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Proton Pump Inhibitor Use, H_2-Receptor Antagonist Use and Risk of Incident Clinical Vertebral Fracture in Women

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Abstract

Background—The few prospective studies examining the relation between proton pump inhibitor (PPI) use and risk of vertebral fracture (VF) suggest a higher risk, but the magnitude of the association has been inconsistent. Moreover, no prospective studies have examined the association between substantially longer duration of PPI use and VF risk. Our objective was to determine the association between PPI use, H_2RA use, and incident clinical VF in women.

Methods—We conducted a prospective study in 55,545 women participating in the Nurses' Health Study. PPI and H_2RA use was assessed by questionnaire every four years. Self-reports of VF were confirmed by medical record.

Results—Our analysis included 547 incident VF cases (2002-2014). The multivariate adjusted relative risk (MVRR) of VF for women taking PPIs was 1.29 (95%CI 1.04-1.59) compared with non-users. Longer duration of PPI use was associated with higher VF risk (MVRR 1.16 [0.90-1.49] for <4 years; 1.27 [0.93-1.73] for 4-7.9 years; 1.64 [1.02-2.64] for ≥ 8 years; p_{trend}=0.01). The MVRR of VF for women taking H_2RAs was 1.22 (0.90-1.67) compared with

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non-users. Longer duration of H_2RA use was not associated with VF risk (MVRR 1.16 [0.88-1.53] for <4 years; 0.98 [0.60-1.59] for ≥ 4 years; p_{trend}=0.72).

Conclusions—PPI use is independently associated with a modestly higher risk of VF and the risk increases with longer duration of use. There was no statistically significant association between H_2RA use and VF risk. Our findings add to the growing evidence suggesting caution with PPI use, particularly with longer duration of use.

Keywords

Proton Pump Inhibitor; H_2-Receptor Antagonist; Vertebral Fracture; Nurses' Health Study; Prospective Study

Introduction

Proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H_2RA), treatments for acid-related upper gastrointestinal disorders, are among the most commonly used medications in the United States. PPIs have been available over-the-counter since 2003 [1], with numerous over-the-counter options now available in addition to prescription options. The prevalence of PPI use increased from 15.7% in 2005 to 18.5% in 2011[2].

Vertebral fracture (VF) is the most common type of osteoporotic fracture [3] and is associated with significant disability [4], morbidity [5] and mortality [6]. Twenty-five percent of postmenopausal women in the United States are estimated to have a vertebral fracture [7] and the prevalence increases with advancing age [8]. In recent years, the incidence of vertebral fracture has risen dramatically in men and women, especially after age 75 years [9]. Risk factors for vertebral fracture may differ from those for fractures at other sites due to different microarchitecture [10-12], biomechanics [13], and compressive loading [14, 15].

Prior studies suggest an increased risk of osteoporotic fracture with PPI use [16-25], but the findings have not been consistent [26, 27]. The few prospective studies to date examining the relation between PPI use and risk of VF also suggest an increased risk [27-29], but the magnitude of the association has been inconsistent. There have been very limited studies on duration of PPI use and risk of VF [22, 27]. There are also limited data on the association between H_2RA use and risk of VF [22, 27]. The one prospective study of the association between H_2RA use and VF risk suggested no association [27].

Potential etiologies for increased fracture risk from the use of these acid-suppressing agents include decreased calcium absorption [30, 31], upregulation of osteoclast activity [32], impaired bone resorption [33, 34] resulting in altered bone remodeling, or hypergastrinemia resulting in parathyroid hyperplasia and decreased bone mineral density [35]. H_2RAs could potentially act through similar mechanisms but are less potent acid-suppressants than PPIs.

Therefore, we studied the prospective association between PPI use, H_2RA use, and risk of incident clinical vertebral fracture in 55,545 women over a 12-year period in the Nurses' Health Study.

Methods

Study Population

The Nurses' Health Study (NHS) is an ongoing, prospective cohort study which began in 1976, enrolling 121,700 female registered nurses 30-55 years of age. The cohort is followed with biennial mailed questionnaires that ask about lifestyle practices, medications and newly diagnosed diseases. The follow-up rate has been >90% of the eligible person-time. Approximately 98% of the cohort is white.

This analysis included 55,545 women who answered the 2012 or 2014 questionnaire, which included questions on history of vertebral fracture, and who also answered the 2002 questionnaire, which first included questions on PPI and H_2RA use, and serves as the baseline year for this analysis. Participants were excluded if they had a prior history of hip or wrist fracture, or history of cancer (other than non-melanoma skin cancer). Updated information on PPI and H_2RA use was obtained every four years during the follow-up period. The study protocol was approved by the Brigham and Women's Hospital Institutional Review Board.

