



Published in final edited form as:

*Am J Med.* 2011 June ; 124(6): 519–526. doi:10.1016/j.amjmed.2011.01.007.

## Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies

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### Abstract

**Background**—Concerns have been raised about the risk of fractures with acid-suppressive medications, such as proton pump inhibitors (PPIs) and histamine<sub>2</sub>-receptor antagonists (H2RAs).

**Methods**—In this meta-analysis, we evaluated the association between PPI or H2RA use and fractures. We performed a systematic search of published literature (1970 to October 10, 2010) in MEDLINE, EMBASE, and other sources. Ten publications reporting 11 studies were considered eligible for analysis.

**Results**—All studies were observational case-control or cohort studies and primarily evaluated older adults. The summary effect estimate for risk of hip fracture was modestly increased among individuals taking PPIs (RR 1.30, 95% CI 1.19–1.43). There was also an increase in spine (RR 1.56, 95% CI 1.31–1.85) and any-site fractures (RR 1.16, 95% CI 1.04–1.30) among PPI users. These findings were similar in both men and women and after stratification by duration of use. In contrast, H2RA use was not significantly associated with increased risk of hip fracture (RR 1.10, 95% CI 0.94–1.30).

**Conclusions**—In this meta-analysis of observational studies, PPIs modestly increased the risk of hip, spine, and any-site fractures, whereas H2RAs were not associated with fracture risk. The possibility of residual confounding cannot be excluded. Further skeletal evaluation should be considered for patients who are taking PPIs and are also at risk for osteoporotic fracture.

### Keywords

Proton pump inhibitor; fracture; osteoporosis; bone mineral density; H2-receptor antagonists; calcium absorption

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**Author attestations:** None of the authors report any conflicts of interest. All authors had access to the data and a role in writing the manuscript.

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## INTRODUCTION

Proton pump inhibitors (PPIs) are potent acid-suppressive medications commonly used for management of acid-related diseases such as gastroesophageal reflux disease (GERD). Since their first introduction in 1989, PPIs have become the third-highest prescription drug seller in the United States, garnering \$13.6 billion in 2009[1]. Histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) are an older class of acid suppressive medication that have a weaker acid suppressive effect than PPIs. Long-term therapy with these medications is increasingly common[2].

In recent years concerns have been raised about the long-term safety profile of acid-suppressive medications, including potential adverse effects such as increased risk of respiratory and enteric infections[3–5], nutritional deficiencies[6, 7] and bone fractures[8–12]. The Food and Drug Administration (FDA) recently published an advisory communicating the possible increased risk of fractures with the use of PPIs, and are recommending that no more than three 14-day treatment courses should be used in one year[13].

The FDA recommendations were based upon several epidemiologic studies that have suggested an association between PPI use and hip, wrist, and spine fractures[8–12, 14, 15]. However, not all studies demonstrate a significant association[14, 15], and no consensus exists about the true magnitude of this risk. In the time since the FDA released its advisory, further data has been published on this topic[16–20]. We quantitatively synthesized all the currently available data in a meta-analysis to estimate the overall effect of PPI use on fracture rates.

## METHODS

### Eligibility criteria

Methods of the analysis were pre-specified in a protocol. To be eligible, studies had to examine the risk of bone fracture attributable to the use of PPIs or H<sub>2</sub>RAs, and include a comparator control group. Medication use had to be documented prior to occurrence of fracture. Analyses had to be adjusted at minimum for age and gender.

### Search strategy

PubMed/MEDLINE (NCBI), EMBASE (Elsevier), Web of Science (ISI Web of Knowledge), and BIOSIS Previews (ISI Web of Knowledge) were searched from 1970 through October 10, 2010 using terms for fractures and for PPIs or H<sub>2</sub>RAs. The search strategy (see Supplemental Table 1) was carried out by a librarian (PB). No language limits or methodology filters were applied. Programs from the annual meetings of the Endocrine Society (1996–2009) and the American Association of Clinical Endocrinologists (2002–2010) were hand-searched. Programs from the annual meetings of the American Society for Bone and Mineral Research, the American Gastroenterological Association, and the American College of Gastroenterology were included in the material searched through BIOSIS Previews. Reference lists of reviews identified in the search were scanned for candidate studies.

