The Relationship Between Proton Pump Inhibitor Use and Longitudinal Change in Bone Mineral Density: A Population-Based From the Canadian Multicentre Osteoporosis Study (CaMos)

Laura E. Targownik, MD, MSHS¹, William D. Leslie, MD, MSc¹, K. Shawn Davison, PhD², David Goltzman, MD³, Sophie A. Jamal, MD, PhD⁴, Nancy Kreiger, MPH, PhD⁴, Robert G. Josse, MBBS⁴, Stephanie M. Kaiser, MD⁵, Christopher S. Kovacs, MD⁶, Jerilynn C. Prior, MD⁷, Wei Zhou, MSc³, and the CaMos Research Group⁸

¹University of Manitoba, Winnipeg, Manitoba, Canada

²University of Saskatchewan, Saskatoon, Saskatchewan, Canada

³McGill University, Montreal, Quebec, Canada

⁴University of Toronto, Toronto, Ontario, Canada

⁵Dalhousie University, Halifax, Nova Scotia, Canada

⁶Memorial University of Newfoundland, St John's, Newfoundland, Canada

⁷University of British Columbia, Vancouver, British Columbia, Canada

Abstract

OBJECTIVES—Proton pump inhibitor (PPI) use has been identified as a risk factor for hip and vertebral fractures. Evidence supporting a relationship between PPI use and osteoporosis remains

Correspondence: Laura E. Targownik, MD, MSHS, Gastroenterology, University of Manitoba, 805G-715 McDermot Avenue, Winnipeg, Manitoba, Canada R3E 3P4. targowni@cc.umanitoba.ca.

⁸See Appendix.

CONFLICT OF INTEREST

Guarantor of the article: Laura E. Targownik, MD, MSHS.

Specific author contributions: study concept and design, acquisition of database data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis: Laura E. Targownik and William D. Leslie; acquisition of participant data, study concept and design, drafting of the manuscript, and critical revision of the manuscript for important intellectual content: K. Shawn Davison, David Goltzman, Sophie A. Jamal, Nancy Kreiger, Robert G. Josse, Stephanie M. Kaiser, Chris S. Kovacs, and Jerilynn C. Prior; acquisition of database data and statistical analysis: Wei Zhou.

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scant. Demonstrating that PPIs are associated with accelerated bone mineral density (BMD) loss would provide supportive evidence for a mechanism through which PPIs could increase fracture risk.

METHODS—We used the Canadian Multicentre Osteoporosis Study data set, which enrolled a population-based sample of Canadians who underwent BMD testing of the femoral neck, total hip, and lumbar spine (L1–L4) at baseline, and then again at 5 and 10 years. Participants also reported drug use and exposure to risk factors for osteoporosis and fracture. Multivariate linear regression was used to determine the independent association of PPI exposure and baseline BMD, and on change in BMD at 5 and 10 years.

RESULTS—In all, 8,340 subjects were included in the baseline analysis, with 4,512 (55%) undergoing year 10 BMD testing. After adjusting for potential confounders, PPI use was associated with significantly lower baseline BMD at the femoral neck and total hip. PPI use was not associated with a significant acceleration in covariate-adjusted BMD loss at any measurement site after 5 and 10 years of follow-up.

CONCLUSIONS—PPI users had lower BMD at baseline than PPI non-users, but PPI use over 10 years did not appear to be associated with accelerated BMD loss. The reasons for discordant findings between PPI use at baseline and during follow-up require further study.

INTRODUCTION

Proton pump inhibitors, or PPIs, are among the most frequently prescribed medications in clinical practice, with 147 million prescriptions for PPIs being dispensed in the United States in 2010 (1). Part of the reason for the widespread use of PPIs has been both their high efficacy for the treatment and prevention of gastroesophageal reflux disease and peptic ulcer disease (2–4), as well as their reputation for being well tolerated and unlikely to lead to long-term complications.

However, over the past decade, there have been an increasing number of studies that have linked the use of PPIs to increases in the risk for a variety of serious adverse events (5–7). Among the associations of highest concern has been the possible link between the long-term use of PPIs and the development of osteoporosis-related fractures, particularly those of the hip (8–15). This association has been primarily detected through the retrospective analysis of pre-existing data, and the strengths of the associations have ranged considerably from study to study. To date, there are no studies using data that were prospectively collected to evaluate the association between PPI use and fracture. Furthermore, the mechanism through which PPI use could increase the risk of fracture has yet to be elucidated (16,17). In spite of these limitations, the US Food and Drug Administration has issued a black-box warning advising that PPI use may increase the risk of subsequent fracture (18).