Assessment of Proton Pump Inhibitor and H_2-Receptor Antagonist Use

On the 2002 questionnaire, nurses were asked whether they regularly took “Prilosec or Prevacid” (the only two PPIs available at that time) or an “H_2 blocker (e.g. Zantac, Pepcid, Tagamet)” in the past two years. On the 2006 and 2010 questionnaires, nurses were asked whether they regularly took “Prilosec, Nexium, Prevacid (lansoprazole), Protonix, Aciphex” or an “H_2 blocker (e.g. Pepcid, Tagamet, Zantac, Axid)” in the past two years. The questions did not ask about dose or frequency of PPI or H_2RA use.

Assessment of Covariates

Potential confounders included age, body mass index (BMI) (<22 kg/m^2, 22-24.9 kg/m^2, 25-29.9 kg/m^2, and ≥30 kg/m^2), race (white or non-white), smoking status (never, past, current), physical activity (quintiles of metabolic equivalent task scores), self-reported history of falls, history of hypertension, diabetes, osteoporosis, postmenopausal hormone use, diuretic use, bisphosphonate use, and physical examination during the previous two years, ascertained from the questionnaires. Self-reported weight was highly reliable (r=0.97) among a subset of participants who underwent direct measurement of their weight [36]. Physical activity reported on the questionnaires has been previously validated in a similar cohort when compared with physical activity diaries (r=0.79) [37]. History of hypertension [38] and diabetes [39] were previously validated in this cohort. Race was self-reported and categorized in this analysis as white and non-white.

Diet was assessed by extensively validated [40, 41] semi-quantitative food-frequency questionnaires that inquired about the average intake of over 130 individual food items and 22 individual beverages, as well as vitamins and supplements during the previous year. The participants were asked to complete food frequency questionnaires in 2002, 2006, and 2010. The variables considered in our models were alcohol intake (none, 0.1-4.9 g/day, 5-14.9 g/day, ≥ 15 g/day), supplemental calcium intake (none, 1-500 mg/day, >500 mg/day),

supplemental vitamin D intake (none, 1-400 IU/day, >400 IU/day), and quintiles of dietary intakes of calcium, vitamin D, vitamin A, protein, phosphorus, magnesium and caffeine.

Ascertainment of Clinical Vertebral Fracture

Participants were asked about lifetime history of a clinician-diagnosed "vertebral (spine) fracture, x-ray confirmed" on the 2012 questionnaire and the year of first diagnosis. They were asked again about a diagnosis of vertebral fracture on the 2014 questionnaire. We mailed a supplemental questionnaire to nurses who reported a vertebral fracture in 2002 or afterwards and asked permission to obtain their medical records related to the vertebral fracture. Among the participants who gave consent to obtain their medical records and for whom we were able to obtain medical records that contained sufficient information to make a diagnosis, we confirmed cases of vertebral fracture by radiology report (e.g. x-ray, computed tomography scan, magnetic resonance imaging, bone scan, vertebral fracture assessment) or medical report (e.g. clinic visit note, operative note, hospital discharge summary) that referred to radiographic imaging confirming the diagnosis of vertebral fracture.

A self-reported vertebral fracture was confirmed as a case if the radiology or medical report contained the word "fracture" (e.g., "vertebral fracture", "spine fracture", "compression fracture", "wedge fracture") or language to suggest a vertebral fracture (e.g., "severe wedge compression", "vertebral collapse", "acute compression"). Medical records that contained less definitive language for a vertebral fracture were adjudicated by one of the authors (HNR), blinded to exposure status, who is an International Society for Clinical Densitometry-trained expert on the reading and interpretation of vertebral fractures. We coded participants as "probable" cases when a diagnosis of vertebral fracture was less certain (e.g. "mild compression deformity", "stable" or "chronic" "compression deformity"); "probable" cases were not included in our analysis.

We included vertebral fractures that were related to low or moderate trauma (e.g. tripping, slipping, falling from the height of a chair or lower). We excluded vertebral fractures due to high trauma (e.g., fall from a ladder, fall down a flight of stairs), motor vehicle accidents, bicycle accidents, or horseback riding accidents. We also excluded cases of cervical or sacral vertebral fracture. We included in the analysis only cases of vertebral fracture that were confirmed by medical record review and diagnosed during the 12 years of follow-up between 2002 and May 31, 2014.