### Data Collection

Eligibility assessment was performed independently by two investigators (EY and DB). Discrepancies were resolved by discussion between the two reviewers; if no agreement could be reached, a third author would decide. Quality assessments were based upon adjustment for confounding. When effect estimates were reported for more than one set of

adjustments, we selected the most adjusted estimate. We contacted 8 authors, all of whom provided additional unpublished data for fracture risk by sites and sub-analyses restricted by duration of medication use.

### Definition of exposure

The majority of studies defined PPI or H2RA exposure as current or recent medication use assessed by prospective questioning of subjects[10, 14, 16, 21] or review of prescription databases[9, 11, 18]. Three studies defined exposure based on cumulative medication use from prescription databases, regardless of exposure timing[8, 12, 20]. Multiple studies examined dose- and duration-effects[8, 9, 11, 12, 14, 18, 20], but incompatible definitions precluded overall pooling of dose-effects.

### Definition of outcomes

The pre-defined primary endpoint was hip fracture, which was assessed either prospectively by self-report and confirmed radiologically[10, 14, 16, 21] or by retrospective review of administrative databases[8, 9, 11, 12, 18, 20]. Secondary endpoints included any-site fractures and spine fractures. For this meta-analysis, the following definitions of any-site fractures were combined: any clinical fracture[9], clinical osteoporotic fractures[11, 14, 19], or clinical non-spine fractures[10]. Clinical spine fractures[9, 14] and morphometric spine fractures[16] were also analyzed together for this meta-analysis.

### Statistical Analysis

Relative risks (RRs) and odds ratios (ORs) were log-transformed and used interchangeably as measures of association since fracture is a rare event and most case-control studies used an open-cohort sampling design. Effect estimates were pooled via DerSimonian and Laird random-effects models[22]. Stratified analyses were conducted to determine whether differences in gender, fracture site, study design, or duration of medication use identified important subgroups or explained heterogeneity across studies[23]. The  $I^2$  statistic was used to determine the percentage of total variability due to heterogeneity rather than chance[24]. We used Begg's and Egger's tests to assess potential publication bias and evaluated the symmetry of individual study estimates around the pooled estimate using Begg funnel plots[25]. All analyses were conducted using STATA 13 (StataCorp, College Station, Texas);  $P < 0.05$  was considered statistically significant.

## RESULTS

### Study selection

The systematic search of MEDLINE, EMBASE, and other sources provided a total of 642 citations, after adjusting for duplicates. Of these, 573 were excluded after initial abstract screening. The full texts of the remaining 69 articles were examined in more detail. Twelve publications met inclusion criteria[8–12, 14–18, 20, 21], however, three of these analyzed the same database (General Practice Research Database, GPRD)[8, 15, 17]; only one was included in the meta-analysis in order to prevent data replication. The included GPRD publication[8] was the first to be published and also had the most inclusive eligibility criteria. Of the two GPRD publications excluded, one examined a subset population that did not have major osteoporotic risk factors[15], and the other used a different comparator group than all other identified studies[17]. These excluded studies were considered in sensitivity analyses. Among the included publications, one publication reported results from 2 separate studies[10] (the Study of Osteoporotic Fractures, Yu 2008a; and the Osteoporotic Fractures in Men, Yu 2008b) which were analyzed separately in the meta-analysis. Thus a total of 10 publications involving 11 studies were included in the meta-analysis (Figure 1). Lastly, one

relevant but as yet unpublished study was identified and included in the sensitivity analysis using data reported in abstract only[19].

### Study characteristics

The primary characteristics of the included studies are shown in Table 1. Seven studies were case-control studies utilizing administrative databases[8, 9, 11, 12, 18, 20, 21] and 4 were prospective longitudinal cohorts[10, 14, 16]; no randomized controlled trials were identified. Although a few studies allowed inclusion of younger subjects, the populations studied were predominantly postmenopausal women and older men. All studies controlled for age and gender; each study also adjusted for multiple other potential confounding factors, including medications and comorbidities, but the precise extent of statistical adjustment varied by study.

