeled all potential confounders that had a prevalence of one percent in at least one of the comparison groups and simultaneously included each in the multi-variable logistic regression model. Potential confounders included: age, gender, body mass index, 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, CRF, Cushing disease, IBD, and prior history of fracture, or seizure disorder. They also took into consideration patients on different classes of medications. These included: anxiolytics, antidepressants, antiparkinsonian drugs, thiazide diuretics, statins, corticosteroids, hormone therapy, bisphosphonates, calcitonin, nonsteroidal anti-inflammatory drugs, anticonvulsants, thyroxine, and calcium and vitamin D supplementation.

A primary analysis for PPIs was repeated, restricting it to those patients who had chronic GERD (>3 diagnoses recorded on different dates in the database). The authors went to great
lengths to exclude the possibility that GERD itself may be associated with an increased fracture risk. However, a separate analysis was not conducted to exclude the same possibility in patients who suffer from peptic ulcer disease.

Yang et al. was the first to comment on the gender specific nature of osteoporosis and how that may skew the results of the study. Osteoporosis affects many more women than men all over the world. It is also accepted that women primarily, purchase and use calcium and vitamin D supplements. Taking this into consideration, the authors used a likelihood ratio test to determine if gender-specific risk played a part in the results of these analyses. Interactions between gender and each form of acid suppression therapy were tested.

**Results**

From the 1.8 million cases in the cohort there were 13,556 incident hip fractures; 2,722 of which were identified among the PPI user group. This group was denoted as the “cases.” Each case was matched with up to ten controls, with each case matching with at least one control. The total number of controls was 135,386. Based on these initial numbers alone, the overall incidence rate of hip fractures was estimated at 4.0/1000 person-years among patients with more than one year of PPI therapy and 1.8/1000 person-years among acid-suppression non-users.

“Controlling only for matching variables, the crude odds-ratio (OR) for hip fracture associated with more than one year of PPI therapy was 1.82, while the multivariate adjusted OR (AOR) for all potential confounders was 1.44. The corresponding AOR associated with more than one year of H2RA use was 1.23. The author’s PPI user group originally contained some users of both PPIs and H2RAs. Due to the likely confounding nature of this heterogeneous group, and to more accurately determine the effect of PPIs taken alone, PPI only users were compared with acid suppression non-users. The AOR for this cohort was found to be 1.62. In a separate secondary case-control analysis, long-term PPI therapy was associated with a higher
fracture risk compared with long-term H₂RA therapy (AOR for > one year cumulative use, 1.34).”

“The regression model in which duration of PPI therapy was included as a continuous variable showed that duration was associated with fracture risk, and was therefore included in the analysis. The strength of the association with hip fractures increased with increasing duration of PPI therapy. Among users of PPI therapy for more than one year, a significant dose-response effect with respect to the average daily dose was observed. 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).” There was also a statistically significant (P = 0.4) relationship between PPI therapy and gender. Men were slightly more likely than women to incur a hip fracture after long-term use of PPIs (AOR 1.78 vs. AOR 1.36).

An analysis was completed for patients with documented GERD who only used PPIs for at least one year; AOR for this group was 1.41. “A significant dose-response effect associated with PPI therapy was again observed in this analysis restricted to patients with GERD. The multivariate AOR associated with high-dose long-term PPI therapy was 3.49.”

**Conclusion**

Yang et al. found a significantly increased risk of hip fracture associated with long-term PPI therapy, particularly among long-term users of high-dose PPI. Yang felt that the sheer size of the cohorts and thus the cases enhanced the precision of his statistical analyses. Yang is unsure as to the exact mechanism of action but postulates that calcium malabsorption due to hypo or achlorhydria is a primary factor. The double effect of proton pump inhibitors on gastric parietal cells and the osteoclast vacuole was also a topic of debate for Yang et al. He postulates that the “protective” effect of the PPI on the osteoclast may have canceled out some of the negative effects of gastric acid suppression by PPIs.
Kaye Study

In 2008 James Kaye, M.D., Dr.P.H. and Hershel Jick, M.D. published “Proton Pump Inhibitor Use and Risk of Hip Fractures in Patients without Major Risk Factors.” Their objective was to estimate the relative risk of hip fracture associated with proton pump inhibitor use in a population without major risk factors. This was a step toward a new direction in this body of literature in that all previous studies primarily focused on patients with some major risk factors for fracture. Their reasoning for conducting such a study was to eliminate as much confounding as possible in the results.

“This study was two-phase, matched, nested, case-controlled pharmaco-epidemiologic study using data taken from the United Kingdom’s General Practice Research Database (GPRD) through 2005, (Kaye, 2008).” Phase one of this study was a preliminary analysis designed solely to identify diagnoses that represented major risk factors for hip fracture. Kaye and Jick identified all patients in the GPRD who were aged 50-79 years and had a first-time recorded hip fracture between January 1, 1995 and the end of 2005. Each “case” identified must have had at least two years of history recorded before the index date. Each case was then matched with up to ten controls, none of which have had a hip fracture, by year of birth, gender, and index date. Each of these patients also must have had at least two years of history recorded in the GPRD prior to the index date.

Kaye and Jick created a “list of all diagnoses and signs and symptoms that were recorded at any time in the GPRD before the index date in at least 1% of the case patients.” The same list was extrapolated to the controls cohort as well. “A conditional logistic regression analysis was conducted by using each of the corresponding ICD-8 codes separately to determine which were associated with an increased risk for first-time hip fracture.” The authors defined an important medical risk factor as one for which the hip fracture odds ratio in this matched case-control
analysis was 2.0 or greater. Any case or control that was found to have any of the designated
codes in the GPRD prior to the index date was excluded.

Phase two began with the newly created list of case patients with no major medical risk
factors for hip fracture. However, the authors chose to select a brand new control population.
This was decided based on the fact that nearly half of the control population would no longer
meet the exclusion criteria set by the phase one guidelines; the goal was to maintain a case to
control ratio of 1:10. The cases were matched to controls in the same manner as had been done
in phase one.

The next step in the Kaye study was to determine the amount and duration of exposure to
proton pump inhibitors. “Exposure was determined for each case and control by utilizing the
computerized prescriptions recorded in the GPRD before the index date.” Patients were
considered “exposed” if he/she received one prescription of omeprazole, lansoprazole,
pantoprazole, rabeprazole, or esomeprazole any time prior to the index date. Cumulative
exposure was measured by assessing the number of prescriptions received; either by a
continuous or a categoric variable (1, 2-9, 10-29, >30). Current use of PPIs was also compared
to with past use of PPIs. “Current use” was defined as the last prescription for the PPI occurring
within ninety days of the index date. Patients with no prescription for any PPI at any time before
the index date constituted the designation of “unexposed.” Effects of the entire class of PPIs on
risk of hip fracture were examined as well as each individual PPI.

Statistical analysis was consistent in both phase one and phase two. In phase one,
conditional logistic regression models were used to determine which ICD-8 codes were
associated with an increased risk for hip fracture. Estimated odds ratios and 95% confidence
intervals for the occurrence of hip fractures were also employed. “In phase two, the same
models were used for various categoric levels of exposure to any PPI or each PPI individually. Odds ratios were reported as relative risks due to hip fracture being a rare outcome in the base population. The number of PPI prescriptions as a continuous variable was analyzed and scaled to estimate the odds ratio for hip fracture associated with each additional ten PPI prescriptions. There was no improvement in the model fit to the data by the addition of a quadratic term. Therefore, all results are published only for the log-linear analysis.”

