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The effect of proton pump inhibitors on fracture risk: report from the Canadian Multicenter Osteoporosis Study

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Abstract

Summary—A large Canadian cohort was studied over 10 years to see if proton pump inhibitor (PPI) use increased the risk of sustaining a fragility fracture. We found an increased risk of fracture in individuals who used PPIs. The risk remained after controlling for other known fracture risk factors.

Introduction—Multiple retrospective studies have linked proton pump inhibitor use with increased risk of fragility fracture. We prospectively studied the association between PPI use and fracture in a large cohort over a 10-year period while controlling for known fracture risk factors.

Methods—We studied 9,423 participants in the Canadian Multicenter Osteoporosis Study. The cohort was formed in 1995–1997 and followed for 10 years with monitoring for incident nontraumatic fracture and PPI use. Cox regression analyses were used to assess the association between PPI use and incident fracture risk.

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Results—PPI use, coded as a time-dependent variable, was associated with a shorter time to first nontraumatic fracture, hazard ratio (HR)=1.75 (95 % confidence interval (CI) 1.41–2.17, $p<0.001$). After controlling for multiple risk factors, including femoral neck bone density, the association remained significant, HR=1.40 (95 % CI 1.11–1.77, $p= 0.004$). Similar results were obtained after controlling for bisphosphonate use, using PPI "ever" use, or when the outcome was restricted to hip fracture.

Conclusions—In this large prospective population-based cohort study, we found an association between PPI use and increased risk of fragility fracture. Although the increased risk found was modest, this finding is important, given the high prevalence of PPI use and the excess morbidity and mortality associated with osteoporosis-related fractures.

Keywords

Fracture; Osteoporosis; Proton pump inhibitors; Risk factor

Introduction

Osteoporosis is a common disorder, and numbers are rising as the population ages. In Canada, 21 % of women and 5 % of men over the age of 50 have osteoporosis [1]. The personal costs of osteoporosis are high, as osteoporotic fractures cause significant morbidity and mortality [2–4]. Similarly, the costs to society are high, in terms of health care costs and lost wages. Therefore, preventing osteoporosis and fragility fractures is of paramount importance [5]. Multiple medications have been implicated as increasing the risk of fragility fractures, including corticosteroids, selective serotonin reuptake inhibitors, anticonvulsants, thiazolinediones, aromatase inhibitors, and antiandrogen therapies [6–9].

In numerous observational studies, proton pump inhibitors (PPI) have been associated with increased fracture risk [10]. These studies led the US Food and Drug Administration in 2010 to issue an advisory warning of increased fracture risk in patients on high-dose or long-term PPIs [11]. PPIs are commonly used medications that are effective for the treatment and prevention of a wide variety of upper gastrointestinal syndromes. In addition, overuse of these medications for nonindicated conditions is prevalent [12, 13]. These medications are generally well tolerated and have traditionally been considered relatively safe and free from adverse effects; although more recently, there have been reports linking PPIs with *Clostridium difficile*-associated diarrhea, hypomagnesemia, increased cardiovascular events in cardiac patients on clopidogrel, and pneumonia [14–17]. Due to the high prevalence of PPI use and the impact of osteoporosis-related fractures on health and quality of life, evidence of even a moderate association between these medications and fragility fractures would have important health implications. However, not all studies, assessing PPIs and fracture risk, have demonstrated this association [18]. The magnitude of the increased fracture risk with PPI therapy that has been reported has also been variable, leading some to suggest that residual confounding may be present [10, 19].

We examined the association between incident nontraumatic fracture and PPI use in a community-dwelling Canadian population-based cohort using the Canadian Multicenter Osteoporosis Study. Our aim was to determine whether PPI use was associated with an

increased risk of incident fragility fracture after controlling for multiple possible confounding variables including bone mineral density (BMD).