Statistical Analyses

The study design was prospective; information on PPI use, H_2RA use and the covariates of interest were collected before the diagnosis of clinical vertebral fracture. For each participant, person-time of follow-up was counted from the date the 2002 questionnaire was returned to: 1) the date the vertebral fracture was diagnosed, 2) death, or 3) May 31, 2014, whichever occurred first. Participants were censored if they developed a hip fracture or any cancer (other than non-melanoma skin cancer) during the follow-up period. Information on PPI use, H_2RA use and other covariates was collected from the baseline questionnaire and updated on subsequent questionnaires. We allocated person-time of follow-up according to

the updated exposure status at the start of each follow-up period. Period-specific categories of PPI use, H_2RA use and other covariates were used in the analysis. We used Cox proportional-hazards models to simultaneously adjust for potential confounders as listed above. All P values are two-tailed.

Results

Proton Pump Inhibitor Use and Vertebral Fracture Risk

During 606,848 person-years of follow-up over a 12-year period, there were 547 confirmed cases of incident vertebral fracture. The characteristics of the cohort according to PPI use in 2002 are shown in Table 1. For our analyses, however, the updated information on PPI use and covariates was used for each time period.

In 2002, 6.2% of the participants were taking PPIs and the percentage increased over time (16.8% in 2006 and 19.1% in 2010). Compared with women not taking a PPI, women who were taking a PPI had higher BMI, were less physically active, and were more likely to have diabetes, hypertension, or osteoporosis. The PPI users had slightly higher calcium supplement intake and lower alcohol intake. In 2002, 99.3% of the women were postmenopausal and PPI users had higher postmenopausal hormone use compared with non-users.

After adjusting for age, PPI use was associated with an increased risk of clinical vertebral fracture (RR 1.44, 95%CI 1.17 to 1.77) (Table 2). After multivariable adjustment, the relative risk of clinical vertebral fracture was 1.36 (95%CI 1.11 to1.68) for PPI users compared with non-users. After further adjustment for history of osteoporosis, the relative risk of clinical vertebral fracture was 1.29 (95%CI 1.04 to 1.59).

H_2-Receptor Antagonist Use and Vertebral Fracture Risk

The characteristics of the cohort according to H_2RA use in 2002 are shown in Table 1. For our analyses, however, the updated responses to H_2RA use as well as covariate information were included for each time period. In 2002, 6.2% of the participants were taking an H_2RA and the percentage remained stable over time (6.1% in 2006 and 6.1% in 2010). Compared with women not taking an H_2RA, women taking an H_2RA had higher BMI, were less physically active, and were more likely to have a history of diabetes or hypertension, and slightly more likely to have a history of osteoporosis. The participants using a H_2RA had slightly lower alcohol intake and were more likely to be on postmenopausal hormone therapy compared with participants not using a H_2RA.

After adjusting for age, H_2RA use was not associated with a statistically significant risk of clinical vertebral fracture (RR 1.34, 95%CI 0.98 to 1.82) (Table 2). After multivariable adjustment, the relative risk was attenuated and not statistically significant (RR 1.26, 95%CI 0.92 to 1.72). After further adjustment for history of osteoporosis, the relative risk of vertebral fracture was further attenuated (RR 1.22, 95%CI 0.90 to 1.67).

Duration of PPI Use, H_2-Receptor Antagonist Use, and Risk of Vertebral Fracture

We examined the association between duration of PPI or H_2RA use and risk of clinical vertebral fracture over the study period. We categorized duration of PPI use into none, <4 years, 4-7.9 years, and ≥ 8 years. Longer duration of PPI use was associated with higher risk of vertebral fracture (Table 3). After multivariable adjustment, compared with participants not taking PPIs, the relative risk of vertebral fracture was 1.22 (95%CI 0.95 to 1.56) for participants with <4 years of PPI use, 1.35 (95%CI 0.99 to 1.85) for participants with 4-7.9 years of PPI use, and 1.75 (95%CI 1.09 to 2.81) for participants with ≥ 8 years of use (p for trend=0.003). After further adjustment for history of osteoporosis, the relative risk of vertebral fracture was slightly attenuated (RR 1.16 [95%CI 0.90 to 1.49] for <4 years of PPI use, 1.27 [95%CI 0.93 to 1.73] for 4-7.9 years of PPI use, and 1.64 [95%CI 1.02 to 2.64] for ≥ 8 years of use; p for trend=0.01). Because there were very few cases with longer duration of H_2RA use, we categorized H_2RA use into none, <4 years and ≥ 4 years. The multivariable-adjusted relative risk of vertebral fracture was 1.19 (95%CI 0.91 to 1.58) for <4 years of H_2RA use and 0.99 (95%CI 0.61 to 1.61) for ≥ 4 years of use (p for trend=0.63). After further adjustment for history of osteoporosis, the relative risk of vertebral fracture remained non-significant (RR 1.16 [95%CI 0.88 to 1.53] for <4 years of H_2RA use and 0.98 [95%CI 0.60 to 1.59] for ≥ 4 years of H_2RA use; p for trend=0.72).