Results

Results were reported separately for phase one and two. In phase one, 4414 case patients met the inclusion and exclusion criteria, of which 72% were women and 28% were men. The population was between the ages of 50 and 79. As mentioned above, the authors began phase one by excluding any patient who had a major medical risk factor for hip fracture. “Major” was defined as a relative risk (RR) of >2.0. However, not a single one of the 96 major risk factors for hip fracture included any codes for diagnoses that are indications for use of PPIs.

“Phase two began after the exclusion of 3316 cases (75% of the phase one cohort) who had at least one of the medical conditions strongly associated with the risk of hip fracture.” The remaining cases totaled 1098. Kaye and Jick matched an entirely new set of controls with the remaining cases and the total population studied was 12,021. Due to the matching, gender, age, and index date distributions among controls were identical to those among cases. The duration of history recorded in the GPRD before the index date ranged for 2.0 – 16.7 years with a median of 6.5 years. Of the 12,021 cases and controls only 132 (12%) of the cases and 1428 (13%) of controls had at least one prescription for any PPI recorded prior to the index date. “The ranges of total number of PPI prescriptions recorded before the index date were 0-85 among cases and 0-159 among controls.”
“The estimated RR of hip fracture for those who received up to nine PPI prescriptions before the index date was 0.9 compared to those never having received a PPI prescription. For each additional ten PPI prescriptions recorded before the index date, the RR of hip fracture was also 0.9.” It is evident throughout the categoric analysis that there is no increased risk of hip fracture with increasing numbers of PPI prescriptions. Kaye and Jick also analyzed the relative risk data for each individual proton pump inhibitor. The combined RR for each PPI is as follows: omeprazole 0.8, lansoprazole 1.0, pantoprazole 1.2, rabeprazole 1.0, and esomeprazole 0.5. “For none of the individual PPIs was there material evidence of an increase in risk of hip fracture with increasing numbers of prescriptions.

Kaye and Jick analyzed the RR of cases and controls that were taking proton pump inhibitors and were also smokers. “Adjusted for PPI use, the RR for hip fracture (compared with nonsmokers) was 1.6 for current smokers, 1.1 among ex-smokers, and 1.4 among those with unknown smoking status.” The authors also analyzed the RR of cases and controls with differing body mass indexes (BMIs). “The RR for hip fracture (compared with those with a BMI <24) was 0.6 for those with BMI 24-28, 0.5 for those with BMI greater than 28, and 0.9 for those with unknown BMI.

**Conclusion**

Kaye and Jick conclude, “the results of their study provide evidence that individuals aged 50-79 years who use PPIs and who are without major clinical risk factors do not have an increased risk of hip fracture.” They postulate that “the cumulative RR estimate was close to 1.0 for current users of PPIs compared with past users and there was no duration of use effect.” There was also no observed increase in risk of hip fracture for any of the individual proton pump inhibitor drugs. The cases included in this study represent approximately 25% of all cases of hip fracture in the GPRD population aged 50-79.
Targownik Study

In 2008 Laura Targownik, et al. published the paper “Use of proton pump inhibitors and risk of osteoporosis-related fractures.” The goal of this paper was to further delineate a correlation between the duration of use of proton pump inhibitors and any risk of decreased bone mineral density-related fractures. As with the two other studies, Targownik describes the clinical significance of hip fractures along with the associated morbidity-mortality rates. Canadians experienced 23,375 hip fractures in 1993-94 with the incidence expected to rise to about 88,124 by the year 2041; according to Papadimitropoulos in 1997.

This paper is a retrospective matched cohort study that employed the Population Health Research Data Repository (PHRDR). This database contains comprehensive health care utilization data for nearly all of the residents of Manitoba, Canada. It is a comprehensive collection of population-based health utilization datasets. “This province provides comprehensive health care coverage for all residents of Manitoba and maintains computerized databases of contacts with the health care system, including all dispensations of prescription medications.” The authors provide two citations validating the database in determining the prevalence of and risk factors for osteoporotic fractures at the hip, spine and wrist.

“Cases were defined as people aged 50 years and older who were seen by a physician or admitted to the hospital with a diagnosis of vertebral fracture, wrist fracture, or hip fracture between April 1996 and March 2004.” Only patients who were continuous Manitoba residents between 1988 and 2004 were included. Patients were excluded if they had used osteoprotective medications in the year before the fracture. Nursing home residents were also excluded due to the inability of the PHRDR to track their medication usage.

Each case was then linked to three controls with no prior history of hip, vertebral, or wrist fractures. The case-control match was based on age at time of fracture, gender, degree of
comorbidity, and ethnic background. Degree of comorbidity was determined using the Johns Hopkins aggregated diagnosis groups. The degree of comorbidity was split into four categories based on the total number of aggregated diagnosis groups (0, 1-2, 3-5, >5). Underlying comorbidities included: epilepsy, diabetes, ischemic heart disease, hypertension, rheumatoid arthritis, chronic obstructive pulmonary disease, prior solid organ transplant, substance use, depression, schizophrenia, dementia or home care use.

Within the Population Health Research Data Repository there is a database specifically used to track drug dispensation throughout Manitoba. The Drug Program Information Network was used to determine the degree of exposure, if any, of the cases and controls to proton pump inhibitors. “A patient was considered to have been exposed to proton pump inhibitors if the ratio of standard doses dispensed to the number of days between dispensations exceeded 0.70 standard doses per day.” Cases and controls were grouped further based on the total duration of exposure. “Continuous exposure” was tantamount to >70% of the patient’s person-time before the fracture date classified as proton pump inhibitors exposure time. “Non-continuous exposure” was ≥ one proton pump inhibitor dispensed, but less than 70% of the patient’s person-time before the fracture date classified as proton pump inhibitors exposure time. “H2RA exposure” was > one H2RA prescription dispensed with no use of proton pump inhibitors. “No exposure” was no person-time before the fracture date classified as proton pump inhibitor or H2RA exposure time.

The Drug Program Information Network was also utilized to determine all medications the cases and controls were using during the index dates. Medications that may affect bone metabolism or increased the risk of falls were specifically noted and included: anti-androgens, anti-estrogens, bisphosphonates, vasodilatory antianginals, antihypertensives, anticoagulants, antidepressants, benzodiazepines, barbiturates, antipsychotics, antiepileptics, hypoglycemic
agents, diuretics, statins, and prescription non-steroidal anti-inflammatory drugs. However, the database was unable to capture medications purchased over the counter, and therefore does not include supplements such as Calcium or Vitamin D. Socioeconomic status was determined via the patient’s area of residence and income quintiles. This information was garnered from the 1996 Statistics Canada census.

The primary outcome variable in Targownik’s paper was whether the occurrence of an osteoporotic fracture is associated with the duration of continuous exposure to proton pump inhibitors. Other measured outcomes included the strength of association between continuous exposure to proton pump inhibitors and combined hip and spine fractures and hip fractures alone. “Differences between categorical baseline measures for cases and controls were measured using the $X^2$ test. Statistical significance was determined if the $p$ value was less than 0.05. $X^2$ tests were also used to compare the use of proton pump inhibitors between cases and controls. The reference group was patients with no prior exposure to PPI or H$_2$RAs.

The authors used conditional logistic regression models for each of seven exposure intervals ($\geq 1$ through $\geq 7$ years at one year intervals). These models were used to generate adjusted odds ratios (AOR) and 95% confidence intervals. Listed confounding variables included: area of residence, income quintile, comorbidity, use of home care services, and use of medications that might have affected the risk of osteoporosis or fracture (see medications listed above).

Results

The total number of patients that qualified as “cases” was 15,792. Each was matched with three controls (47,289 total control patients). “Overall, patients with a hip, spine or wrist fracture were significantly more likely than controls to have been diagnosed with dementia or
substance abuse and were more likely to have received home care services.” Cases were also two percent more likely to have used anti-epileptics, benzodiazepines, antidepressants, and non-steroidal anti-inflammatory drugs.