The primary PPI and hip fracture analyses included 10 studies with a total of 1,084,560 subjects, 62,210 PPI users, and 71,339 hip fractures[8–12, 14, 16, 18, 20]. Eight studies examined the association of H2RA use and hip fractures, encompassing 1,018,544 subjects, 58,334 H2RA users, and 66,997 hip fractures[8–10, 12, 14, 18, 21]. For PPIs, other outcomes included 161,179 any-site fractures[9–11, 14] and 5,728 spine fractures[9, 14, 16]. An unpublished study reporting 13,873 any-site fractures was included in a sensitivity analysis[19]. For association with H2RAs, 147,801 any-site fractures[9, 10, 14] and 5,679 spine fractures were evaluated[9, 14]. Seven studies analyzed fracture rates in the context of PPI or H2RA dose and duration of use[8, 9, 11, 12, 14, 18, 20], but definitions of dose-response and duration use varied significantly.

### PPIs and fracture

The risk of hip fracture was modestly increased among individuals taking PPIs (RR 1.30, 95% CI 1.19–1.43; Figure 2). There was also an increase in spine (RR 1.56, 95% CI 1.31–1.85) and any-site fractures (RR 1.16, 95% CI 1.02–1.32) among PPI users. Evidence of heterogeneity was present among the hip fracture studies ( $I^2$  58%) and any-site fracture studies ( $I^2$  67%), but there was no evidence of heterogeneity among the findings of the spine fractures ( $I^2$  6%). There was no evidence of publication bias (Begg's test  $p=0.22$ ).

Results from stratification and sensitivity analyses are shown in Table 2. Risk of hip fracture was similar when stratified by gender. Substitution of the two excluded GPRD studies[15, 17] did not significantly change the results for any of the reported fracture sites. After limiting the meta-analysis to studies with patient-level data adjustments, we found a diminished link between PPI use and hip fracture that was no longer statistically significant. Lastly, inclusion of unpublished data[19] weakened the association between PPI use and any-site fracture (RR 1.10, 95% CI 0.95–1.28).

### H2RAs and fracture

H2RA use was not significantly associated with increased risk of hip fracture (RR 1.10, 95% CI 0.94–1.30, Figure 3). Sensitivity analyses with substitution of the GPRD studies did not significantly change the results relating H2RA to hip fracture (RR 1.12, 95% CI 0.98–1.27). There was significant heterogeneity present (hip  $I^2$  78%). Sensitivity analyses removing the results of Vestergaard et al. removed heterogeneity ( $I^2=0\%$ ) but revealed that H2RA was associated with hip fracture risk (RR 1.20, 95% CI 1.13–1.27). H2RA use was not associated with an increased risk of any-site fracture (RR 0.99, 95% CI 0.86–1.15). Only two studies reported spine fracture outcomes, and neither study found a relationship with H2RAs. There was no evidence of publication bias (Begg's test  $p=0.81$ ).

### Effect of duration and dose

The increase in hip fracture risk persisted after stratification by short-term (< 1 year) and long-term ( $\geq$  1 year) PPI use (Table 2). Several studies also analyzed further stratification beyond 1 year of duration, but these effects could not be quantitatively pooled due to the use of inconsistent strata across studies. Yang et. al. (n=148,942) found increasing risk of fracture with increasing duration of PPI use over several years[8]. Targownik et. al. (n=63,081) similarly noted a duration effect, although the authors did not find a statistically significant increased risk of fracture until 5 or more years of PPI exposure[11]. In contrast, several other studies (pooled n=359,133) did not find a consistent trend in fracture risk with prolonged duration of PPI or H2RA use[12, 14, 18].

Dose effects were unable to be quantitatively pooled due to incompatible definitions of dose and medication exposure across studies. Four studies (pooled n=348,751) reported increased fracture rates with higher doses of PPI or H2RA[8, 12, 18, 20], whereas Vestergaard et. al. (n=498,942) did not find evidence of a significant dose-response relationship[9]. Two studies (n=662,840) determined that fracture risk diminishes after discontinuation of PPI for more than one or two years[9, 12]. On the other hand, one smaller study (n=2,482) found evidence of persistently increased risk of fracture despite discontinuation of PPI[20].