Additional Analyses

We performed a mediation analysis to quantify the proportion of the association between PPI use and risk of vertebral fracture explained by osteoporosis as an intermediate condition. Osteoporosis explained 17.3% (8.0% - 33.4%; p < 0.001) of the association between PPI use and vertebral fracture.

We examined whether the associations with vertebral fracture for PPI use and H_2RA use varied with age (above and below age 70 years), history of osteoporosis, and bisphosphonate use. There was no statistically significant interaction for PPI use with age (p for interaction > 0.88), history of osteoporosis (p for interaction > 0.26), or bisphosphonate use (p for interaction > 0.36). There was no statistically significant interaction for H_2RA use with age (p for interaction 0.59), history of osteoporosis (p for interaction > 0.63), or bisphosphonate use (p for interaction > 0.08).

Discussion

In this prospective study of over 55,000 women, we observed an independent higher risk of incident clinical vertebral fracture with PPI use. We also observed an independent higher risk of vertebral fracture with longer duration of PPI use. We did not observe a statistically significant association between H_2RA use and VF risk. Our study has several strengths that distinguish it from other reports, including the large number of incident clinical vertebral fracture events that were confirmed by medical record review, repeated assessment of PPI and H_2RA use over time, as well as information on duration of PPI and H_2RA use over a longer period of time than prior studies.

While the association between PPI use and hip fracture risk has been studied more extensively, including within the NHS cohort [18] which observed a positive association (RR 1.36; 95% CI 1.13-1.63), few prospective cohort studies have examined the association between PPI use and vertebral fracture and reported findings were inconsistent [27-29]. Some of these differences could be related to different methods of ascertaining the outcome of vertebral fracture, including self-report,[27] follow-up x-ray [28], and claims data [29] as well as varying sample sizes. We confirmed cases of vertebral fracture through medical record review. Our findings are consistent with the other prospective studies that reported an increased risk of vertebral fracture with PPI use, although our magnitude of risk is lower compared with the other studies, which ranged from 1.47 to 3.50.

Emerging research has raised concerns over long-term use of PPIs due to adverse outcomes [42]. The only prospective study to date examining the association between duration of PPI use and VF risk, the Women's Health Initiative [27], looked at duration of 3 or more years (duration of PPI use was categorized into none, <1 year, 1-3 years, and > 3 years), whereas our study examined substantially longer duration of PPI use. While the Women's Health Initiative reported an increased risk of vertebral fracture with longer duration of PPI use, this risk was attenuated with longer duration of use (<1 year: 1.67, 95%CI 1.22-2.27; 1-3 years: 1.40, 95%CI 1.02-1.92; and > 3 years: 1.11, 95%CI 0.59-2.07). Given the wide confidence interval for the longest duration group (> 3 years), it is likely that there were few cases in that category, and the follow-up was too short to draw definitive conclusions about long-term use. Our results might differ from the WHI study because our shortest duration category (< 4 years) encompasses the duration examined by the WHI study. Our vertebral fracture cases were also confirmed by medical record review, whereas the WHI used self-reports.

While the mechanism for the association between longer duration of PPI use and vertebral fracture is not clearly understood, studies suggest that it is less likely to be completely mediated through changes in bone mineral density [19, 27, 43-45]. In our mediation analysis, osteoporosis accounted for less than 20% of the association between PPI use and vertebral fracture. For this reason, we created multivariate models with and without a history of osteoporosis. Inclusion of osteoporosis attenuated the association between PPI use and vertebral fracture, but the results remained statistically significant. Inclusion of osteoporosis in our multivariate model also attenuated the association between H_2RA use and vertebral fracture.

Our study did not find a statistically significant association between H_2RA use and clinical vertebral fracture. It is postulated that H_2RAs act through similar mechanisms as PPIs, but with less potency. Our findings are consistent with the WHI study [27], the only other prospective study to date on the association between H_2RA use and vertebral fracture, which reported no significant association between H_2RA use and vertebral fracture, as well as no significant association between duration of H_2RA use and vertebral fracture.