“There was no statistical association between use of PPIs and the development of any osteoporosis-related fracture for patients with one to six years of continuous proton pump inhibitor exposure. There was, however, a statistically significant association between long-term use (> seven years) and any osteoporosis-related fracture (AOR 1.92). Use of PPIs was associated with an increased risk of hip fracture after five or more years of exposure (AOR 1.62). The magnitude of risk for hip fracture also increased with increasing durations of exposure (AOR after six years of use 2.49 and AOR after seven years of use 4.55).

**Conclusion**

Targownik et al. concludes that the use of proton pump inhibitors increases the risk of hip fracture alone after five or more years of continuous exposure and increases the risk of any osteoporotic fracture after seven or more years of continuous exposure. Therefore, patients who used PPIs for four years or less were not at a significantly increased risk of hip fracture, while patients with less than six years of use had no increase in risk for any osteoporotic fracture.

As with the other primary authors referenced, Targownik remains unsure of the exact mechanism by which long-term exposure to PPIs increases the risk of fracture. She does make a connection, however, to the acid-inhibiting effects of PPIs accelerating the rate of bone mineral loss. “This is consistent with PPI exposure being more strongly associated with hip fracture than with the combined outcomes of hip, spine and wrist fractures because low bone mineral density is much more strongly associated with hip fracture than with the combined outcomes of hip, spine, and wrist fractures.” To speak about the precise mechanism of acid inhibition on BMD over time, she falls back on the malabsorption of calcium as the primary culprit.
**Yu Study**

Elaine W. Yu, M.D., et al. published “Acid-Suppressive Drugs: Bone Loss & Fracture Risk” in late 2008. Yu’s goal was to examine the association between acid-suppressive medications and bone density, rates of hipbone loss, and fracture risk in prospective cohorts of men and women over the age of 65 who were enrolled in the Osteoporotic Fractures in Men Study (MrOS) and the Osteoporotic Fractures Study (SoF). The primary hypothesis was that “the deleterious effects of acid suppression would be most apparent among participants with lower calcium intakes.” Yu’s article is a secondary data analysis based off of the design of the MrOS and SoF studies which are ongoing prospective parallel analyses of large cohorts of men and women who were recruited from several communities in the United States.

“Study of Osteoporotic Fractures (SoF) participants were community-dwelling women 65 years of age and older. Caucasian women were recruited from 1986 to 1988 through population-based listings from four clinical centers in the United States: Kaiser Permanente Center in Portland Oregon, the University of Minnesota, the University of Maryland, and the University of Pittsburgh.” Beginning in 1996 an additional cohort of black women was recruited to the SoF study and was therefore included into Yu’s study population. Excluded patients included those who were unable to walk without help and those that had a history of bilateral hip replacement.

Yu’s analysis was limited to active surviving women who participated in the sixth clinic visit (1997-1999), when a detailed listing of medication use was obtained, and those who had technically adequate hip BMD measurements. The study population was 5339 women, after these limitations were placed. Participants completed follow-up measurements at an eighth clinical exam an average of 4.9 years later, at which time medication history (N=3283) and hip BMD measurement (N=2856) were repeated.
Beginning in March of 2000 through April 2002, a total of 5995 men 65 years of age and older were recruited for participation in the MrOS study from six areas of the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Portland, Oregon; and San Diego, California. In keeping with the standards previously set by the SoF study, exclusion criteria remained the same: men with a history of bilateral hip replacement and those who were unable to walk without assistance were excluded. “Yu’s analysis was limited to those 5755 men with information on medication use and technically adequate hip BMD measurements at baseline. Participants completed follow-up measurements at the second clinic visit an average of 4.6 years later, at which time medication history and hip BMD was repeated (N=4230).”

“In both the MrOS and the SoF cohorts, participants were asked to bring all current prescription medications, defined as any use in the previous four weeks to the clinic visit. In the SoF study, women were also asked to bring nonprescription medications to all visits. In the MrOS study, nonprescription medications were not documented until the follow-up visit.”

However, only in the SoF cohort was duration of medication use notated. All medications were then coded by a computerized medication coding dictionary and the primary analysis was performed by classifying participants into categories of “users of PPIs,” “users of H2RAs,” and “non-users of either PPIs or H2RAs.” A secondary predictor variable was developed for a category of “users of PPIs and H2RAs.” “Time dependent analysis was used for the fracture analysis to allow for crossover and discontinuous PPI or H2RA medication use as documented over subsequent visits.”

Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (DXA) scanners. All repeat measurements were performed on the same machines used in the initial measurements. “All rates of change in BMD was expressed as an annualized percentage
of the \[\text{difference between the follow-up BMD and the initial BMD}/\text{the initial BMD}\].” In both the MrOS and SoF cohort’s participants were contacted every four months either by telephone or post card to determine the occurrence of fractures. Both studies averaged 95% completeness of the follow-up contacts. All reported fractures were confirmed by review of either the radiographs or the radiographic reports by a study radiologist.

“In SoF, fractures that occurred after visit six (when the medication use list was obtained) but before August 2007 were included in the analysis. In MrOS, all confirmed fractures up until August 2007 were included. Also excluded were self-reported vertebral fractures. Fractures that were sustained under majorly traumatic conditions were included in Yu’s data analysis. However, a secondary analysis was performed in which this group of participants was excluded. Participants were also excluded if a previous hip fracture was found in the analysis of incident hip fractures.

In both the MrOS and the SoF studies each participant was interviewed initially and then self-reported questionnaires were employed. Patients were asked about medical history, smoking status, alcohol intake, physical activity, and self-reported health. A full current medication history was obtained as well as body weight and height via a balance-beam scale and stadiometer. Dietary calcium intake and calcium supplements were assessed in similarly in both the MrOS and SoF studies.

“Each study was analyzed separately but in parallel fashion using chi-squared tests for categorical variables, t-tests for normally distributed continuous variables, and Wilcoxon rank sum tests for continuous variables with skewed distributions. Linear regression models were used to examine differences between acid-suppressive medication users and non-users, and the least square means procedure was used to calculate the adjusted means per group. Proportional
hazard models (reported as relative hazard, RH) were used to examine the association between the use of acid-suppressive medications (expressed as a time-dependent covariate) and risk of subsequent fractures. The use of the time-dependent covariate allowed patients the ability to switch between the user and non-user groups over time within the model. All models were minimally adjusted for clinic and age, then further for those characteristics related to either PPI or H$_2$RA use at the p <0.10 level.”

“Secondary analyses were performed on the subset of participants who were not taking hormone replacement therapy (HRT) or a medication for osteoporosis, defined as the use of bisphosphonates, raloxifene, calcitonin, fluoride, or teriparatide.” As mentioned above, a secondary analysis was also conducted excluding traumatic hip fractures. Models evaluating the interaction between the use of calcium supplements and acid-suppressive medication were also examined.

**Results**

Baseline characteristics for users and non-users are well described in Yu’s paper. Of note, participants using PPIs and H$_2$RAs tended to have higher BMIs, reported more inactivity, had poorer self-reported health, and used more prescribed drugs, including corticosteroids and NSAIDs. “In the SoF cohort mean duration of H$_2$RA and PPI use at the initial visit was 3.6 years and 1.8 years respectively.” A large increase in the proportion of participants taking PPIs at the follow-up visits was noted, (five percent at the SoF initial visit vs. sixteen percent at the follow-up visit.) An increase was also noted for a greater proportion of participants to be using any form of acid-suppressive therapy, (14.3% at the SoF initial visit vs. 22.8% at the follow-up visit). The trends propagated through the MrOS study with an increase of 50% in the use of PPIs from the initial to the follow up visit.
After adjustment for multiple covariates, men in MrOS who were PPI users had slightly lower total hip BMD and femoral neck BMD at the initial visit when compared to non-users of these drugs. After adjustment for multiple covariates, there was no association between PPI or H2RA users and bone mineral density noted in the SoF cohort. Neither was there a statistically significant difference in the annualized percent change of total hip or femoral neck BMD, as a measure of rate of bone loss, in patients using PPIs or H2RAs.