Methods

CaMos

The Canadian Multicenter Osteoporosis Study (CaMos) is an ongoing population-based cohort study examining osteoporosis and fracture risk in community-dwelling Canadians (cohort inception period 1995–1997). The study has been described in detail elsewhere; areas relevant to the current analysis are summarized below [20]. All women and men involved in CaMos were included in the analyses. The institutional review boards of all sites, participating in CaMos, approved the study, and informed consent was obtained from all participants.

Study participants and methods

Participants were recruited from within 50 km of one of nine study centers across Canada (St. John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Saskatoon, Calgary, and Vancouver), and 9,423 individuals (6,539 females and 2,884 males) aged 25 years and older, representing an age-stratified-, sex-, and region-specific sample, were identified from lists of random telephone numbers over an 18-month period. An extensive interviewer-administered questionnaire was performed at baseline (and at years 5 and 10), and participant medications were documented in detail. During other years, a two-page questionnaire was mailed to participants asking about hospitalizations and fractures within the past year and current use of prescription bone medications. BMD testing was performed at baseline, by dual-energy X-ray absorptiometry using Hologic QDR 1000, 2000, 4500, or GE Lunar DPX machines. Densitometers were calibrated daily, and quality assurance was performed following a standard daily and weekly schedule. Initially, cross-calibration of the machines was performed at the nine centers using a European Spine Phantom. After this, the Bone Fide phantom was performed at baseline and in the year of every examination.

All clinically recognized nontraumatic fractures (including hip and clinical vertebral and nonvertebral fractures) were included in our analysis. Any fracture associated with trauma or described as a fall from more than a standing height was excluded [21, 22]. At baseline, previous fractures were obtained by self-report, but subsequent fractures that occurred after enrolment were reported by patients and confirmed by medical or radiographic reports.

Statistical analysis

All CaMos participants were included in the analyses. Baseline characteristics of the CaMos participants are described using mean (standard deviation) for continuous variables and count (percentage) for nominal variables. *P* values for baseline characteristics were calculated using *t* tests for continuous variables and chi square statistics for nominal variables. Participants were considered "PPI users" at a certain time point if they were on one or more of: pantoprazole, omeprazole, lansoprazole, rabeprazole, or esomeprazole. Participants were considered PPI "ever" users if they reported use of PPI therapy at any time point. In order to account for changes in PPI use over time, a stepwise time-dependent

variable was created for “PPI use” during the 10 years of observation [23]. Information on PPI use was available only at study baseline, years 5 and 10. Where PPI use was confirmed at two adjacent time points (e.g., baseline and year 5 or years 5 and 10), PPI use was coded as 1.0 for all time points between these 2 years. Where PPI use changed between two adjacent time points, then, it was approximated as a stepwise function in yearly discrete steps of 0.2. For instance, if a subject reported being on PPI therapy at year 0 (use=1.0), but not at year 5 (use=0.0), then at years 1, 2, 3, and 4, they were assigned PPI use values of 0.8, 0.6, 0.4, and 0.2, respectively. This process was repeated for years 6, 7, 8, and 9, based upon PPI use from years 5 and 10. Defining PPI use as a stepwise time-dependent variable better accommodates when PPI therapy was discontinued (or started) but assumes a linear onset/offset of effect.

Cox proportional hazards regression analyses were performed for the outcome time to first nontraumatic fracture. Subjects were censored from the analysis for death and loss to follow up. The model was first run using stepwise time-dependent PPI use as described above and, then again, with PPI ever use at any time point in order to test the robustness of the model. As a further sensitivity analysis, a discrete (yes/no) time-dependent PPI variable was examined in which an individual was considered a PPI user during years 0 to 5 only if they reported PPI therapy during years 0 and 5. Individuals were then coded as PPI users during years 5 to 10 only if they reported PPI use in the years 5 and 10 surveys. Covariates were based on their known association with fractures. Covariates were assessed at study baseline and included: gender, age, femoral neck T-score, history of previous nontraumatic fracture, body mass index (BMI), alcohol use, cigarette use, regular exercise, and corticosteroid use. Alcohol use was reported as number of drinks per week and was included as a continuous variable. Cigarette use was defined as ever use of daily tobacco for >6 months. Corticosteroid use included oral or IV ever use, daily for >1 month. Regular exercise was defined as an individual’s self-identification as participating in a regular exercise program or activity. A sensitivity regression was performed that adjusted for bisphosphonate use (any of alendronate, clodronate, etidronate, pamidronate, risedronate, and zoledronic acid) at any time point over the 10-year study. Covariates were considered to be statistically significant if the p value was 0.05 or less. All statistics were performed using IBM SPSS version 19 (Ireland).