There are several limitations to our study that merit discussion. Given the observational design, there is the possibility of residual confounding. For example, although we did have information on self-reported osteoporosis, we did not have data on actual bone mineral density or morphometric fracture assessment. There is the possibility of confounding by

indication which could occur because of a history of osteoporosis or through bisphosphonate use prescribed for osteoporosis. However, additional analyses did not find confounding by indication. Our definition of clinical vertebral fracture required coming to medical attention, rather than being asymptomatic such as those that may be discovered incidentally by radiographic studies. Our definition of clinical vertebral fracture was based on medical record review, so for some participants who self-reported a vertebral fracture, we did not have permission or were not able to obtain their medical record, or there was insufficient evidence in the medical record to make a definitive diagnosis of vertebral fracture. We recognize that the observed incidence rate therefore is lower because of our method of case ascertainment. We were unable to assess adherence to PPI or H_2RA use. Finally, since our study population was female and almost entirely white, our findings are not necessarily generalizable to men or other races.

In this large prospective cohort study, PPI use was independently associated with a higher risk of clinical vertebral fracture in women and the risk increases with longer duration of PPI use. There was no statistically significant association between H_2RA use and vertebral fracture. Our findings add to the growing observational evidence suggesting caution with PPI use, particularly with longer duration of use. The risks and benefits of PPI use should be taken into consideration when starting or with continued use of PPIs in older women. Further research is warranted on PPI and H_2RA use and vertebral fracture risk, particularly with longer duration of use, since the use of these acid-suppressing agents is so common amongst older women who are at the highest risk for vertebral fracture.

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References

1. Menees SB, Guentner A, Chey SW, Saad R, Chey WD. 2015; How Do US Gastroenterologists Use Over-the-Counter and Prescription Medications in Patients With Gastroesophageal Reflux and Chronic Constipation? Am J Gastroenterol. 110:1516–1525. [PubMed: 26054623]
2. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. 2016; Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. JAMA Intern Med. 176:473–482. [PubMed: 26998708]
3. Riggs BL, Melton LJ 3rd. 1995; The worldwide problem of osteoporosis: insights afforded by epidemiology. Bone. 17:505S–511S. [PubMed: 8573428]
4. Nevitt MC, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, Segal M, Genant HK, Cummings SR. 1998; The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Annals of internal medicine. 128:793–800. [PubMed: 9599190]
5. Barrett-Connor E. 1995; The economic and human costs of osteoporotic fracture. The American journal of medicine. 98:3S–8S. [PubMed: 7709931]
6. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. 1999; Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Archives of internal medicine. 159:1215–1220. [PubMed: 10371229]
7. Melton LJ 3rd. 1997; Epidemiology of spinal osteoporosis. Spine (Phila Pa 1976). 22:2S–11S. [PubMed: 9431638]