If the association between PPIs and fracture is indeed causal, then one would expect to also see an effect of PPIs on the intermediate pathways that predispose to fracture. In particular, determining that PPI use is associated with the development of low bone mineral density (BMD) from which the diagnosis of osteoporosis could be made, or with accelerated loss of longitudinally assessed BMD, would provide tangible support for the causality of the PPI – fracture association. Previous studies, which have analyzed the association between PPI use

and BMD, have yielded conflicting results (8,19,20); and thus, the true relationship between PPIs and changes in BMD remains poorly characterized. Therefore, we sought to use a large population-based cohort to determine the relationships between prior PPI use and BMD at the time of enrollment and, using longitudinal assessments of BMD, to determine whether those with chronic PPI use have a different rate of BMD change than non-PPI-treated people.

METHODS

Description of population studied

This study was performed using data collected as part of the Canadian Multicentre Osteoporosis Study (CaMos). CaMos consists of a population-based stratified random sample of the Canadian population. Between 1995 and 1997, a combination of random digit dialing and random household member selection was used to identify potential subjects aged 25 years or older who lived within 50 km of one of nine urban Canadian recruitment centers (Vancouver, Calgary, Saskatoon, Toronto, Hamilton, Kingston, Quebec City, Halifax, and St John's) (21).

All subjects who agreed to enroll underwent a comprehensive in-person interviewer-administered questionnaire (IAQ) at baseline (y0) designed to gather information on medical history and numerous risk factors for osteoporosis and fracture, a complete dietary assessment focusing on intakes of calcium and Vitamin D, as well as socio-demographic information and anthropomorphic measurements. BMD assessment was performed using dual X-ray absorptiometry (DXA) scanning on all enrolled subjects. Standardization between DXA scanners was assured by use of a common phantom that was circulated to each of the centers. Adequacy of the cross-calibration and quality control procedures was evaluated by performing all analyses with and without adjustment for recruiting center and confirming that results were unaffected. BMD measurements were obtained at the lumbar spine (L1–L4), femoral neck, and total hip. Medication use was assessed by asking subjects to bring into the study center any actively used medications. Subjects were asked about osteoprotective medications and glucocorticoids by name. Subjects were asked to show the interviewers all other medications which they took regularly. The dose and indication for these medications were not specifically recorded.

At year 5 (y5) and year 10 (y10) following initial enrollment, the IAQ was repeated, medication use was again captured, and BMD was remeasured. Duration of medication use was not specifically collected; dose and strength of medication was recorded only at the initial visit. A full description of the methodology and survey design employed in CaMos has been previously published (21).

Description of analyses

We performed a cross-sectional analysis to determine the relationship between PPI use at y0 and BMD at each anatomic site. We then performed longitudinal analyses of the relationship between PPI use and the change in BMD at each anatomic site between y0 and y5, between y0 and y10, and between y5 and y10. In the cross-sectional analyses, a subject was

considered to be a PPI user if PPI use was reported in the y0 IAQ. In the longitudinal analyses, a subject was considered to be a continuous PPI user if PPI use was reported at all time points included in the analysis. We also evaluated the effect of current PPI use (use at year 5 for the y0–y5 analysis and use at year 10 for the y0–y10 analysis).

We used multivariate general linear regression to control for the effects of multiple potential confounders, including age, sex, age – sex interactions, body mass index, personal history of minimal trauma fracture, family history of minimal trauma fracture, presence of rheumatoid arthritis, inflammatory bowel disease, chronic liver disease, chronic kidney disease, thyroid disease, current smoking, heavy alcohol use (defined as 14 drinks per week or greater), history of falls, and study center. We also controlled for the use of concomitant medications that may influence BMD, including systemic glucocorticoids, thiazide diuretics, β -blockers, nitrates, anti-epileptics, selective serotonin receptor inhibitors, tamoxifen, and osteoprotective medications (including menopausal hormone therapy, bisphosphonates, and selective estrogen receptor modulators). A participant was considered to have a potential confounding medical condition if the presence of that condition was recorded at any time point. A subject was considered to be exposed to a confounding medication if there was recorded use at the most recent time point, reflective of ongoing use. We also controlled for total calcium intake and Vitamin D intake, with subjects considered to have adequate use of calcium and Vitamin D if their reported daily intake from both diet and supplementary sources met or exceeded 1,200 mg calcium and / or 400 IU of Vitamin D. Interaction terms for PPI use and bisphosphonate use were also included in the model to test for the reported possible negative interaction between PPIs and bisphosphonates (22). No stepwise selection techniques were utilized for entry of covariates into any of the models, and covariates were considered to be statistically significant if the *P*-value was <0.05. All statistical analyses were performed using Statistica 10 (Statsoft Inc., Tulsa, OK).