“In the SoF cohort, during a mean follow-up time of 7.6 years, 1410 non-spine fractures occurred, of which 451 were incident hip fractures. In multivariate-adjusted time-dependent proportional hazard models, an increase in the risk of non-spine fractures among users of PPIs as compared to non-users was found (RH 1.34).” Similar results were noted for non-spine fractures when users of PPIs were pooled with users of H2RAs to compare against non-users. “Neither PPI nor H2RA use was associated with incident hip fracture risk. In the MrOS cohort, during a mean follow-up time of 5.6 years, 489 non-spine fractures occurred, of which 89 were incident hip fractures.” In multivariate-adjusted time-dependent proportional hazard models there was no statistically significant increase in the risk of non-spine fractures among users of PPIs compared to non-users, (RH 1.21).

The impact of calcium supplementation on the relationship between acid-suppressive medication use and fracture risk was tested in both the SoF and MrOS cohorts. “Stratified analyses demonstrated that among men who were not taking calcium supplements, PPI use was associated with an increase in fracture risk (RH 1.49), but not among men who were taking calcium supplements (RH 0.88).” No significant findings were noted in the SoF cohort.

**Conclusion**

As per Yu, et al., the primary findings of her article are as follows: (1) after adjustment for potential confounders use of PPIs in men was associated with a mildly lower BMD at the hip;
there was a suggestion of increased bone loss in men and women on PPIs but it was not statistically significant; (3) proton pump inhibitor use was associated with a 34% increase in risk of non-spine fractures in females; (4) among men not taking calcium supplements there was a 49% increase in risk of a non-spine fracture; and (5) men taking calcium supplements did not have a statistically significant increase in risk of a non-spine fracture while taking PPIs. “Based on the non-spine fracture data in the SoF cohort, the estimated PPI number-needed to harm is such that one extra non-spine fracture would be expected for every ten women treated for five years with a PPI. This means that 3.6% of non-spine fractures in women of this age group could potentially be attributed to use of PPIs.” Finally Yu et al., states that “PPIs may have unintended negative skeletal effects, although they are likely minor on the individual level.”

**Gray Study**

Shelly Gray, PharmD et al. published “Proton Pump Inhibitor Use, Hip Fracture, and Change in Bone Mineral Density in Postmenopausal Women” in May 2010; just a few days before the FDA released its decision to changes labels on PPIs due to a possible increase in fracture risk. Gray published this paper to discuss the growing concern that there are potentially deleterious side effects to long-term use of PPIs. She, along with every other author presented, delineates the multiple issues related to hip fracture; including increased morbidity, mortality, and health care costs. Most importantly Shelly et al. state that exploration of any association is pertinent because the use of medication is a modifiable risk factor.

This study is prospective and uses data from the Women’s Health Initiative (WHI) to examine the associations of PPI use with fracture risk of the hip, spine, forearm, wrist, and total fractures as well as changes in 3-year bone mineral density (BMD). The WHI is comprised of two main groups; an observational group and a clinical trial group. Women were recruited over a five-year span from over 40 clinical centers in the United States. Eligibility was determined as
women who were postmenopausal, aged 50-79 years, and had an estimated life span of at least three years. The primary analysis included 161,806 women who had no prior hip fracture. Follow up was conducted through 2005 for a mean duration of 7.8 years.

Fractures were defined as self-reported clinical fractures other than those of the ribs, sternum, skull or face, fingers, toes, and cervical vertebrae. The incidence of fracture was collected either semi-annually or annually via mail and/or telephone questionnaires. When self-reported fractures were confirmed by physician review, self-report was accurate anywhere from 51% - 81% of the time; dependent on site. Spine fractures were the least accurate at 51% while forearm/wrist fractures were the most accurate at 81%. Bone mineral density at the total hip, posterior-anterior spine, and total body was measured at baseline with dual-energy x-ray absorptiometry. “Complete case analyses for hip, spine, and total body were 6695, 6629, and 6677 participants respectively,” (Gray, 2010).

PPI exposure was measured at baseline and at the three-year visit. All patients were asked to bring current medication bottles to the interview so clinic interviewers could enter as much information as possible. Women self-reported their data on duration of use for each of their medications. Information was entered into the WHI database for PPIs and H2RAs. Duration of medication use was then split into three categories; <1 year, 1-3 years, and >3 years. However, information on dosages was not recorded and patients using both PPIs and H2RAs were classified together.

Confounding variable information was ascertained via self-reporting at the baseline visit. Points of interest included: race, ethnicity, history of fracture, current and past smoking history, several physician-diagnosed conditions, physical function, and physical activity. Use of other medications was also self-reported and included: use of psychoactive meds, corticosteroids,
hormone therapy, and bisphosphonates. BMI was measured for each woman. Dietary intake calcium and vitamin D was measured by using a food-frequency questionnaire.

\(X^2\) tests for categorical variables or 2-sample \(t\) tests for continuous variables were used to compare women taking a PPI and/or H2RA at baseline with those of non-users of both medications. Multivariate analyses were used for patients with a complete set of data. Hazard ratios (HR) and confidence intervals for fracture among PPI users of H2RA users vs. non-users were computed for each fracture outcome. “Two models were fitted for each fracture outcome to examine the effect of potential confounding. Model one adjusted for age, race or ethnicity, and BMI. Model two adjusted for variables predictive of hip fracture from a prior WHI analysis (eg, smoking, physical activity, self-reported health, having a parent who broke a hip after age 40, treated diabetes mellitus, history of fracture at age >55, and corticosteroid use) and other variables that might confound based on a prior literature search,” (Gray, 2010). Change in PPI use over time was measured by entering the variable as a time-dependent exposure. Multivariate linear regression methods were used to assess the association of baseline BMD with any PPI use and duration of PPI use, as well 3-year changes in BMD.

**Results**

The total cohort at baseline was 161,806. Of those women, only 2.1% (3,396) were taking a PPI and 6.2% (10,016) were taking a H2RA. The majority of women who were taking PPIs had used them for less than three years; only 392 women used the PPIs for greater than three years. Generally, the women who were taking PPIs tended to have more obesity, more osteoporosis and fractures, more incidences of diabetes and self-reported poor/fair health.

Gray et al. reported a total of 1,005,126 person-years of follow up, 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and 21,247 total fractures. “The annualized rate of hip fractures was 0.15% for nonusers and 0.19% for PPI medications users,”
(Gray 2010). After fully adjusting for confounding, PPI use was not related to risk for hip fracture (HR 1.00), but it was modestly related to clinical spine, forearm or wrist, and total fractures. Those women using PPIs had an approximate 47% increased risk for clinical spine fracture (HR 1.47), a 26% increased risk for forearm or wrist fracture (HR 1.26), and a 25% increased risk for total fracture (HR 1.25).

No association between H2RA use and increased risk for fractures of the hip, clinical spine, forearm or wrist was revealed. However, there was a miniscule increase in total fracture risk for those patients taking H2RAs. There was no consistent trend to establish duration of PPI use effect. The authors were not able to establish significant changes in BMD from baseline in those women taking PPIs when compared to non-users. In fact some women experienced a slight increase in their BMD due to concomitant use of experimental calcium and vitamin D supplementation.