Results

All 9,423 CaMos participants were included in the analyses. A gradual decline in participant numbers occurred over time due to death and study drop-out, such that 5,569 individuals remained in the study and completed the full questionnaire at year 10. There were 1,295 individuals who experienced one or more nontraumatic clinical fractures over the 10 years of observation, including 158 hip fractures. Characteristics of baseline PPI users and nonusers at study baseline are presented in Table 1. PPI users at baseline were older, more likely to be female, had higher BMIs, and were less active than non-PPI users. PPI users also tended to be more likely to have had a prior fragility fracture, to have used corticosteroids, or be on a bisphosphonate. At baseline, 261 individuals (2.8 %) were using PPI therapy. This number increased over time, with 530 participants (6.9 %) on PPI therapy at year 5 and 675 (12.1 %) on therapy at study year 10.

PPI use, examined as a stepwise time-dependent variable for incident nontraumatic fracture, gave an unadjusted hazard ratio (HR) for fracture in PPI users of 1.75 (95 % confidence interval (CI) 1.41–2.17, $p<0.001$). After adjusting for age, gender, BMI, prior nontraumatic fracture, femoral neck T-score, corticosteroid use, alcohol intake, smoking status, and activity levels, the adjusted HR for PPI use was 1.40 (95 % CI 1.11–1.77, $p=0.004$). Further adjustment for bisphosphonate use at any time point during the 10-year study gave virtually identical results (HR 1.40, 95 % CI 1.11–1.76, $p=0.005$). When the analyses were performed using PPI ever use (instead of time-dependent PPI use), the unadjusted HR for incident fracture was 1.52 (95 % CI 1.31–1.75, $p<0.001$), with adjusted HR 1.33 (1.15–1.56, $p<0.001$) and, additionally, bisphosphonate-adjusted HR 1.32 (1.13–1.54, $p<0.001$) (Fig. 1). Of the 261 individuals reporting PPI use at year 0 and the 530 who reported use at year 5, only 130 reported use at both time points. Similarly, of the 675 PPI users identified in the year 10 surveys, only 216 individuals reported PPI use during both years 5 and 10. When a discrete (yes/no) time-dependent Cox regression was run, including only these individuals in the PPI group, the unadjusted HR was 1.72 (95 % CI 1.23–2.32, $p<0.001$). The adjusted HR was similar to our stepwise time-dependent PPI analysis but was no longer significant, HR 1.32 (95 % CI 0.95–1.81, $p=0.104$). Other variables associated with increased risk of fracture in our primary analysis included older age, female gender, higher BMI, prior nontraumatic fracture, lower femoral neck T-score, prior corticosteroid use, and bisphosphonate use during the 10-year study period (Table 2). Past cigarette use was associated with a decreased fracture risk.

When time to first hip fracture was examined using time-dependent PPI exposure the unadjusted HR was 2.24 (95 % CI 1.27–3.96, $p=0.005$). After adjusting for the multiple variables listed above, this association was slightly attenuated and no longer statistically significant (HR 1.75, 95 % CI 0.94–3.26, $p=0.079$). The results were similar when PPI ever use was used, with an unadjusted HR for time to first hip fracture of 1.76 (95 % CI 1.15–2.71, $p=0.010$) and an adjusted HR of 1.52 (95 % CI 0.99–2.35, $p=0.059$) (Fig. 2). A summary of the results for each definition of PPI use for all nontraumatic fractures and for hip fractures only is detailed in Table 3.