RESULTS

Overall, 9,423 subjects were enrolled in the original CaMos cohort, of whom 8,340 completed the initial IAQ and underwent initial BMD assessments. In all, 6,458 participants (77 %) underwent repeat assessments of the full IAQ and measurement of BMD at 5 years, and 4,512 (55 %) completed the full 10 years of follow-up. Description of the participants included in the baseline analyses and in the longitudinal analyses is summarized in Table 1. In the baseline cross-sectional analyses, 228 (2.7 %) subjects reported using PPIs. PPI use increased to 7.6 % at year 5 and 11.5 % at year 10. Continuous use of PPI at all time points was limited to 0.9% of the cohort.

Baseline comparisons of PPI users and non-users are shown in Figure 1 and Table 2. Users of PPIs had significantly lower unadjusted BMD at each of the measurement sites. PPI users were also significantly older, had a higher mean BMI, greater intakes of calcium and Vitamin D, and reported a slightly higher rate of prior fracture than non-PPI users. PPI users were also much more likely to have many of the concurrent medical conditions, and were more likely to be using many of the medications, including bisphosphonates, glucocorticoids, selective serotonin receptor inhibitors, thiazides, nitrates, and β -blockers.

After adjusting for multiple confounders, PPI use was associated with lower baseline BMD at both the total hip ($-0.019 \pm 0.008 \text{ g/cm}^2$, $P=0.028$) and the femoral neck ($-0.022 \pm 0.007 \text{ g/cm}^2$, $P=0.002$), but not at the lumbar spine ($-0.014 \pm 0.011 \text{ g/cm}^2$, $P=0.179$) (Table 3). When users of osteoprotective medications and glucocorticoids were excluded, PPI use was again associated with lower adjusted baseline BMD at the femoral neck ($-0.026 \pm 0.008 \text{ g/cm}^2$, $P=0.002$) and total hip ($-0.026 \pm 0.010 \text{ g/cm}^2$, $P=0.008$). Limiting the analysis to subjects over the age of 50 years did not significantly affect the parameter estimates for PPI use (total hip: $-0.021 \pm 0.010 \text{ g/cm}^2$, $P=0.028$, femoral neck: $-0.025 \pm 0.008 \text{ g/cm}^2$, $P=0.002$).

After adjustment for potential confounders, the regression models did not demonstrate a significant association between continuous PPI use and the rate of change in BMD at any of the measurement sites between y0 and y5, between y0 and y10, or between y5 and y10 (Table 4). The lack of an association between PPI use and change in BMD remained when PPI use was defined as being current at the time of the most recent BMD assessment. There were also no significant changes in BMD attributable to PPI use in analyses restricted to subjects over age 50 years and to those not using glucocorticoids or osteoprotective medications. The use of bisphosphonates and menopausal hormone therapy was uniformly associated with increasing BMD. BMD gains of lower magnitude were also associated with the use of thiazide diuretics, whereas glucocorticoid use was often predictive of BMD loss. Interactions between PPI and bisphosphonate use were not detected in any of the longitudinal analyses.

DISCUSSION

In this large, population-based, prospective assessment of BMD, the use of PPIs was associated with lower covariate-adjusted BMD at baseline at the total hip and femoral neck. However, continuous PPI use for both 5 and 10 years was not associated with a significant negative influence on the change in BMD over time.

These are a number of potential explanations for the apparently discordant findings of lower BMD at y0 among PPI users and the lack of further PPI-associated decline in BMD in up to 10 years of follow-up. As this was not an experimental study, there may have been significant differences in the cohort among persons who reported PPI use at baseline, and those who were non-users. It is possible that PPI users had unmeasured variables which predisposed to low BMD, and that these factors were not completely accounted for through the regression analysis. While there are no obvious reasons why low BMD should directly promote higher rates of PPI use, low BMD may be a marker for other comorbidities that may predispose participants to PPI use. Previous studies have suggested that PPI use is much more common among subjects with indicators of frailty, including the use of multiple distinct medications, higher levels of overall comorbidity, and poor mobility (23). These markers of frailty may also be associated with low BMD and increased fracture (24). Although we did make attempts to control for concomitant medical conditions and drug use known to affect BMD, we could not control for the severity of these diseases, nor could we control the duration and/or dose of medication usage. If individuals with low BMD, who are also presumably at higher fracture risk, are more likely to be started on PPIs, then this may