## DISCUSSION

In this study level meta-analysis, PPI use was associated with a modestly increased risk of hip fractures. Spine fractures were also more frequent among individuals taking PPIs, and there was a slight increase in risk of any-site fractures as well. These findings were similar in both men and women. Furthermore, pooling revealed that short-term use (<1 year) and longer use (>1 year) were similarly associated with increased fracture risk. Parallel examination of H2RA use did not find any statistically significant association with fracture.

While the negative effect of PPI use may be modest on an individual level, the public health implications of an increase in fracture risk are potentially large. Based on our estimates, 4.7% of hip fractures might be attributable to PPI use. PPIs are highly effective medications for many gastrointestinal disorders, but overuse is common and they are frequently given for inappropriate indications or indefinite duration[26–28]. They also can be purchased over-the-counter, and therefore are available for general use without the supervision of a physician. PPI use is even more common among the population most at risk for fracture: older adults, and those who have been prescribed bisphosphonates. In one study, nearly one-third of individuals taking bisphosphonates were prescribed concomitant PPIs[17]. Furthermore, use of bisphosphonates did not mitigate the increased fracture risk associated with PPI use. Two other studies have suggested that the association of PPI use and fracture is only evident among adults who have major osteoporotic risk factors[12, 15].

The potential mechanisms behind this increased risk are not yet clear. In this meta-analysis, we observed an increased risk of fracture that was present even with PPI use of <1 year. This suggests there may be a mechanism that has direct effects upon bone mineralization or bone quality and is not necessarily mediated by bone density changes. In vitro studies suggest that PPIs may have a direct effect on bone via inhibition of the osteoclastic H<sup>+</sup>-ATP-ase pump[29], but this would lead to inhibition of bone resorption. Clinical trials have reported conflicting results on the effect acid suppression and biochemical measurements of bone resorption in humans[30–32]. Furthermore, discordant effects on bone mineral density have been reported[10, 14, 33, 34].

Alternatively, PPI therapy induces hypochlorhydria, and achlorhydric patients have poor absorption of calcium carbonate[35]. Animal models suggest that omeprazole inhibits

calcium absorption[36], but trials of short-term omeprazole use in healthy volunteers have found conflicting effects on fractional calcium absorption[32, 37, 38]. Furthermore, it is not clear whether these results are generalizable for long-term PPI therapy or for an older population with a higher baseline incidence of hypochlorhydria. In one epidemiologic study, fracture risk among men using PPIs was modified by calcium intake, suggesting that high calcium intake may mitigate the adverse skeletal effects of PPI use[10].

There are other possible mechanisms by which PPIs might increase fracture risk. Prolonged PPI use can lead to vitamin B12 deficiency[39, 40], which might increase risk of falls by causing peripheral neuropathy. B12 deficiency has also been linked to high homocysteine levels, which may disrupt collagen cross-linking and is associated with increased fracture risk[41, 42]. PPI use might also lead to hypomagnesemia[43], which may independently predispose to fractures[44]. Additional studies of acid suppression and skeletal outcomes, particularly randomized trials, are needed to test these hypotheses.

### Study strengths and limitations

One of the major strengths of this study is our inclusion of previously unpublished data from 8 authors to perform additional analyses of fracture site, dose and duration. Other strengths include following a pre-specified meta-analysis protocol, examination of the differing effects of PPI and H2RA use, careful consideration of study inclusion criteria, and use of sensitivity analyses for secondary data that did not qualify for the main meta-analysis. However, this study also has several limitations. As with any pharmacoepidemiologic study, one concern is for confounding by indication. However, H2RAs and PPIs are often prescribed for similar diseases, and no association was observed between H2RAs and fractures. In addition, secondary analysis performed by Yang et al. that was restricted to patients with chronic gastroesophageal reflux revealed similar increased risk of fracture with PPIs[8]. Residual confounding from unmeasured covariates remains a possibility, but only data from multivariate adjusted models were included in the meta-analysis. In sensitivity analysis, fracture risk was abrogated by restriction of the data to those studies that were able to adjust for additional patient-level characteristics (e.g. BMI, smoking); however this excluded the largest studies and may have resulted in loss of statistical power to detect this modest association. Heterogeneity was present between the studies for hip fracture and any-site fracture outcomes, perhaps due to varying definitions of PPI or H2RA exposure and different methods of classifying fractures. We received clarifications and additional primary data from study authors to better explore these effects. We also found that overall point estimates for PPI and fracture did not change appreciably after stratification and with sensitivity analyses. For H2RA, sensitivity analyses excluding the large study by Vestergaard et. al.[9] unexpectedly revealed an association with fracture. There was no obvious design difference between this study and the others and therefore the interpretation of these results is difficult. Lastly, we were unable to pool the dose response effects of PPI exposure due to incompatible definitions across studies; instead we provided a qualitative synthesis of these effects.