**Conclusion**

Gray et al. published a large prospective case-controlled study of postmenopausal women aged 50-79 years without history of hip fracture. Statistical analysis revealed that PPI use was not significantly associated with an increased hazard of incident hip fracture. Also, they found no evidence that the duration of PPI use was related to incidence of fracture. There was some evidence, however, that PPI use was related to an increased risk for other fracture outcomes, including clinical spine, forearm or wrist, and total fractures.

**Corley Study**

Douglas Corley, et al. published “Proton Pump Inhibitors and Histamine-2 Receptor Antagonists are Associated with Hip Fractures Among At-Risk Patients” in 2010; right on the heels of the FDA press release. Corley set out to provide some literature to address the issue of the lack of large study, long-term exposure data on PPIs and fracture risk. He cites hip fractures
causing major morbidity and mortality as the importance of this study. One aspect the authors looked at, which sets it apart from the other literature, is that they examined whether fracture risk was associated with other commonly used medications, because they believed this would suggest confounding.

Corley et al. conducted a case-control study within the Kaiser Permanente, Northern California integrated health care delivery system. The KPNC system has been validated for statistics on prescription drug benefits through several pharmacy databases. Cases were defined as “KPNC members who met the following criteria: an incident diagnosis of a hip fracture between January 1995 and September 2007, using ICD-9 codes for hip or femur fractures; at least 18 years of age at the index date; no prior hip/femur fracture diagnosis; and at least two years of membership before the index date,” (Corley, 2010). Controls were matched by gender, year of birth, duration of membership, first year of membership, and race or ethnicity. There were up to four matched controls for every one case and they were randomly selected from the KPNC membership, using density sampling. Each control must have been over 18 years of age who lacked a hip fracture diagnosis at the index date of the matched case and had at least two years membership prior to the index date.

Corley et al. used the KPNC prescription pharmacy databases to determine medication exposures. All prescriptions were prior to the index date. The databases contain information since January 1994 and details number of dispensed medications, frequency of refills, and directions for use. The author’s primary variable for analysis was cumulative dose, which was defined as days supply. Exposure duration was measured as the interval between the first and last prescription in addition to the number of days supplied for the last prescription. Dose intensity was evaluated, along with compliance, using the average daily dose. Three dose
categories were then created: occasional use (<0.75 pills per day), approximate daily use (0.75 – 1.49 pills per day), and twice-daily use (>1.49 pills per day). Exposure was defined as a PPI prescription dispensed prior to index date, unexposed (reference subjects) had prescriptions for neither PPIs nor H2RAs. H2RA use was also analyzed in the same fashion as PPIs. However, subjects were excluded from all H2RA exposure categories if they had any PPI prescriptions.

Corley attempted to control for confounding and for effect modifications. The confounders controlled for included: arthritis, cerebrovascular disease, hemiplegia, asthma, dementia, psychoses, diabetes mellitus, thyroid disease, ischemic heart disease, epilepsy, gait disorder, peptic ulcer disease, GERD, visual impairment, chronic kidney disease, smoking, and alcohol abuse. The authors also analyzed whether there were expected associations present for other medications known to modify fracture risk. These medications included: glucocorticoids, estrogen, thiazide diuretics, thyroid supplementation, bisphosphonates, and anxiolytics. In an attempt to control for unexpected confounding medications that are not known to be associated with fracture risk were also evaluated; including angiotensin-converting enzyme inhibitors, calcium channel blockers, and non-narcotic analgesics. Exposure was determined as a patient receiving >364 days supply prior to index date, unexposed if they received no prescriptions, and not included in the analysis if there was an intermediate value.

Statistical analysis included techniques for evaluating case-control studies and conditional logistic regression. Confounding was evaluated by contrasting odds ratios and the final model included factors that altered the odds ratios by about 10%. However, only smoking met that criterion. Differences in PPI effect across age strata, (effect modification) was analyzed using logistic regression models. Nevertheless, all results used the conditional regression models.
Results

Corley et al. identified 33,752 cases and 140,471 controls for the main analyses. Cases were primarily women (67%), 70 years of age or older (69.4%), and non-Hispanic white (79.6%). Only 39.3% of cases had been prescribed either a PPI or H2RA. However, of that group only 4.6% (1558) were dispensed a PPI with greater than a two year supply, and 2.6% (875) were dispensed a H2RA with greater than a two year supply.

Long-term users were defined as those with a >2 year supply of medication and the authors found that the risk of fracture was 30% higher (OR 1.30) among that group of PPI users compared to non-users. They found the same to be true among long-term users of H2RAs (OR 1.18). Of note, the association between >2 years of PPI use and hip fracture was only present among subjects with at least one other risk factor for hip fracture (OR of 1.25). “The trends for increased risk were most notable for fracture risk factors associated with decreased bone density (diabetes, renal insufficiency, and glucocorticoids use),” (Corley 2010).

A general trend for increased fracture risk among patients taking higher average daily doses was noted; OR of 1.30 for patients taking 0.75 – 1.49 pills per day and OR of 1.41 for patients taking >1.49 pills per day. Although there was a slight statistically significant increase in risk with longer durations, the authors did not establish a meaningful increase in fracture risk with increased dose duration. However, the author did establish a diminishing association between PPI use and hip fracture from current use to discontinuation of the PPI. Among current long-term users the fracture risk associated with PPI use was an OR of 1.30 but that risk trended lower to an OR of 1.09 in patients with use of PPI 2 - 2.9 years prior to the index date.

The connection between >2 years of PPI use and fracture risk was significantly dependent on age. Risk was increased for all decades between the ages of 40 and 89 years. The connection between long-term PPI use and hip fracture was comparable between males and
females as well as by race/ethnicity. The known associations between other medication classes and the risk of hip fracture were found to be in general concordance with previously published values.

**Conclusion**

Corley’s group found an association between the use of PPIs and H2RAs and the risk of hip fracture. As to be expected the risk was more significant amongst users of PPIs than users of H2RAs. The caveat is that the risk is conferred upon only those patients with at least one other fracture risk factor. If hypothetical causality is assumed the increase in risk is miniscule. Furthermore the risk attributable to acid suppression in the general public is low. Although the findings were statistically significant, the authors do not recommend against using acid suppressive medications where indicated. They provide no known mechanism of action but postulate, as others have, that diminished calcium absorption from acid inhibition is most intuitive.
Discussion

Vestergaard

There are two primary strengths of the Vestergaard study. One is that it was designed to capture the average dosages of antacid medications. The author described in his study how the defined daily dosage (DDD) algorithm has been validated by the WHO. By using the DDD algorithm, the author was able to analyze a dose-response relationship with antacids. However, no dose-response relationship was detected. This may be attributed to the duration of follow up maxing out at around five years. Second, Vestergaard attempted to minimize the recall bias that would typically plague a retrospective case control study. This can in part be attributed to the nationalized healthcare system in Denmark and the seemingly high quality of the research collected.

A weakness of this study was that although they were able to collect medication dosage data, they were unable to control for medication compliance. “The physical redeeming of a prescription was used as a proxy for actual use of a drug.” Secondly, a confounding issue may be present. The authors were able to control for many covariates but important issues not addressed were complications like differences in body weight, physical activity, smoking, and use of calcium/vitamin D supplementation.

In regards to the comparison the author made between H2RAs and PPIs, an interesting trend was observed. He found that patients taking the less effective H2RA class actually had protection from fractures; while the patients taking PPIs had an increase in relative fracture risk. This relationship detracts from the argument that the increase in fracture risk from PPIs is due to a substantial hypochlorhydria causing calcium malabsorption. It is reasonable to assume that a minimal hypochlorhydria would not protect against fracture risk but would be either null or show a small increase in relative risk. Or, is it because PPIs cause a near achlorhydria with
simultaneous work on osteoclasts and H₂RAs produce a hypochlorhydria by working directly on the parietal cell without action on the osteoclast?