conceivably explain the findings of other studies that report an association between PPI use and fracture. As is suggested in Table 2, PPI users were significantly more likely to use other medications known to negatively influence BMD, and were also more likely to have rheumatoid arthritis, COPD, thyroid disease, chronic renal disease, or inflammatory bowel disease.

In contrast, as only 0.9% of the sample used PPIs continuously over the 10 years of the study, we may not have had sufficient power to detect a clinically significant change in BMD associated with PPI use. However, even in the y5–y10 analysis, during which time 4.3 % of subjects were continuous PPI users, our findings do not support a clinically significant effect of PPI use on the rate of BMD change (e.g., mean femoral neck loss -0.3% over 5 years with the lower limit of the 95% confidence interval -1.4%). Another possible explanation is that the majority of any negative effect on BMD occurs relatively soon after initiation of PPI therapy, and thus the failure to detect further changes in the BMD over time among those who continued to use PPIs was due to a ceiling effect. Some of the prior research studying the relationship between PPI use and fractures detected an increase in fracture risk early in the course of therapy with no further increases over time, while others have shown greater increases in risk with longer durations of use (12,25).

Though there have been many papers discussing the possible relationship between PPI use and osteoporosis-related fracture, there is a relative paucity of the published research concerning the association of PPI use with the development of osteoporosis based on DXA-measured BMD, the structural defect which most commonly predisposes to the development of fragility fracture. Yu *et al.* (8) used prospectively collected data from the Osteoporotic Fractures in Men Study (MrOS) and the Study of Osteoporotic Fractures (SOF, women only) to study the effects of PPI use on BMD over time, and observed no significant difference in the annualized rate of total hip BMD decline between PPI users and non-users (MrOS: -0.70% per year vs. -0.48% per year, $P=0.08$; SOF: -0.38% per year vs. -0.34% per year, $P>0.2$). In MrOS, PPI use at baseline was associated with a borderline difference in baseline BMD at the total hip (PPI user vs. non-user: 0.946 vs. 0.958g/cm^2 , $P=0.05$), whereas the total hip difference in BMD at baseline in SOF was not significant (PPI user vs. non-user, 0.729 vs. 0.736g/cm^2 , $P>0.2$). Gray *et al.* (20) analyzed data from the Women's Health Initiative and determined that both PPI users and non-users had an increase in BMD at the total hip from baseline to year 3, but the annualized rate in BMD increase was significantly lower among PPI users than non-PPI users (0.21% per year vs. 0.45% per year, $P=0.05$). Finally, a retrospective analysis of a large clinical DXA registry in Manitoba, Canada, found no relationship between BMD measurement at the lumbar spine or total hip and cumulative PPI exposure in the 5 years before BMD testing (19); furthermore, PPI use was not associated with a more rapid rate of BMD decline among subjects who received a follow-up DXA 1–3 years following the initial test.

Taking the results of these previous studies and the current analysis into account, the weight of the evidence suggests an absence of an association between PPI use and BMD change over time. This further increases the likelihood that the reported association between PPI and fractures may represent baseline differences in fracture risk between PPI users and non-users, which are unrelated to the actual use of the medication.

Further supporting our finding is the lack of a definitive physiologic mechanism through which PPI use would negatively affect BMD. It had long been assumed that PPIs decrease the fractional absorption of calcium by decreasing the solubility of ingested calcium salts (26,27). Over time, this might promote secondary hyperparathyroidism and osteoclast activation, which in turn can promote increased bone turnover and accelerated BMD decline (28). Studies in animal models have also suggested that PPI-induced hypergastrinemia may also promote hypertrophy of the parathyroid glands (29,30). While PPIs have been shown to cause decreased bone mass in adolescent rats (31), there have yet to be any human studies which have demonstrated that PPI use is associated with significant bone loss (32). However, the only studies that have demonstrated decreased calcium absorption among PPI users have been those that specifically assessed absorption of supplemental calcium carbonate in fasting individuals (26,27). In all other scenarios using different formulations of supplemental calcium or calcium ingestion associated with meals, no effects of PPIs on calcium absorption have been shown (33–35). It remains possible, nevertheless, that very marginal decrements in net calcium absorption may, over long periods of time, induce a large enough net calcium loss to cause clinically meaningful reductions in BMD (36). In other studies, PPIs have been shown, *in vitro*, to directly inhibit osteoclast function through a blockade of the vacuolar proton pump located on the osteoclast ruffled border, and therefore may prevent bone resorption and potentially actually increase BMD (37). Further to this point, people with congenital osteopetrosis, who do not express the vacuolar proton pump, develop marked cortical thickening and increased BMD, yet have a significantly increased risk of fracture (38). Nevertheless, there is currently no evidence of a direct effect of PPIs on osteoclast activity *in vivo*. Therefore, while there are putative lines of evidence to suggest that chronic PPI use may affect bone metabolism, the precise mechanism through which PPIs may affect bone turnover and BMD remains unexplained.