8. Melton LJ 3rd, Kan SH, Frye MA, Wahner HW, O'Fallon WM, Riggs BL. 1989; Epidemiology of vertebral fractures in women. Am J Epidemiol. 129:1000–1011. [PubMed: 2784934]
9. Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ 3rd. 2014; Trends in fracture incidence: a population-based study over 20 years. J Bone Miner Res. 29:581–589. [PubMed: 23959594]
10. Stein EM, Liu XS, Nickolas TL, Cohen A, McMahon DJ, Zhou B, Zhang C, Kamanda-Kosseh M, Cosman F, Nieves J, Guo XE, Shane E. 2012; Microarchitectural abnormalities are more severe in postmenopausal women with vertebral compared to nonvertebral fractures. J Clin Endocrinol Metab. 97:E1918–1926. [PubMed: 22821893]
11. Genant HK, Delmas PD, Chen P, Jiang Y, Eriksen EF, Dalsky GP, Marcus R, San Martin J. 2007; Severity of vertebral fracture reflects deterioration of bone microarchitecture. Osteoporos Int. 18:69–76. [PubMed: 17028792]
12. Yeni YN, Zinno MJ, Yerramshetty JS, Zauel R, Fyhrie DP. 2011; Variability of trabecular microstructure is age-, gender-, race- and anatomic site-dependent and affects stiffness and stress distribution properties of human vertebral cancellous bone. Bone. 49:886–894. [PubMed: 21802536]
13. Christiansen BA, Bouxsein ML. 2010; Biomechanics of vertebral fractures and the vertebral fracture cascade. Curr Osteoporos Rep. 8:198–204. [PubMed: 20838942]
14. Myers ER, Wilson SE. 1997; Biomechanics of osteoporosis and vertebral fracture. Spine (Phila Pa 1976). 22:25S–31S. [PubMed: 9431641]
15. Duan Y, Seeman E, Turner CH. 2001; The biomechanical basis of vertebral body fragility in men and women. J Bone Miner Res. 16:2276–2283. [PubMed: 11760842]
16. Yu EW, Bauer SR, Bain PA, Bauer DC. 2011; Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. Am J Med. 124:519–526. [PubMed: 21605729]
17. Zhou B, Huang Y, Li H, Sun W, Liu J. 2016; Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int. 27:339–347. [PubMed: 26462494]
18. Khalili H, Huang ES, Jacobson BC, Camargo CA Jr, Feskanich D, Chan AT. 2012; Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. Bmj. 344:e372. [PubMed: 22294756]
19. Yu EW, Blackwell T, Ensrud KE, Hillier TA, Lane NE, Orwoll E, Bauer DC. 2008; Acid-suppressive medications and risk of bone loss and fracture in older adults. Calcif Tissue Int. 83:251–259. [PubMed: 18813868]
20. Fraser LA, Leslie WD, Targownik LE, Papaioannou A, Adachi JD. CaMos Research G. 2013; The effect of proton pump inhibitors on fracture risk: report from the Canadian Multicenter Osteoporosis Study. Osteoporos Int. 24:1161–1168. [PubMed: 22890365]
21. Yang YX, Lewis JD, Epstein S, Metz DC. 2006; Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 296:2947–2953. [PubMed: 17190895]
22. Vestergaard P, Rejnmark L, Mosekilde L. 2006; Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. Calcif Tissue Int. 79:76–83. [PubMed: 16927047]
23. Kwok CS, Yeong JK, Loke YK. 2011; Meta-analysis: risk of fractures with acid-suppressing medication. Bone. 48:768–776. [PubMed: 21185417]
24. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. 2008; Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ. 179:319–326. [PubMed: 18695179]
25. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. 2011; Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol. 106:1209–1218. [PubMed: 21483462]
26. Kaye JA, Jick H. 2008; Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. Pharmacotherapy. 28:951–959. [PubMed: 18657011]
27. Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, Chen Z. 2010; Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. Arch Intern Med. 170:765–771. [PubMed: 20458083]
28. Roux C, Briot K, Gossec L, Kolta S, Blenk T, Felsenberg D, Reid D, Eastell R, Glüer C. 2009; Increase in vertebral fracture risk in postmenopausal women using omeprazole. Calcif Tissue Int. 84:13–19. [PubMed: 19023510]

29. Ding J, Heller DA, Ahern FM, Brown TV. 2014; The relationship between proton pump inhibitor adherence and fracture risk in the elderly. Calcif Tissue Int. 94:597–607. [PubMed: 24706060]
30. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. 2005; Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med. 118:778–781. [PubMed: 15989913]
31. Recker RR. 1985; Calcium absorption and achlorhydria. N Engl J Med. 313:70–73. [PubMed: 4000241]
32. Joo MK, Park JJ, Lee BJ, Kim JH, Yeon JE, Kim JS, Byun KS, Bak YT. 2013; The effect of a proton pump inhibitor on bone metabolism in ovariectomized rats. Mol Med Rep. 7:1267–1272. [PubMed: 23426758]
33. Mizunashi K, Furukawa Y, Katano K, Abe K. 1993; Effect of omeprazole, an inhibitor of H+, K(+)-ATPase, on bone resorption in humans. Calcif Tissue Int. 53:21–25. [PubMed: 8102318]
34. Tuukkanen J, Vaananen HK. 1986; Omeprazole, a specific inhibitor of H+-K+-ATPase, inhibits bone resorption in vitro. Calcif Tissue Int. 38:123–125. [PubMed: 3006888]
35. Gagnemo-Persson R, Samuelsson A, Hakanson R, Persson P. 1997; Chicken parathyroid hormone gene expression in response to gastrin, omeprazole, ergocalciferol, and restricted food intake. Calcif Tissue Int. 61:210–215. [PubMed: 9262512]
36. Rimm E, Stampfer M, Colditz GA, Chute C, Litin L, Willett W. 1990; Validity of self-reported waist and hip circumference in men and women. Epidemiology. 1:466–473. [PubMed: 2090285]
37. Wolf A, Hunter D, Colditz G, Manson J, Stampfer M, Corsano K, Rosner B, Kriska A, Willett W. 1994; Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol. 23:991–999. [PubMed: 7860180]
38. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. 1986; Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. American Journal of Epidemiology. 123:894–900. [PubMed: 3962971]
39. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH. 1991; A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med. 151:1141–1147. [PubMed: 2043016]
40. Willett W, Sampson L, Stampfer M, Rosner B, Bain C, Witschi J, Hennekens C, Speizer F. 1985; Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 122:51–65. [PubMed: 4014201]
41. Yuan C, Spiegelman D, Rimm EB, Rosner BA, Stampfer MJ, Barnett JB, Chavarro JE, Subar AF, Sampson LK, Willett WC. 2017; Validity of a Dietary Questionnaire Assessed by Comparison With Multiple Weighed Dietary Records or 24-Hour Recalls. Am J Epidemiol. 185:570–584. [PubMed: 28338828]
42. Freedberg DE, Kim LS, Yang YX. 2017; The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology. 152:706–715. [PubMed: 28257716]
43. Solomon DH, Diem SJ, Ruppert K, Lian YJ, Liu CC, Wohlfart A, Greendale GA, Finkelstein JS. 2015; Bone mineral density changes among women initiating proton pump inhibitors or H2 receptor antagonists: a SWAN cohort study. J Bone Miner Res. 30:232–239. [PubMed: 25156141]
44. Targownik LE, Lix LM, Leung S, Leslie WD. 2010; Proton-pump inhibitor use is not associated with osteoporosis or accelerated bone mineral density loss. Gastroenterology. 138:896–904. [PubMed: 19931262]
45. Targownik LE, Leslie WD, Davison KS, Goltzman D, Jamal SA, Kreiger N, Josse RG, Kaiser SM, Kovacs CS, Prior JC, Zhou W. CaMos Research G. 2012; The relationship between proton pump inhibitor use and longitudinal change in bone mineral density: a population-based study [corrected] from the Canadian Multicentre Osteoporosis Study (CaMos). Am J Gastroenterol. 107:1361–1369. [PubMed: 22777336]