Discussion

In this large Canadian population-based cohort, we found an association between PPI use and incident fragility fracture, which persisted after adjusting for multiple risk factors. Our study supports the growing body of literature linking PPI use with greater fracture risk. A recent meta-analysis, examining 11 different observational studies, found the relative risk of fracture in PPI users to be 1.30 (95 % CI 1.04–1.30) for hip fractures, 1.56 (95 % CI 1.31–1.85) for vertebral fractures, and 1.16 (95 % CI 1.04–1.30) for fracture at any site [10]. Similarly, we found a significant increase in risk of fractures at any site in PPI users (adjusted HR 1.40; 95 % CI 1.13–1.77; $p=0.004$), with higher hazard ratios for hip fracture (lack of statistical significance in the adjusted models could relate to the small number of hip fractures observed).

The nature of the association between increased fracture risk and PPI use has been questioned with the suggestion that residual confounding due to unmeasured or

unmeasurable factors may be a source of bias [19]. There are no randomized control trials looking at this question, and therefore, we must rely on observational studies. Unfortunately, observational studies, especially those examining administrative databases, are often limited by the information collected. As such, many previous studies on PPIs and fracture risk have controlled for a limited number of risk factors. CaMos, however, was specifically designed to study osteoporosis and fractures. Therefore, detailed information on many different fracture risk factors was available to include in our analysis. It has been suggested that PPI users tend to have more fracture risk factors than the general population. At study baseline, we did find that multiple known fracture risk factors were more common in the PPI user group than the non-PPI user group. However, the elevated fracture risk remained even after these variables were controlled for in our analysis. Bone mineral density, an important fracture risk factor, has only been controlled for in one other prospective study to date [24], in which a significantly increased risk of incident morphometric vertebral fractures was found in PPI users (RR 3.5, 95 % CI 1.14–8.44). However, this study had several limitations; it included only postmenopausal women using omeprazole (not accounting for the use of other PPIs) and was small, consisting of only 61 omeprazole users.

Bisphosphonate therapy, currently considered a first-line treatment for osteoporosis and fracture prevention, can cause gastrointestinal adverse effects, and therefore, it is not uncommon for patients on bisphosphonate therapies to be on PPIs concomitantly with their treatment [25]. In some populations, as many as 22 % of patients on bisphosphonates are also on PPIs [26]. One could argue that individuals, who fractured, were being started on bisphosphonate therapy and, subsequently, were more likely to start treatment with a PPI to deal with gastrointestinal side effects, confounding by indication. However, when we examined “new” PPI users at study year 5 (not on PPIs at year 0, but on PPIs at year 5), we found that only 15 % were also new bisphosphonate users (not on bisphosphonate therapy at year 0, but on at year 5) at year 5. Similarly, 17 % of new PPI users at year 10 (not on PPIs at years 0 or 5, but on PPI therapy at year 10) were also new bisphosphonate users at year 10. Although it is impossible for us to decipher, between time points, whether the PPI or the bisphosphonate was initiated first, these results do show that the majority of PPI therapy was started independently with new bisphosphonate prescriptions.

Our study suggests (Figs. 1 and 2) a rapid divergence in fracture risk between PPI users and non-PPI users, with this difference increasing as treatment time continued. The recent meta-analysis by Yu et al. also found an early increased fracture risk present in PPI users (with use of less than 1 year) in the course of their therapy [10]. Although not all studies have supported an increased risk of fracture with ongoing PPI use [27], the strength of the association between hip fracture and PPI use has been shown previously to increase with the duration of PPI therapy over a 4-year period [28]. Similarly, a Canadian study showed that hip fracture risk progressively increased in PPI users after 5 years of therapy, and all osteoporotic fractures increased after 7 years of PPI therapy [29]. Our study shows a similar trend and extends this observation to a 10-year period.