**Yang**

Yang, like Vestergaard, also compared a group of H₂RA users to a group of PPI users. However, his results differed from Vestergaard. Yang was able show a mild increase in fracture risk in those patients taking H₂RAs. The group was able to establish a dose-response relationship. This is likely attributable to the nearly 15 years of follow up; compared to only five years in the Vestergaard study. A flaw in the Vestergaard study that became apparent after the Yang counterpart is that Vestergaard included very short-term users of PPIs in his data. This would have likely skewed his results away from a dose/duration response.

Strengths of this study include a repetition of the primary analysis. This was done to control for patients who had been diagnosed with GERD. This restriction analysis was intended to exclude the possibility that GERD itself may be associated with fracture risk. In the end this could help assess the extent of residual confounding by co-morbidity in the original primary analysis. On the other hand, peptic ulcer disease (PUD) should also have been controlled for; but Kaye’s study addressed it later. The weakness of Yang’s paper lies in possible confounding due to the uncontrolled variables of complete duration of PPI exposure and calcium and vitamin D supplementation.

**Kaye**

One strength of this paper is that the authors excluded 96 diseases, diagnoses, signs, and symptoms that may predispose a patient to suffering an acute hip fracture. The relative risk odds ratio that was used was “two.” The level of any likely interaction at an RR of two is fairly low and to many professionals has negligible clinical significance. One of the strongest statements made in this paper is that out of the 96 excluded diagnoses not a single one had anything to do
with GERD, PUD, erosive esophagitis, gastritis, or dyspepsia; all of which are the primary indications for the use of proton pump inhibitors. This is the only study to date that has excluded patients with all of those diagnoses; detracting from the theory that perhaps the GI disease processes increase the risk of fracture.

Another strong feature of this paper is that the authors were able to include information on the risk of fracture for those taking patients taking PPIs that smoke and also that have differing body mass indices. There were however several cases and controls that had incomplete data on smoking status and BMI. To date, no other study has been able to capture a large percentage of their respective cohorts to report on risk of fracture with PPI use in smokers and those patients with differing body mass indices.

Within the GPRD, any pharmacy system used to dispense the medications and tally refills, a.k.a. a more reliable method for tracking usage, is not mentioned in either the Yang or the Kaye paper. This becomes a major weakness of both of these papers. Because the strongest research to date does not show a relationship between hip fracture and PPI use alone. However, the relationship becomes apparent and stronger when dose and duration are analyzed in light of osteoporotic fractures.

Another problem with this paper is that the duration of history recorded in the GPRD for cases and controls ranged from 2.0 – 16.7 years. The lack of delineation of this time continuum lends bias to the results. There was no quadratic term studied for the time range of recorded history and the possibility of a stronger association for those with longer recorded histories was never explored. This can also be said for the Yang study.

This study lacked power. The GPRD is an amazing database with power due to its sheer strength in numbers. However, this study was only able to accumulate 132 cases and 1428
controls that met the inclusion and exclusion criteria. The weakest portion of this study stems from the fact that data was never published to compare how many prescriptions were written for a patient over any specified amount of time. Hence, there is no telling how many prescriptions were given to any of the cases or controls. In fact only eleven cases and 217 controls (three percent of total cohort) took greater than 30 (30 day or one month as per the Kaye’s description of common prescribing practices in the United Kingdom) prescriptions over what was described as the median 6.5 years. The maximum number of prescriptions any case received was 85 and maximum number of prescriptions any control received was 159. Furthermore the article does not mention the strength of any of these medications nor the time intervals in which they were prescribed (daily, BID, etc).

Targownik

Unlike Vestergaard and Yang, Targownik et al. did not compare the use of PPIs to that of H2RAs. Her primary end point was to establish a connection between duration of use and increased risk of osteoporotic related fractures. The results of the Targownik study, again, show a small but relevant increase in the relative odds of a fracture. The primary discussion point elevated is whether or not the adjusted odds ratios (all between 1-2) confer a larger risk on society due to the increasing incidence and prevalence of osteoporotic related fractures. The authors postulate that yes, small increases in relative risk may have very relevant effects on the absolute risk of events and associated costs to society. Most importantly, Targownik points out that “the calculated odds ratios for exposure to PPIs are also similar in size to those for other established osteoporotic-fracture risk factors, such as smoking, low BMI, and excessive alcohol intake.”

The authors talk at length about the strength of their study being the fact that the results were consistent with those of Yang. Weaknesses of the study include the lack of
anthropomorphic data and information about the use of over the counter supplements, and
tobacco and alcohol use. Another point of interest the authors bring up, not addressed in many
of the other studies, is the question of whether the increased fracture risk from PPIs in related to
reduced bone density or the increased risk for falls. Unfortunately they did not assess this
relationship to make a hypothesis.

Yu

There are several weaknesses in the Yu study. The primary flaw of this study is that it attempted to compare two different studies; one on females and the other on men. Each study was conducted differently and measured slightly different confounding variables. This was difficult to read and understand, making it difficult to interpret as well. One weakness is that the major exclusion criteria were patients who couldn’t walk without help, those with bilateral hip replacements, and all patients who had had a previous hip fracture. This leaves one to ponder all of the other exclusion criteria set forth by the studies listed above; including patients with GERD, patients on certain medications including bisphosphonates, and those patients with unilateral hip replacements.

Another weakness is that only white women were studied up until 1996 when finally a cohort of black women was recruited. This leaves the question of does the study pertain to all females in America? All medications and falls were self-reported but all falls with reported fractures were allegedly confirmed. During the statistical analysis Yu mentions that the authors had an 80% power to detect unadjusted relative hazards. Therefore it is assumed that 20% of unadjusted relative hazards were not detected, increasing confounding bias. It did not appear as if they controlled for the finding that patients who used non-steroidal anti-inflammatory drugs and steroids were much more likely to be using other drugs, including PPIs and H₂RAs. In other
studies the use of corticosteroids has been shown to increase the risk of osteoporosis and fracture.

Within the results section of Yu’s study it describes the mean duration of H2RA and PPI use as 3.6 years and 1.8 years respectively. Duration of use is much lower when compared to the other studies included in this paper, detracting from the credibility of results. The authors were also not able to gather data on vertebral fractures; severely limiting their ability to report on “non-spine” fractures. Most importantly, Yu reported an increase in hip fracture risk but the amount of patients with hip fractures was miniscule therefore severely limiting the power of the study.

One strength is that both the SoF and the MrOS studies examined over the counter medications. The authors did complete a secondary analysis to decrease the likelihood of confounding variables causing bias. They excluded and thus controlled for women who were not taking hormone replacement therapy or a medication for osteoporosis, patients with traumatic fractures, and the interaction of over the counter calcium supplements and acid suppressive medications.

Gray

This was a well-done, well-controlled study with minor weakness. Those weaknesses include the fact that fractures and duration of medication use were self-reported. Self-reporting can lend toward inaccuracy. Also, the authors did not examine dose response but were, however, able to capture duration response.

Strengths include the ability to ascertain information on smoking, BMI, calcium intake, exercise, and controlling for several classes of medications that can alter bone mineral density and increase the risk for fracture. Another strength of the Gray study is that they were able to
include 392 women who had used PPIs for greater than 3 years. These numbers were very hard
to come by in many of the other studies.

Corley

Corley showed an increased hip fracture risk in those patients taking not only PPIs but
also H₂RAs. This is in direct concordance with Yang’s study using the GPRD from the UK.
Corley et al. did establish a dose but not a duration response. An interesting qualifier was used
in Corley’s discussion though. He states “the increased risk was confined to persons with certain
other risk factors for hip fracture.”