This study has several notable strengths. Other studies of the relationship between PPI use and BMD have been performed in restricted populations. The SOF and MrOS cohorts were not drawn from population-based data sources, and were restricted in enrollment to women or men over the age of 65 years; the previous study using the Manitoba DXA registry was based on a population referred for BMD testing. CaMos enrolled randomly sampled participants from across the age spectrum, and therefore the results obtained from this study may be more generalizable to the general population. The study population in CaMos had up to 10 years of follow-up, allowing for detection of small changes that may accrue over time. CaMos also captures nearly all of the factors that may potentially influence BMD, making it less likely that there was omission of significant confounders, which might importantly bias the results.

This analysis also had limitations that are worthy of mention. Although attempts were made to capture a study population representative of the Canadian population at large, the potential for subject recruitment and retention bias still exists. However, previous analyses have suggested that the composition of the non-responding population was similar to those who have enrolled, and there is little reason to believe that PPI use/non-use would have influenced the decision to enroll or drop-out, making it an unlikely source of bias (21). Second, as data on the past medical history, diet, smoking, and alcohol use was based on self-report, there is the potential for misreporting biases. It is also possible that, as PPI use

was only queried at specific time points, subjects who reported PPI use at the y5 or y10 were using PPIs only recently, or perhaps were using them discontinuously, mitigating against any deleterious effects on BMD. Furthermore, our inability to determine whether or not PPIs were being utilized in between survey points may potentially lead to misclassification, which may bias our results toward minimizing the presence of a true drug effect. Further prospective research may be required to better delineate the relationship between the timing and duration of PPI use on BMD. Once again, any misclassification is unlikely to be related to PPI use, and thus any bias would likely be toward the null, i.e., a lack of effect. Finally, as subjects were aware that they were part of a prospective cohort studying BMD-related outcomes, they may have adopted behaviors or made health-care choices that they would not have made if they were not participating in a study on osteoporosis. Participants in CaMos have higher rates of osteoprotective medication use than in the general population, and also report higher mean intakes of calcium and Vitamin D. However, none of these choices should influence the direct effect of PPIs on BMD, an objectively measured outcome. Thus, although we believe that some limitations are present, they do not greatly affect the validity of our findings.

In conclusion, PPI use is associated with lower baseline femoral neck and total hip BMD values, but there does not appear to be an increased rate of BMD loss on subsequent measurements extending out to 10 years. These findings provide support for the view that PPI use does not have a significant effect on bone mineral loss, and that the increase in PPI-associated fracture risk described in other studies may be due to residual confounding, or alternatively, a BMD-independent cause for fracture. Further studies to better delineate or rule out potential mechanisms through which PPIs may affect bone strength or fracture risk are needed to provide additional evidence about whether PPIs truly have a clinically meaningful, direct relationship with bone health.

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APPENDIX

CaMos Research Group

David Goltzman (co-principal investigator, McGill University, Montreal), Nancy Kreiger (co-principal investigator, University of Toronto, Toronto), Alan Tenenhouse (principal investigator emeritus, Toronto).

CaMos Coordinating Centre, McGill University, Montreal, Quebec: Suzette Poliquin (national coordinator), Suzanne Godmaire (research assistant), Claudie Berger (study statistician).

Memorial University, St John's Newfoundland: Carol Joyce (director), Christopher Kovacs (co-director), Emma Sheppard (coordinator).

Dalhousie University, Halifax, Nova Scotia: Susan Kirkland, Stephanie Kaiser (co-directors), Barbara Stanfield (coordinator).