### Conclusions

This meta-analysis of observational studies found that PPI use modestly increased the risk of hip, spine, and any-site fractures, whereas H2RA use was not associated with increased fracture risk. The biologic mechanism is not yet clear, and we cannot rule out the possibility of residual confounding. But even a slight increase in fracture risk due to PPIs may lead to a large number of additional fractures on a public health scale. The FDA is now requiring more rigorous post-marketing data for PPIs[45]. Until such data are available, we suggest that physicians counsel their patients to avoid overuse of PPIs and/or consider further

skeletal evaluation for patients who are taking PPIs and are also at risk for osteoporotic fracture.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We thank Drs. Yu-Xiao Yang, Douglas Corley, Shelley Gray, Laure Gossec, Frank de Vries, Peter Vestergaard, and Ms. Terri Blackwell for providing additional data for this meta-analysis.

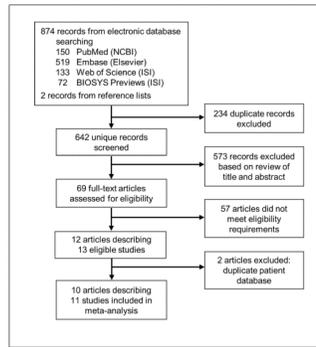
**Funding sources:** Dr. Bauer is supported by NIH grant K24 ARO51895.

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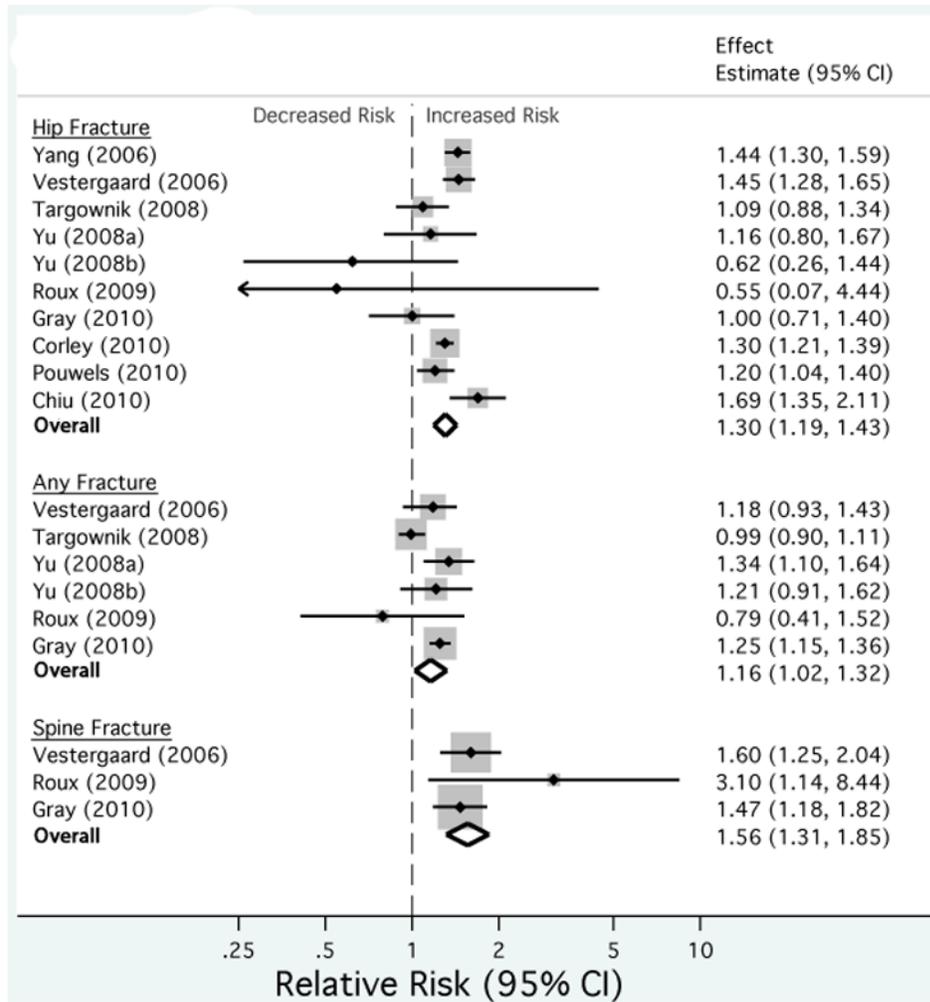
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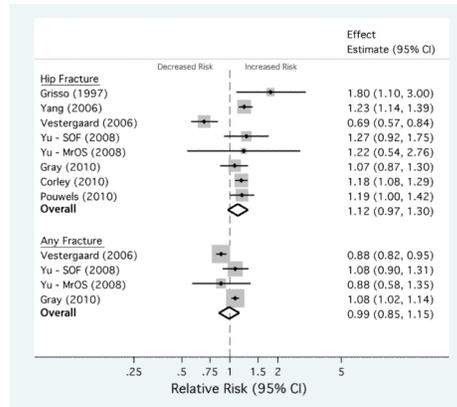
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**Figure 1.**  
Flowchart of the literature search