Table 1

Age-Standardized Baseline Characteristics of Women According to PPI and H_2-Receptor Antagonist Use in 2002

	PPI Use		H_2-Receptor Antagonist Use	
	No (n=52,078)	**Yes (n=3,467)**	**No (n=52,084)**	**Yes (n=3,461)**
Age, years *	65.9 (6.5)	66.2 (6.6)	65.9 (6.5)	66.3 (6.5)
Body Mass Index (kg/m^2)	26.8 (5.2)	28.6 (5.6)	26.9 (5.2)	28.4 (5.5)
Physical Activity (METS/week) †	18.8 (22.6)	15.1 (18.3)	18.8 (22.5)	15.6 (18.7)
Dietary Calcium (mg/day) #	855.3 (320.1)	848.3 (314.3)	855.8 (319.8)	841.5 (318.6)
Calcium Supplement (mg/day)	620.2 (523.4)	657.5 (543.5)	622.1 (524.5)	631.9 (529.7)
Calcium Supplement Use (yes/no), %	80	81	80	81
Total (Dietary and Supplemental) Vitamin D Intake (IU/day) #	562.4 (334.3)	582.4 (337.2)	563.1 (334.5)	573.2 (335.7)
Phosphorus Intake (mg/day) #	1,253 (257)	1,260 (250)	1,254 (256)	1,249 (254)
Magnesium Intake (mg/day) #	373.3 (122.6)	373.1 (121.8)	373.6 (122.8)	369.3 (119.1)
Total Protein Intake (gm/day) #	70.1 (13.0)	71.1 (12.8)	70.1 (13.0)	70.6 (13.0)
Animal Protein Intake (gm/day) #	46.3 (13.7)	47.7 (13.2)	46.3 (13.7)	47.3 (13.4)
Total (Dietary and Supplemental) Vitamin A Intake (mcg/day) #	1,918 (1,382)	1,908 (1,354)	1,917 (1,379)	1,921 (1,402)
Alcohol Intake (gm/day) Smoking status	6.3 (10.76)	4.7 (9.1)	6.3 (10.7)	5.0 (9.5)
Never smoker, %	47	46	47	44
Past smoker, %	46	50	46	50
Current smoker, %	7	4	7	7
History of Falls	8	12	8	11
History of Diabetes, %	8	11	8	11
History of Hypertension, %	49	67	49	67
Self-Reported Osteoporosis, %	14	17	14	16
Postmenopausal Hormone Use, %	38	48	38	47
Bisphosphonate Use, %	11	11	11	11

* Value is not age adjusted

† Physical activity and history of falls was not asked about in 2002 so data are from the 2000 questionnaire.

Energy adjusted.