Laval University, Quebec City, Quebec: Jacques P. Brown (director), Louis Bessette (co-director), Marc Gendreau (coordinator).

Queen's University, Kingston, Ontario: Tassos Anastassiades (director), Tanveer Towheed (co-director), Barbara Matthews (coordinator).

University of Toronto, Toronto, Ontario: Bob Josse (director), Sophie Jamal (co-director), Tim Murray (past director), Barbara Gardner-Bray (coordinator).

McMaster University, Hamilton, Ontario: Jonathan D. Adachi (director), Alexandra Papaioannou (co-director), Laura Pickard (coordinator).

University of Saskatchewan, Saskatoon, Saskatchewan: Wojciech P. Olszynski (director), K. Shawn Davison (co-director), Jola Thingvold (coordinator).

University of Calgary, Calgary, Alberta: David A. Hanley (director), Jane Allan (coordinator).

University of British Columbia, Vancouver, British Columbia: Jerilynn C. Prior (director), Millan Patel (co-director), Brian Lentle (radiologist), Yvette Vigna (coordinator).

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Proton pump inhibitor (PPI) use has been associated with an increased risk of osteoporosis-related fractures of the hip and spine in multiple previous studies.
- There is no established mechanism through which PPIs might affect fracture risk.
- The effects of PPIs on change in bone mineral density (BMD) potentially leading to low BMD, which predisposes individuals to fracture, has never been studied prospectively in a population-based sample.

WHAT IS NEW HERE

- Proton pump inhibitor (PPI) use was associated with a lower bone mineral density (BMD) at baseline measurement.
- After 10 years of follow-up, PPI use was not associated with an increased rate of BMD loss, after adjustment for multiple potential confounders.

Figure 1. Unadjusted cross-sectional bone mineral density at baseline for proton pump inhibitor (PPI) users and non-users.

Table 1

Characteristics of Canadian Multicentre Osteoporosis Study population at each time point

	Year 0 (N=8,340)	Year 5 (N=6,458)	Year 10 (N=4,512)
<i>Demographics</i>			
Age at enrollment (years)	61.0±13.0	59.9±12.1	58.0±11.6
% women	68.9	70.2	70.8
<i>Anthropomorphics</i>			
Weight (kg)	72.8±14.7	73.1±14.9	73.2±15.2
Body mass index (kg/m ²)	27.0±4.7	27.3±4.8	27.3±4.9
Body mass index (kg/m ²)	n/a	+ 0.43±2.02	+ 0.42±2.52
<i>Dietary factors</i>			
Calcium intake (mg/day)	1,001±605	1,260±717	1,293±727
% 1,200 mg/day	29.3	41.0	44.1
Vitamin D intake (IU/day)	264±564	376±864	546±866
% 400 IU/day	24.4	45.7	36.7
History of low trauma fracture (%)	18.4	18.0	16.9
Family history of fracture (%)	65.6	72.4	76.7
History of falls (%)	6.5	29.4	43.8
<i>Concurrent medical conditions (%)</i>			
Rheumatoid arthritis	5.5	7.3	7.1
Inflammatory bowel disease	5.3	8.9	9.4
Thyroid disease	12.9	13.7	13.5
COPD	7.6	13.8	15.2
Chronic kidney disease	1.5	2.4	2.4
Chronic liver disease	2.5	3.8	4.1
Heavy alcohol use (> 14/week)	7.6	11.0	13.4
Smoking (active)	15.3	15.2	14.6
<i>Medication use (%)</i>			
PPIs (all time points)	2.7 (y0 only)	1.6 (y0 and y5)	0.9 (y0, y5, and y10)
PPIs (current time point)	2.7	7.6	11.5
Menopausal hormone therapy ^a	24.0	29.4	11.5
Bisphosphonates	1.5	13.3	19.4
SERMs	0.1	1.2	2.0
Glucocorticoids	1.2	1.3	1.1
Thiazide diuretics	9.6	17.6	22.2
β-Blockers	8.4	15.2	16.6
Nitrates	3.2	4.0	4.2
SSRIs	2.8	6.1	7.8
Anti-epileptics	0.6	1.3	1.5

	Year 0 (N=8,340)	Year 5 (N=6,458)	Year 10 (N=4,512)
Tamoxifen ^a	1.3	1.6	1.9

Abbreviations: PPI, proton pump inhibitor; SERMs, selective estrogen receptor modulators; SSRIs, selective serotonin receptor inhibitors.

^aPercentage of women only.