**Figure 2.** Association of PPI use and risk of fractures  
 Analyses of the association between PPI use and risk of hip fractures, any fractures, and nonspine fractures. CI indicates confidence interval.



**Figure 3.** Association of H2RA use and risk of fractures  
Analyses of the association between H2RA use and risk of hip fractures and any fractures. CI indicates confidence interval.

Table 1

Study Characteristics

Study	Study Design	Study Population (# of subjects)	Mean age (years)	Definition of PPI or H2RA use	Fracture Site (# of subjects)	OR/RR for PPI (95% CI)	OR/RR for H2RA (95% CI)	Adjustments
Grisso, 1997 <sup>21</sup>	Case control	U.S. men age >45 (758)	87% older than 65	ever use (cimetidine)	hip (356)	not studied	1.8 (1.1–3.0)	Matched for age, geography; adjusted for BMI, comorbidities, medications, physical activity, smoking, and alcohol
Yang, 2006 <sup>8</sup>	Case control	U.K. adults age>50, 80% women (148942)	77	Rx database, cumulative use >1 year	hip (13556)	1.44 (1.30–1.59)	1.23 (1.14–1.39)	Matched for age, gender, calendar period, duration of follow-up; adjusted for BMI, medication use, comorbidities, smoking, alcohol, and prior fractures
Vestergaard, 2006 <sup>9</sup>	Case control	Danish adults, 52% women (498617)	43	Rx database, any use in past 1 year	hip (10530) any (124655) spine (3364)	1.45 (1.28–1.65) 1.18 (1.12–1.43) 1.60 (1.25–2.04)	0.69 (0.57–0.84) 0.88 (0.82–0.95) 1.00 (0.71–1.41)	Matched for age, gender; adjusted for alcoholism, employment status, Charlson index (comorbidities), medications, days hospitalized, number of contacts with doctor, marital status, prior fracture, education, and income
Yu, 2008a <sup>10</sup>	Cohort	postmenopausal U.S. women age >65 (5339)	80	current use	hip (451) nonspine (1410)	1.16 (0.80–1.67) 1.34 (1.1–1.64)	1.27 (0.92–1.75) 1.08 (0.90–1.31)	Adjusted for age, clinic, race, BMI, alcohol, physical activity, medications, calcium supplements, self-reported health, weight, and caffeine use
Yu, 2008b <sup>10</sup>	Cohort	U.S. men age >65 (5755)	74	current use	hip (89) nonspine (489)	0.62 (0.26–1.44) 1.21 (0.91–1.62)	1.22 (0.54–2.76) 0.88 (0.58–1.35)	Adjusted for age, clinic, race, BMI, alcohol, exercise, medications, calcium supplements, self-reported health, and history of stomach surgery
Targownik, 2008 <sup>11</sup>	Case control	Canadian adults age>50, 70% women (63081)	60% older than 70	Rx database, recent use and duration >1 year	hip (3448) any (13378)	1.09 (0.88–1.34) 0.99 (0.90–1.11)	not studied not studied	Matched for age, gender, number of comorbidities, ethnicity; adjusted for income, region, comorbidities, and medications