The exact mechanism by which PPI therapy causes an increase in fracture risk remains unclear. One potential mechanism is interference with calcium absorption, which is known to be associated with increased fracture risk [30]. PPIs are potent inhibitors of gastric acid

secretion, which is thought to be necessary for calcium absorption by increasing the solubility of insoluble calcium salts. However, studies looking at calcium absorption in achlorhydric or hypochlorhydric states have found differing results with some studies showing no effect on calcium absorption [31, 32] and other studies showing impaired absorption of calcium carbonate in fasting individuals [33, 34]. Impaired absorption of folate and vitamin B_{12} in PPI users, leading to alterations in homocysteine levels, has also been suggested as factors contributing to the increased fracture risk [35].

Studies looking at the effect of PPI therapy on bone mineral density have yielded conflicting results. Some studies have found no difference in BMD scores and rates of BMD, which decline between PPI and non-PPI users [36, 37], whereas other studies have identified a small decrease in BMD levels associated with PPI use [38, 39]. Another possible mechanism linking PPI use with fracture risk is direct action of PPI therapy on skeletal cells. Osteoclasts, responsible for bone resorption, are known to contain proton pumps which have been shown to be inhibited by PPI therapy. This results in decreased bone turnover, presumably by interfering with acidification at resorption lacunae [40, 41]. Although the significance of this interaction in not fully determined, this decrease in osteoclast function would be expected to lead to decreased bone resorption, the opposite that we would expect in states of increased fracture risk. Further study is necessary to better delineate the physiologic mechanisms through which PPI use may promote the development of decreased bone strength and subsequent fracture.

The major strength of our study is the access we had to prospective information over a 10-year period, detailing when PPI therapy was initiated (and discontinued) relative to the incidence of new fragility fractures. This enabled us to account for the time-dependent component of the association between PPI use and nontraumatic fracture incidence. Similarly, we were able to control for multiple possible confounding variables which are known to be risk factors for fracture, including bone mineral density. Incident fractures in CaMos were confirmed by medical or radiographic reports, decreasing the incidence of recall bias or error in patient self-reporting. Another strength is that we were able to look at a broad range of community-dwelling male and female participants from across Canada, giving our results generalizability. There are, however, several limitations to our study. We only had PPI drug use data for years 0, 5, and 10 of the study, and therefore, it is impossible for us to know exactly when individuals started or stopped PPI therapy between any two time points, and hence, if fractures that occurred between two time points occurred before or after PPI therapy was initiated. To better account for PPI initiation/discontinuation between time points, we developed a stepwise PPI time-dependent variable. We also looked at ever PPI use a nontime-dependent variable and obtained similar results. To test our most conservative definition of PPI “user,” we then did a sensitivity analysis using a discrete (yes/no) time-dependent PPI variable where an individual was only considered a PPI user for the duration of time between two time points in which they reported PPI use. These findings were very similar to our original stepwise PPI time-dependent variable (adjusted HR of 1.32 vs. adjusted HR of 1.40), but the adjusted HR was no longer statistically significant. This was likely the result of the large loss of power that occurred by limiting the PPI user group to this conservative definition (n=293 vs. n=1107 for PPI ever users). The HRs for incident nontraumatic fracture in PPI users were similar, and the 95 % confidence intervals

overlapped, with all three of the PPI user definitions that we tested. Another limitation is that PPI dose was not accounted for in our study. Previous studies have identified a dose–response association between average daily PPI dose and fracture risk, indicating that long-term high-dose PPI users are at the greatest risk of fracture [28]. Finally, as with any observational study, residual confounding by unmeasured variables is possible in our study.

In summary, we found that PPI use is associated with increased incident nontraumatic fracture at any site in community-dwelling men and women in Canada independent of multiple known fracture risk factors. The magnitude of the increased fracture risk found in our study is modest and in line with previous studies. However, given the widespread use of PPIs and the economic and health impact of osteoporotic fractures, this finding is of importance to clinicians and patients.