Table 2

Comparison of characteristics of proton pump inhibitor (PPI) users and non-users at baseline in the Canadian Multicentre Osteoporosis Study cohort

	PPI users (N=228)	Non-PPI users (N=8,112)	P value
<i>Demographics</i>			
Age	66.3	60.9	< 0.001
% women	79.4	68.6	< 0.001
<i>Anthropomorphics</i>			
Weight (kg)	74.5	72.8	0.091
Body mass index (kg/m ²)	28.3	26.9	< 0.001
<i>Dietary factors</i>			
Calcium intake	1,086	999	0.050
% 1,200 mg/day	34.6	29.1	0.076
Vitamin D intake	434	249	0.021
% 400 IU/day	26.8	24.4	> 0.2
Personal history of low trauma fracture	24.8	18.3	0.015
Family history of fracture (%)	71.1	65.5	0.090
History of falls (%)	7.5	6.4	> 0.2
<i>Concurrent medical conditions (%)</i>			
Rheumatoid arthritis	12.1	5.4	< 0.001
Inflammatory bowel disease	10.1	5.2	0.003
Thyroid disease	18.9	12.8	0.009
COPD	14.9	9.0	0.008
Chronic kidney disease	3.9	1.4	0.007
Chronic liver disease	2.5	2.2	> 0.2
Heavy alcohol use (> 14/week)	6.6	7.6	> 0.2
Current smoking	57.0	52.9	> 0.2
<i>Concurrent medication use (%)</i>			
Hormone replacement therapy ^a	26.0	24.0	> 0.2
Bisphosphonates	3.0	1.3	0.046
Selective estrogen receptor modulators ^a	0.0	0.2	> 0.2
Glucocorticoids	4.4	1.1	< 0.001
Thiazide diuretics	16.2	9.4	< 0.001
β-Blockers	13.2	8.3	0.015
Nitrates	8.3	3.0	< 0.001
Selective serotonin reuptake inhibitors	8.3	2.7	< 0.001
Anti-epileptics	0.9	0.6	> 0.2
Tamoxifen	0.9	1.0	> 0.2

COPD, chronic obstructive pulmonary disease.

^aPercentage of women in the population only.

Table 3

Association of proton pump inhibitor (PPI) use at baseline and adjusted bone mineral density at each measurement site

	Total hip	Femoral neck	Lumbar spine
PPI use at baseline	−0.019 g/cm ² (−0.035, −0.002)	−0.022 g/cm ² (−0.037, −0.008)	−0.014 g/cm ² (−0.035, 0.007)
PPI use at baseline (glucocorticoid and osteoprotective medicine*users excluded)	−0.026 g/cm ² (−0.044, −0.006)	−0.026 g/cm ² (−0.042, −0.010)	−0.016 g/cm ² (−0.040, 0.006)

Abbreviations: BMD, bone mineral density; SERMs, selective estrogen receptor modulators; SSRIs, selective serotonin receptor inhibitors.

Linear regression models controlled for the following variables at year 0: age (grouped in 10 year intervals), sex, age–sex interactions, body mass index, calcium intake, Vitamin D intake; report of: rheumatoid arthritis, inflammatory bowel disease, chronic kidney disease, chronic liver disease, hyper- and hypothyroidism; and use of: bisphosphonates, hormone replacement therapy, SERMs, calcitonin, tamoxifen, β -blockers, nitrates, SSRIs, thiazide diuretics, anti-epileptics; current smoking, and heavy alcohol use. Results are expressed as the mean difference in year 0 BMD attributable to PPI use. Shaded results are statistically significant ($P < 0.05$).

Table 4
Effects of proton pump inhibitors (PPIs), other medications, and calcium and vitamin D intake on longitudinal changes in BMD