Table 2

Age- and Multivariable-Adjusted Relative Risks for Clinical Vertebral Fracture According to PPI and H_2-Receptor Antagonist Use*

	PPI Use	
	No	**Yes**
Cases of Vertebral Fracture (n)	426	121
Person-years (n)	523,600	83,248
Age-adjusted Relative Risk (95% CI)	1.00 (reference)	1.44 (1.17, 1.77)
Multivariate Relative Risk (95% CI) † (Model without osteoporosis)	1.00 (reference)	1.36 (1.11, 1.68)
Multivariate Relative Risk (95% CI) †† (Model with osteoporosis)	1.00 (reference)	1.29 (1.04, 1.59)
	H_2-Receptor Antagonist Use	
	No	Yes
Cases of Vertebral Fracture (n)	503	44
Person-years (n)	569,267	37,580
Age-adjusted Relative Risk (95% CI)	1.00 (reference)	1.34 (0.98, 1.82)
Multivariate Relative Risk (95% CI) † (Model without osteoporosis)	1.00 (reference)	1.26 (0.92, 1.72)
Multivariate Relative Risk (95% CI) †† (Model with osteoporosis)	1.00 (reference)	1.22 (0.90, 1.67)

*PPI and H_2-Receptor Antagonist use were updated throughout the analysis period (2002-2014). Relative risks are for the risk of vertebral fracture compared with the group that did not use PPIs or H_2-Receptor Antagonists.

†The multivariate model includes body mass index, race, physical activity, history of falls, smoking status, alcohol intake, supplemental calcium intake, quintiles of diet calcium intake, total vitamin D intake, vitamin A intake, total protein intake, history of diabetes, postmenopausal hormone use, and recent physical exam.

††The multivariate model includes body mass index, race, physical activity, history of falls, smoking status, alcohol intake, supplemental calcium intake, quintiles of diet calcium intake, total vitamin D intake, vitamin A intake, total protein intake, history of diabetes, self-reported osteoporosis, postmenopausal hormone use, and recent physical exam.

Table 3

Age-Adjusted and Multivariate Relative Risks for Clinical Vertebral Fracture According to Duration of PPI or H_2-Receptor Antagonist Use*

PPI Use	**None**	**< 4 years**	**4 – 7.9 years**	**≥ 8 years**	**P for Trend**
Cases of Vertebral Fracture (n)	396	78	48	19	
Person-years (n)	488,126	64,894	25,970	6,458	
Age-adjusted Relative Risk (95% CI)	1.00 (reference)	1.28 (1.00, 1.63)	1.48 (1.09, 2.01)	1.93 (1.21, 3.08)	0.001
Multivariate Relative Risk (95% CI) † (Model without osteoporosis)	1.00 (reference)	1.22 (0.95, 1.56)	1.35 (0.99, 1.85)	1.75 (1.09, 2.81)	0.003
Multivariate Relative Risk (95% CI) †† (Model with osteoporosis)	1.00 (reference)	1.16 (0.90, 1.49)	1.27 (0.93, 1.73)	1.64 (1.02, 2.64)	0.01
H_2-Receptor Antagonist Use	None	< 4 years	≥ 4 years		P for Trend
Cases of Vertebral Fracture (n)	464	60	17		
Person-years (n)	526,606	47,448	11,394		
Age-adjusted Relative Risk (95% CI)	1.00 (reference)	1.32 (1.01, 1.73)	1.10 (0.68, 1.79)		0.21
Multivariate Relative Risk (95% CI) † (Model without osteoporosis)	1.00 (reference)	1.19 (0.91, 1.58)	0.99 (0.61, 1.61)		0.63
Multivariate Relative Risk (95% CI) †† (Model with osteoporosis)	1.00 (reference)	1.16 (0.88, 1.53)	0.98 (0.60, 1.59)		0.72

*PPI and H_2-Receptor Antagonist use were updated throughout the analysis period (2002-2014). Relative risks are for the risk of vertebral fracture compared with the group that did not use PPIs or H_2-Receptor Antagonists. This analysis includes 541 cases since 6 cases were missing information on duration of PPI and H_2RA use.

†The multivariate model includes body mass index, race, physical activity, history of falls, smoking status, alcohol intake, supplemental calcium intake, quintiles of diet calcium intake, total vitamin D intake, vitamin A intake, total protein intake, history of diabetes, postmenopausal hormone use, and recent physical exam.

††The multivariate model includes body mass index, race, physical activity, history of falls, smoking status, alcohol intake, supplemental calcium intake, quintiles of diet calcium intake, total vitamin D intake, vitamin A intake, total protein intake, history of diabetes, self-reported osteoporosis, postmenopausal hormone use, and recent physical exam.