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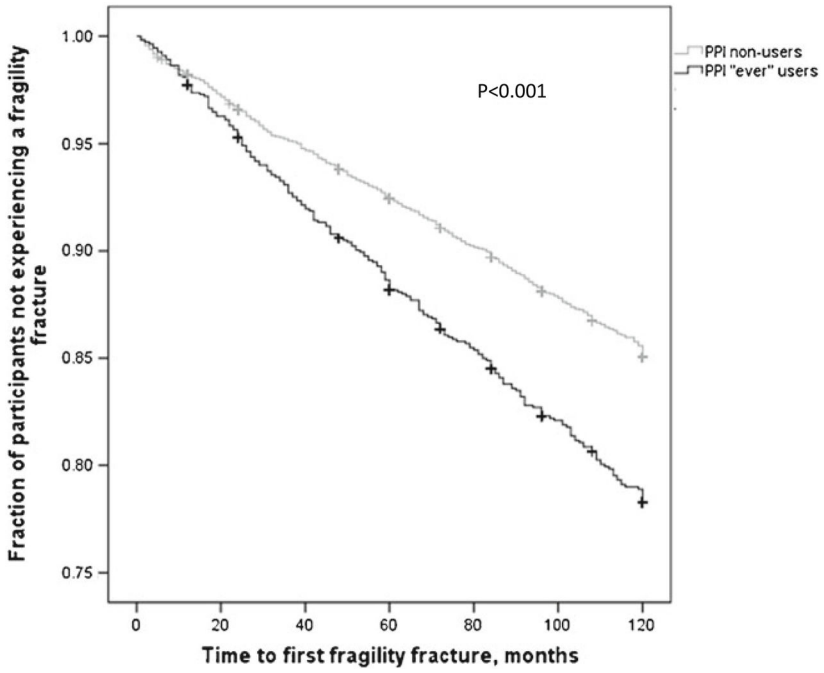

Fig. 1.

Kaplan–Meier curve showing unadjusted fragility fracture-free survival by PPI use (defined as PPI ever use). PPI= proton pump inhibitor. P-value from the log rank test

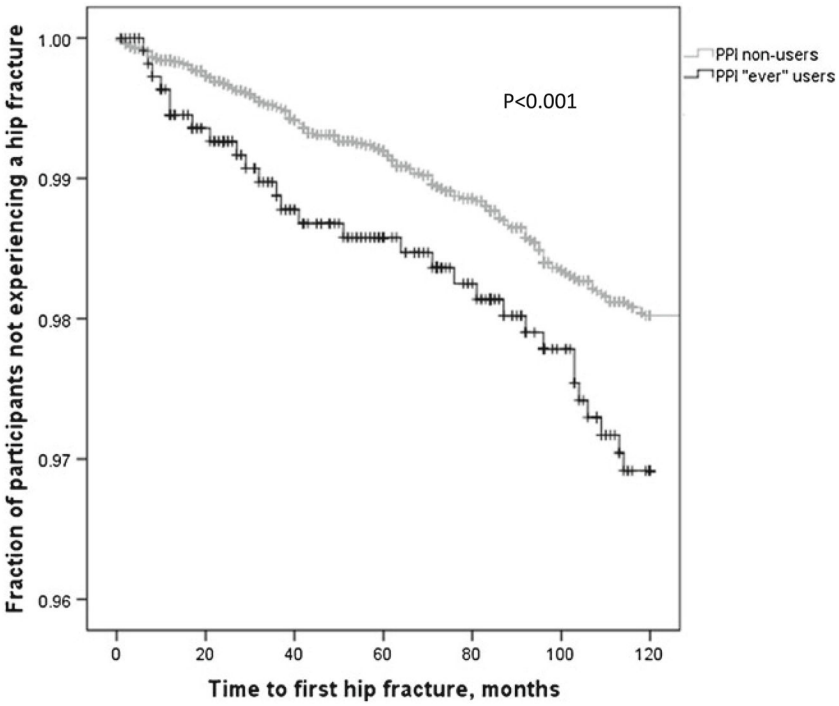

Fig. 2.