The authors outline an answer to a question they posed in the discussion; “do acid
inhibitors directly increase the risk of hip fractures?” They list several factors pointing toward
causation. They state that a casual relationship is supported by the presence of increased risk
with greater acid suppression (PPI vs H₂RA), dose response, decreased risk with discontinuation
of acid suppression, and the presence of increased risk among person with other risk factors for
osteoporosis. They do go on to list one result pointing away from causation: “the absence of a
clear trend for increased risk with longer durations of use.”

Strengths of this study include the sheer size of the available population database. Corley
was able to isolate almost five times the number of cases with greater than one year of PPI use
from the GPRD. The follow up averaged approximately 10 years for the cases; this lends toward
reliability.

There are a few weaknesses and limitations of this study. Exposure may have been
underestimated in patients who had early index dates. This is due in part to the fact that the
database began recording dispensed medications in 1995; perhaps missing remote dispensations.
Also, as with the rest of the studies included, this was a case control design, which cannot
completely control for unknown confounders and detailed data on some confounders. These uncontrolled for confounders include over the counter acid suppression medication use, alcohol use, diet, body mass index, smoking, etc.
Conclusion

Randomized, double blind, placebo-controlled studies are the gold standard in medicine today. They are most likely to produce accurate and unbiased results because the two study groups tested are hypothetically identical. On the other hand, case control studies are considered to be observational and may carry an increased risk for bias and inaccuracy. They are retrospective in nature and the variable of interest is usually identified via screening previously recorded diagnostic codes. Furthermore the exposure of interest may carry confounding factors that were not accurately reported at the index date.

However, randomized, double blind, placebo-controlled studies may not be practical when studying rare events or events that require a long time to unfold. In fact, observational studies have an advantage in that they allow for “real life” settings rather than the highly structured and controlled environment created for randomized double blind studies. Once known confounders are identified the authors of observational studies statistically adjust the results accordingly. The measure of the magnitude of association is different in controlled versus randomized trials. However, when events are rare (such as hip fractures) the two measures, odds ratio and relative risk, provide nearly identical results, (Laine, 2009).

It is important to note that “observational studies only provide a measure of association between the variable and the outcome; they do not prove cause and effect,” (Laine, 2009). Stronger associations lean more towards causality than weaker ones, and a ratio below two is generally considered to be a weak association, (Shakir, 2002 and Shapiro, 2000).

Another version of this dilemma is addressed by the question, should studies with small odds ratios (<2.0) affect prescribing habits? Because the odds ratios were less than 2.0 in virtually all of the major studies, clinical consequences of this relationship may be limited.
Nevertheless, even small relative risk increases in common diseases can have important public health implications,” (Shapiro, 2000). “Data from Finland indicate that the annual incidence of hip fractures in people >50 years is 0.438%. Yang et al. found a crude annual incidence of 0.18% among acid suppression nonusers in the United Kingdom. If we assume a background annual incidence of 0.3% and an overall relative risk increase of 44-45% based on Vestergaard and Yang, this would translate into an additional 0.13% of the population over 50 developing fractures annually,” (Laine, 2009).

Yu stated that while the individual risk is minimal, through the widespread use of PPIs, 3.6% of non-spine fractures in post-menopausal women could potentially be attributed to use of PPIs. Through the sustained increase in prescribing and availability of these medications, the attributable fraction may become significantly higher. In addition, individuals that are initiated on PPI therapy tend to remain on the medication for many years, if not indefinitely.

The odds ratios found by Targownik in her 2008 study were also between 1-2; showing low magnitude. However, she states that even though the increase in risk may be small, the sheer number of people taking PPIs may confer a larger risk to the general public. Furthermore, the effects on the associated costs to the individual and society will be great. Interestingly, Targownik notes “the calculated odds ratios for exposure to PPIs are similar in size to those for other well-established osteoporotic-fracture risk factors, such as smoking, low BMI, and excessive ETOH consumption,” (Targownik, 2008).

The plausibility of the mechanism of action for the association should also be tested when examining causal relationships. The studies that evaluated the relationship between gastric acid secretion and calcium absorption are controversial and discordant; with several studies finding inconclusive evidence (Bo-Linn, Ivanovich, Gueguen, Wood & Lacrossniere, O’Connell). There
is only one in-vivo study, by Mizunashi in 1993, which evaluated if omeprazole was a possible osteoclastic inhibitor via the ATPase mechanism. The lack of experimental evidence documenting a mechanism of action for increased fracture risk limits any cause and effect claim.

Another aspect of statistical analysis that would increase the likelihood of causality is a represented dose-response effect. Three of the principle studies identified a low powered, but statistically significant increase in fractures with increased PPI dosage or duration. Yang evaluated this relationship and found that the association of fractures significantly increases with the increased duration of PPIs. While Targownik did realize an association, it was only after greater than six years of continuous PPI use. Corley outlined a general trend for increased fracture risk among subjects taking higher daily doses. Neither Vestergaard, Yu, Kaye, nor Gray was able to establish a dose or duration response effect.

Taking all of the above into consideration, a correlation between the long-term use of proton pump inhibitors and an increase in fracture risk is supported by several factors. Causality is defended by the presence of increased risk with greater acid suppression (PPIs vs. H2RAs) as described by Vestergaard, Yu, and Corley. The presence of elevated risk with higher daily doses or longer duration of use was indicated in the Yang, Targownik, and Corley studies. Finally Corley illustrated causality through an association of decreased risk with discontinuation of acid suppression, as well as the presence of risk among persons with other risk factors for osteoporosis.

The possibility that the differences between PPI use and non-use are due to bias found in uncontrolled confounding is cause for concern; even in light of the employment of statistical methods such as case-control matching and conditional logistic regression models. Nonetheless, the relative consistency of several studies, a dose/duration response, and one or more plausible
mechanisms of action supports a causal relationship. Most importantly, findings from the seven papers are not powerful enough to recommend against acid suppression for patients with clear indications for treatment. Therefore, the strongest conclusion one can contemplate is: Health care providers must advocate judicious use of PPIs, including prescribing the minimum effective dose for the shortest duration possible, to help limit any possible adverse effects; including increased fracture risk.

**Areas for further research**

Randomized, double blind, placebo-controlled studies are needed by the FDA and the drug manufacturers; as the prescribing community looks to these as the gold standard. Randomized studies will in some ways help to eliminate the bias and inaccuracy found in observational case-controlled studies. However, the focus should not only be on long-term use of PPIs and increased fracture risk, but on the true role of gastric acid secretion and calcium absorption. Data is discordant to date regarding the effect of PPIs on calcium absorption. In the likelihood that the gold standard type of study remains unavailable it is pertinent to control for confounders such as BMI, physical activity levels, vitamin D status, Ca-Vitamin D supplementation, smoking, and active GI processes in which PPIs are indicated. The inability to thoroughly assess these potential confounding factors has limited the establishment of causality.

The potential effect of PPIs on osteoclast vacuolar ATPase is an interesting and not well-researched mechanism of action for increased fracture risk. Henceforth, the question remains, at what point does the anti-resorption effect on osteoclasts change from protective to harmful. Stopping physiologic remodeling may only be beneficial for so long before the inability to repair causes severe long-term consequences. The Black article in The New England Journal of Medicine (2010) details a possible link between long-term bisphosphonate use and fracture
incidence. This may just be a hint of what’s to come for yet another class of medications that are frequently prescribed.