Study	Study Design	Study Population (# of subjects)	Mean age (years)	Definition of PPI or H2RA use	Fracture Site (# of subjects)	OR/RR for PPI (95% CI)	OR/RR for H2RA (95% CI)	Adjustments
Roux, 2009 <sup>16</sup>	Cohort	postmenopausal European women age 55–79, (1211)	66	any use of omeprazole in past 1 year	hip (9) spine (49)	0.057 (0.07–4.44) 3.10 (1.14–8.44)	not studied not studied	Adjusted for age, BMI, history of fracture, medications, calcium/vitamin D supplements, smoking, alcohol, falls, self-reported health, and bone density
Gray, 2010 <sup>14</sup>	Cohort	postmenopausal U.S. women age 50–79 (161806)	63	current use	hip (1500) any (21247) spine (2315)	1.00 (0.71–1.40) 1.25 (1.15–1.36) 1.47 (1.18–1.82)	1.07 (0.87–1.30) 1.08 (1.02–1.14) 1.02 (0.87–1.02)	Adjusted for age, race/ethnicity, BMI, study cohort, smoking, physical activity, self-reported health, parental history of fracture, previous fracture, osteoporosis, calcium/vitamin D supplements, medications, and comorbidities
Corley, 2010 <sup>12</sup>	Case control	Kaiser adults age>18, 65% women (164223)	80% older than 50	Rx database, cumulative use >2 years	hip (33752)	1.30 (1.21–1.39)	1.18 (1.08–1.29)	Matched for age, gender, duration of membership, first year of membership, race/ethnicity; adjusted for smoking, comorbidities and medications not included in final model because did not meet criteria for significantly affecting the model
Pouwels, 2010 <sup>18</sup>	Case control	Dutch adults, 73% women (33104)	75	Rx database, current use in past 30 days	hip (6763)	1.20 (1.04–1.40)	1.19 (1.00–1.42)	Matched for age, gender, region; adjusted for comorbidities and medications
Chiu, 2010 <sup>20</sup>	Case control	Taiwanese adults age>50, 58% women (2482)	75	Rx database, any use since 1996	hip (1241)	1.69 (1.35–2.11)	not studied	Matched for age, gender, index date; adjusted for medications; comorbidities not included in final model because of high colinearity with medications

Rx = prescription

BMI = body mass index

**Table 2**  
Stratified Analyses and Sensitivity Analyses for the Associations between PPI use and Risk of Hip Fracture

	No. of participants	Relative Risk (95%CI)
<b>STRATIFIED ANALYSES</b>		
Total population	1,084,560	1.30 (1.19–1.43)
Women	417,209	1.25 (1.15–1.36)
Men	101,960	1.45 (1.16–1.82)
Duration of PPI use		
< 1 year	890,469	1.39 (1.10–1.74)
> 1 year	976,001	1.24 (1.19–1.29)
<b>SENSITIVITY ANALYSES</b>		
Limited to studies with patient-level data adjustments	323,053	1.15 (0.88–1.50)
Substituting GPRD studies		
Excluding Yang <sup>8</sup> , including Kaye <sup>15</sup>	947,639	1.21 (1.08–1.36)
Excluding Yang <sup>8</sup> , including de Vries <sup>17</sup>	1,169,762	1.27 (1.16–1.38)