	Total hip			Femoral neck		Lumbar spine	
	Attributable change in BMD (years 0–5)	Attributable change in BMD (years 5–10)	Attributable change in BMD (years 0–10)	Attributable change in BMD (years 0–5)	Attributable change in BMD (years 5–10)	Attributable change in BMD (years 0–5)	Attributable change in BMD (years 5–10)
<i>PPI use</i>							
Continuous PPI use All subjects	0.5% (–0.5%, 1.5%)	–0.2% (–1.2%, 0.7%)	0.9% (–1.0%, 2.9%)	–0.3% (–1.4%, 0.8%)	–0.5% (–2.9%, 1.8%)	–0.7% (–2.0%, 0.5%)	0.2% (–0.9%, 1.3%)
Continuous PPI use Subjects 50 only	0.7% (–0.4%, 1.7%)	–0.2% (1.3%, 0.8%)	0.1% (–2.0%, 2.2%)	–0.3% (–1.5%, 0.9%)	–0.9% (–3.4%, 1.6%)	–0.8% (–2.1%, 0.6%)	0.4% (–0.8%, 1.7%)
Continuous PPI use Users of GCs/ HRT/Ops excl.	1.1% (–0.1%, 1.3%)	–0.3% (–1.4%, 0.9%)	–0.9% (–3.7%, 1.5%)	–0.4% (–1.9%, 1.2%)	–0.7% (–3.8%, 2.2%)	–0.4% (–1.9%, 1.1%)	1.1% (–0.3%, 2.5%)
Current PPI use	–0.4% (–1.0%, 0.4%)	–0.6% (–1.1%, 0.0%)	–0.5% (–1.1%, 0.2%)	–0.1% (–0.5%, 0.4%)	–0.6% (–1.4%, 0.1%)	–0.2% (–0.8%, 0.4%)	–0.4% (–1.2%, 0.3%)
<i>Other medications, calcium, and vitamin D</i>							
Current glucocorticoid use	–1.5% (–2.5%, –0.5%)	–1.1% (–2.5%, 0.5%)	–2.5% (–4.2%, –0.8%)	–1.3% (–2.5%, –0.0%)	–0.3% (–2.2%, 1.7%)	–0.2% (–1.4%, 1.1%)	–0.7% (–2.6%, 1.1%)
Current bisphosphonate use	2.7% (2.4%, 3.1%)	3.0% (2.6%, 3.4%)	3.8% (3.3%, 4.3%)	2.7% (2.3%, 3.2%)	3.7% (3.1%, 4.3%)	3.9% (3.5%, 4.4%)	3.6% (3.1%, 4.2%)
Current hormone replacement therapy use	2.7% (2.4%, 3.0%)	2.1% (1.5%, 2.7%)	3.4% (2.7%, 4.1%)	2.6% (2.3%, 3.0%)	3.3% (2.5%, 4.1%)	3.3% (2.9%, 3.7%)	2.2% (1.4%, 2.9%)
Calcium intake 1,200 mg/day	0.1% (–0.2%, 0.0%)	–0.0% (–0.4%, 0.4%)	0.3% (–0.1%, 0.7%)	0.2% (–0.1%, 0.5%)	0.1% (–0.3%, 0.6%)	0.0% (–0.3%, 0.3%)	0.0% (–0.4%, 0.5%)
Vitamin D intake 400 IU/day	0.4% (0.2%, 0.7%)	0.0% (–0.3%, 0.4%)	0.4% (–0.1%, 0.8%)	0.4% (0.1%, 0.7%)	0.1% (–0.2%, 0.8%)	0.1% (–0.2%, 0.4%)	0.2% (–0.2%, 0.6%)
Current thiazide use	0.4% (0.1%, 0.8%)	0.1% (–0.3%, 0.6%)	0.9% (0.4%, 1.4%)	0.6% (0.1%, 1.0%)	–0.1% (–0.7%, 0.4%)	0.9% (0.5%, 1.3%)	0.5% (–0.1%, 1.1%)
Current SSRI use	–0.6% (–1.2%, –0.1%)	0.5% (–0.3%, 1.3%)	0.1% (–0.8%, 0.9%)	–0.6% (–1.2%, 0.1%)	0.9% (–0.1%, 1.9%)	0.2% (–0.4%, 0.9%)	–0.2% (–1.2%, 0.8%)

Abbreviations: BMD, bone mineral density; BMI, body mass index; GC, glucocorticoid; HT, hormone therapy; SERMs, selective estrogen receptor modulators; SSRIs, selective serotonin receptor inhibitors.

Linear regression models controlled for: age (grouped in 10-year intervals), sex, BMI at baseline, change in BMI, calcium intake, Vitamin D intake, report of: rheumatoid arthritis, inflammatory bowel disease, chronic kidney disease, chronic liver disease, hyper- and hypothyroidism, and use of: bisphosphonates, hormone replacement therapy, SERMs, calcitonin, tamoxifen, β -blockers, nitrates, SSRIs, thiazide diuretics, anti-epileptics, smoking, and heavy alcohol use. Results are expressed as the mean percentage change from the baseline BMD. Bolded results are statistically significant ($P < 0.05$).