Finally, the third area of future research lies in the possible induction of hyperparathyroidism through hypergastrinemia caused by hypo or achlorhydria. The description of the complicated physiologic nature of the parathyroid hormone axis was beyond the scope of this clinical review article and was therefore excluded from discussion. However it is briefly evaluated in the Yang’s 2008 paper titled “Proton Pump Inhibitor therapy and Osteoporosis.”
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## Appendix (A)

<table>
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<tr>
<th>Study Author</th>
<th>Date of Publication</th>
<th>Major Findings</th>
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| Vestergaard  | August 2006         | - PPIs and H2RAs  
                |                     | - Use of H2RAs showed decreased overall fracture risk  
                |                     | - Increased overall, hip, and spine fracture risk with PPIs  
                |                     | - No dose response with PPI use |
| Yang         | December 2006       | - Studied use of PPIs on hip fracture risk  
                |                     | - Increased hip fracture in patients taking high dose PPIs for > one year |
| Kaye*        | February 2008       | - Studied use of PPIs on hip fracture risk in those pts without risk factors for osteoporosis  
                |                     | - NO increased risk of hip fracture with PPI use |
| Targownik    | August 2008         | - No increased risk of overall fracture for PPI use less than six years  
                |                     | - Increased risk of hip fracture with PPI use >5 years  
                |                     | - Increased risk of any fracture with PPI use >7 years |
| Yu           | October 2008        | - PPIs and H2RAs  
                |                     | - Measured fracture risk and bone loss  
                |                     | - Men using PPIs or H2RAs had lower bone mass. No change in women  
                |                     | - Increased risk of non-spine fracture in women using PPIs  
                |                     | - No increase in fracture risk for those patients on H2RAs |
| Gray         | May 2010            | - Studied PPIs on fracture risk and change in bone mineral density  
                |                     | - No change in BMD while using PPIs  
                |                     | - Increased spine, wrist, and overall fracture risk with PPI use.  
                |                     | - No increase in hip fracture risk with PPI use |
| Corley       | July 2010           | - Studied PPIs and H2RAs  
                |                     | - Increase in hip fracture risk after two years of PPI or H2RA use AND at least one other fracture risk factor  
                |                     | - Dose response but no duration response |

*The only study that did NOT show an increase in relative fracture risk with PPI/H2RA use.*
Appendix (B)

Definitions

Achlorhydria: A state where gastric acid production is absent. It is technically defined as the peak acid output in response to a maximally effective stimulus that results in an intragastric pH of greater than 5.09 in mean and greater than 6.81 in women. Achlorhydria can be caused by chronic gastric *H. pylori* infection, proton pump inhibitor therapy, and pernicious anemia and is sometimes found in type one diabetes.

Bone Mineral Density: A measure of the amount of minerals (mostly calcium and phosphorous) contained in a certain volume of bone. Bone mineral density measurements are used to diagnose osteoporosis (a condition marked by decreased bone mass), to see how well osteoporosis treatments are working, and to predict how likely the bones are to break, (http://www.cancer.gov/dictionary/?CdrID=415875 accessed January 11, 2010).

Calcium Carbonate: A calcium salt CaCO$_3$ that is found in limestone, chalk, marble, plant ashes, bones, and many shells, that is obtained also as a white precipitate by passing carbon dioxide into a suspension of calcium hydroxide in water, and that is used in dentrifices and in pharmaceuticals as an antacid and to supplement bodily calcium stores, (www.merrriam-webster.com accessed January 12, 2010).


Canaliculi: An adaptation of the gastric parietal cell to increase the surface area for gastric acid secretion. The adaptation causes a deep in-folding of the cell, otherwise known as a little channel.
**DXA Scan:** DXA is dual-energy x-ray absorptiometry. DXA evaluates bone mineral content of the spine, hip, wrist, femur or any other selected portion of the skeleton using X-rays to measure how many grams of calcium and other bone minerals are packed into a segment of bone. It does this by focusing the x-ray on a body site and measuring the proportion of light rays that pass through the tissue as opposed to being blocked by minerals in the bone. Using computer software, it then divides that number by the surface area of the bone being measured to create bone mineral density (BMD). The higher your bone mineral content, the denser your bones are. Furthermore, the denser the bones, the stronger they are and the less likely they are to break, (Mayo clinic.com and Marcelle Pick, OB/GYN NP on womentowomen.com accessed January 11, 2009).

**Dyspepsia:** Otherwise known as indigestion. Dyspepsia includes upper GI tract symptoms including abdominal pain, bloating without distention, early satiety, nausea, and belching. (www.medterms.com).

**Erosive Esophagitis:** Single or multiple erosions of the lining of the esophagus. Erosive esophagitis is the most common complication of gastroesophageal reflux disease and is usually diagnosed via endoscopy. (www.emedicine.medscape.com)

**Gastroesophageal Reflux Disease:** Chronic symptoms or mucosal damage produced when contents from the stomach “reflux” back into the esophagus. The problem usually lies in transient or permanent decreased tone of the lower esophageal sphincter; the smooth muscle ring that connects the esophagus to the stomach. GERD is also often attributed to hiatal hernias. (www.medterms.com)

**H⁺/K⁺ ATP-ase:** The proton/protein pump of the stomach and is the primary enzyme responsible for the acidification of stomach contents. The pump is found in the parietal cells,
which are highly specialized epithelial cells located in the inner cell lining of the stomach called the gastric mucosa, (www.wikipedia.com accessed January 12, 2010).

**Osteoporosis:** Low bone mass, micro-architectural disruption, and increased skeletal fragility. In addition, the World Health Organization (WHO) has defined osteoporosis based upon dual-energy x-ray absorptiometry (DXA) measurements (a value for BMD 2.5 or more standard deviations below the young adult female reference mean, T-score less than or equal to -2.5). The relative risk of fracture increases as BMD decreases, (UpToDate accessed January 11, 2010).

**Peptic Ulcer Disease:** A hole or holes in the lining of the esophagus, stomach, or duodenum. The ulcer occurs when the acidic digestive juices produced by the parietal cells of the stomach corrode one of the aforementioned organs. A major worldwide cause of PUD is the bacteria Helicobacter pylori; as well as non-steroidal anti-inflammatory drugs, and cigarette smoking. (www.medterms.com)

**Proton Pump Inhibitor:** any group of drugs that inhibit the activity of pumps transporting hydrogen ions across cell membranes. This class of drug is primarily used to inhibit gastric acid secretion. Current drugs in this class include Aciphex (rabeprazole), Nexium (esomeprazole), Prevacid (lansoprazole), Prilosec (omeprazole), and Protonix (pantoprazole). Omeprazole was the first drug in this class and most research conducted has used omeprazole as its drug of choice, (www.merriam-webster.com accessed January 12, 2010).

**Vacuolar ATP-ase:** The primary machinery of a multinucleated osteoclast that allows the cell to resorb bone. It is a proton/protein pump that excretes H⁺ ions into the potential space between the osteoclast’s plasma membrane and the bone surface. The acidic environment allows solubilization of calcium, therefore breaking down the bone matrix, (Georg Schett, 2007).
Objective

Safety concerns have arisen regarding the long-term use of proton pump inhibitors (PPIs). The objective was to critically analyze peer-reviewed journal articles that evaluated the hypothesis that high doses or increased duration of PPIs leads to an increase in osteoporosis-related fractures.

Methods

Articles were identified using MEDLINE and PubMed via MESH database and cross-matched to those articles evaluated in the FDA drug safety communication. Each article was systematically reviewed and discussed.

Results

Seven primary papers were identified that evaluated the effects of PPIs on fracture risk. Six of seven reported an increase in fracture risk for those patients taking varying doses of PPIs, for varying lengths of time.

Conclusion

Although there was a finding for increased risk of fracture with use of PPIs, the interred risk appears minimal. Judicious use of PPIs, prescribing the minimum effective dose for the shortest duration, will limit adverse effects; including increased fracture risk.