Kaplan–Meier curve showing unadjusted hip fracture-free survival by PPI use (defined as PPI ever use). PPI= proton pump inhibitor. P-value from the log rank test

Table 1

Baseline characteristics of baseline PPI users and nonusers

Characteristic	PPI users (*n*=261)	Non-PPI users (*n*=9,162)	*p* values
Age, mean (SD) (years)	67.6 (11.1)	61.9 (13.4)	<0.001
Female gender (%)	204 (78.2)	6,334 (69.1)	0.001
BMI, mean (SD)	28.3 (5.3)	26.9 (4.8)	<0.001
Femoral neck T-score, mean (SD)	−1.4 (1.0)	−1.1 (1.0)	<0.001
Prevalent clinical fragility fracture (%)	97 (37.1)	2,392 (26.1)	<0.001
Daily calcium supplement use (%)	113 (43.3)	3,592 (39.2)	0.103
Cigarette use (%)[a]	147 (56.3)	4,859 (53.0)	0.162
Alcohol use, mean (SD), drinks per week	2.3 (4.9)	3.0 (5.9)	0.052
Regular physical activity (%)	108 (41.4)	5,085 (55.5)	<0.001
Corticosteroid use (%)[b]	42 (16.1)	414 (4.5)	<0.001
Bisphosphonate use (%)[b]	88 (33.7)	2,220 (24.2)	<0.001

SD standard deviation, *BMI* body mass index, *BMD* bone mineral density

[a] Ever use daily for >6 months

[b] Oral or IV, ever use daily for >1 month

Table 2

Variables associated with risk of incident nontraumatic fracture over 10 years (multivariate analysis including bisphosphonate use)

Variable	Hazard ratio	95 % confidence interval	Significance (*p* value)
PPI use	1.40	1.11–1.76	0.005
Female gender	1.52	1.28–1.79	<0.001
Previous nontraumatic fracture	1.56	1.38–1.76	<0.001
Body mass index (per unit increase)	1.03	1.02–1.05	<0.001
Age (per year)	1.02	1.01–1.03	<0.001
Femoral neck T-Score (per SD increase)	0.70	0.64–0.76	<0.001
Cigarette use[a]	0.88	0.78–0.99	0.033
Corticosteroid use[b]	1.35	1.08–1.69	0.007
Alcohol use (with increasing number of drinks/week)	1.01	1.00–1.02	0.113
Self-reported regular physical activity	0.96	0.85–1.08	0.500
Bisphosphonate use	1.51	1.33–1.73	<0.001

PPI proton pump inhibitor

[a] Ever use daily for >6 months

[b] Oral or IV, ever use daily for >1 month

Table 3

Risk of incident nontraumatic fractures in PPI users, using different definitions for PPI use

Definition of PPI use	Unadjusted hazard ratio (95 % Confidence interval)	Adjusted hazard ratio (95 % Confidence interval)
PPI use as a stepwise time-dependent variable	1.75 (1.41–2.17), $p<0.001$	1.40 (1.11–1.77), $p=0.004$
PPI use as a discrete yes/no time-dependent variable	1.72 (1.23–2.32), $p<0.001$	1.32 (0.95–1.81), $p=0.104$
PPI “ever use”	1.52 (1.31–1.75), $p<0.001$	1.33 (1.15–1.56), $p<0.001$
PPI use as a stepwise time-dependent variable (hip fracture only)	2.24 (1.27–3.96), $p=0.005$	1.75 (0.94–3.26), $p=0.079$
PPI ever use (hip fracture only)	1.76 (1.15–2.71), $p=0.010$	1.52 (0.99–2.35), $p=0.059$