Proton pump inhibitors and the risk of fractures in older adults: a population-based retrospective cohort study

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Abstract

Proton pump inhibitors and the risk of fractures in a population of older adults

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OBJECTIVES: To examine the association between proton pump inhibitor (PPI) use and the incidence of fractures.

DESIGN: Prospective population-based cohort

SETTING: Group Health, an integrated health maintenance organization in Seattle, WA using data from 1994-2014.

PARTICIPANTS: Four thousand four hundred and forty-one participants aged 65 and older who had not sustained a fracture in the year prior to study enrollment.

MEASUREMENTS: Follow-up occurred every 2 years to identify incident fractures using ICD-9 codes from medical records for fractures of the hip, forearm, humerus, clavicle or scapula, rib or sternum, tibia or fibula, or ankle. Exposure to PPIs was determined from automated pharmacy data. Cumulative exposure (time-varying) was examined based on summing SDDs across all fills.

RESULTS: Over a mean follow-up of 5.9 years, 764 subjects experienced a fracture. No overall association was found between cumulative PPI use and risk of fracture . The adjusted HR comparing various groups to the reference group (≤ 30 standard daily doses (SDD)) was 1.08 (95% CI 0.83-1.42) for those with little use (31-540 SDD), 1.41 (95% CI 0.94-2.14) for moderate use (541-1080 SDD), and 1.10 (95% CI 0.78-1.55) for heavy use (≥1081 SDD).

CONCLUSION: No association was found between PPI use and risk of fractures among older adults .

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Introduction

Proton pump inhibitors (PPIs), introduced into practice in the 1980s, are used to treat gastroesophageal reflux (GERD) and gastric or duodenal ulcers.[1] In the US, six PPIs (omeprazole, pantoprozole, esomeprazole, lansoprazole, rabeprazole, dexlansoprazole) are currently available with a prescription and three of these (omeprazole, esomeprazole, and lansoprazole) are also available over the counter (OTC). About a third of the adult population in the United States utilizes PPIs, making them among the most commonly used drugs.[2, 3] Not only has the use of PPIs increased since omeprazole became available OTC in 2003, in recent years the duration of prescription use has also increased, with numerous people now taking these medications for several years or longer.[4]

Fractures are a critically important outcome for older adults because these events often give rise to severe complications or even mortality.[5-7] It has been hypothesized that the use of PPIs increases the risk of fractures[8]. PPI medications target hydrogen and potassium ATPase pumps, of the gastric parietal cells, resulting in decreased stomach acidity. PPIs are thought to diminish bone mineral density (BMD) through their effects on stomach acidity and the consequent reduction in the absorption of calcium. If BMD is reduced as a result of the use of PPIs, people may be more susceptible to a fracture. However, to date, studies of people using PPIs have not found changes in BMD to support this mechanism of action.[9, 10]

In addition to mechanistic uncertainties, the presence and magnitude of an association between PPI use and fractures in the epidemiologic literature is inconsistent, with some studies reporting evidence of an increased fracture risk [2, 4, 9] and others finding no association. [11] Of those studies that observed an increased risk of fractures, multiple found associations with short-term PPI use of one year or less.[12, 13] However, the mechanism described previously would have a long induction period before clinically measurable effects on BMD or fracture risk would appear, making the presence of a causal influence with rapid onset implausible.

The reasons for discrepant results among epidemiologic studies are not clear. A limitation of prior longitudinal studies is the lack of detailed information on dose, inaccurate means of identifying exposure status between follow-up visits, and reliance on self-reported use. Additionally, many of the administrative data sources used previously did not allow for adequate control of likely confounders such as concomitant medication use and smoking status. The present study draws on data from a prospective cohort study set within an integrated health care system with electronic pharmacy data extending back to 1977, allowing the measurement of PPI exposure, health behaviors, functional status measures, and medical histories of study participants so as to enhance our ability to control for confounding factors.

Our primary aim was to examine the association between PPI use and the incidence of fractures.

Methods

This study utilized data from a prospective cohort of older adults enrolled in Group Health (GH), an integrated healthcare delivery system with approximately 600,000 members residing in the Pacific Northwest. The demographic characteristics of GH members are similar to those of residents of the surrounding region. The exposure of interest was cumulative use of proton pump inhibitor (PPI) medication, and the outcome of interest was a fracture of the hip, forearm, humerus, clavicle or scapula, rib or sternum, tibia or fibula, or ankle. Outcomes were measured based on the presence of one or more relevant International Classification of Diseases, Ninth Revision (ICD-9) codes from emergency department records, inpatient information, and data on outpatient visits.

Overview and setting

Participants were part of the Adult Changes in Thought (ACT) cohort, a prospective cohort study whose main goal has been to study incident dementia. ACT study methods have been described in detail

elsewhere. (14) Briefly, study participants were randomly sampled from Seattle-area members of GH who were aged 65 years and older. The original cohort of 2,581 cognitively-intact men and women was enrolled between 1994 and 1996, followed by an additional 811 participants who were enrolled between 2000 and 2002 (the "expansion cohort"). Then, in 2004, the study began continuous enrollment (n=1,555 available for this study) to replace those who died or dropped out, resulting in a total of 4,947 enrolled participants as of the end of April 2014 who were available for this study.
For the current analyses, participants were required to have had at least 5 years of continuous GH membership before baseline to ensure more complete capture of PPI exposure. Additionally, participants with record of a fracture of interest within one year prior to baseline were excluded in order to ensure that only incident fracture events were included. Applying these inclusion criteria yielded 4,441 participants (see Figure 1). This research was approved by the Group Health Human Subjects Review board.

Exposure measurement

The GH pharmacy database includes all prescriptions dispensed from March 1977 to the present including drug name, strength, and amount dispensed. It includes prescription fills at GH pharmacies and from outside pharmacies (for which information is obtained via claims). In prior studies, 96% of older GH members have reported filling all or most of their prescriptions at a GH pharmacy. [(15)] The exposure of interest was cumulative use of any PPI medication (Supplemental Table). In order to calculate cumulative use, we first converted each prescription to standard daily doses (SDDs) by multiplying the number of tablets dispensed by the tablet strength and then dividing by the equivalent daily dose for each PPI prescription.[(16)] We then summed across all prescriptions starting 5 years prior to baseline and extending until end of study or a censoring event for all participants to derive a measure of total cumulative use. This resulted in a time-varying measure that was non-decreasing and would reflect changes as person moved through study time and accrued exposure. Cumulative exposure was used

because this measure has the most biologic plausibility for influencing fracture risk. We categorized participants into the following categories based on cumulative use: ≤30 SDD, 31-540 SDD, 541-1,080 SDD, ≥1,081 SDD, which corresponds to <1 month, 1-18 months, 19-36 months, or >36 months of daily PPI use at the SDD. In addition to pharmacy data, self-reported PPI use was collected at each follow-up interview, thereby allowing us to investigate whether any participants had reported OTC PPI use that was not identified through the electronic pharmacy records. We found that less than 5% of participants reported OTC PPI use that was not captured in pharmacy records.

Ascertainment of fracture

We identified all participants who experienced a fracture of the forearm (radius, ulna, wrist), humerus, clavicle or scapula, rib or sternum, tibia or fibula, ankle, or hip during follow-up. These fracture sites were chosen because prior work at GH has shown that all of these sites, with the exception of hip, have high positive predictive values (>80% PPV). Hip fractures were included because they have a moderately high PPV (73%), and they are very clinically important.[17] . Information on fracture events was found using electronic health data by searching for ICD-9 codes 807, 810-814,820, 823, and 824. A fracture was defined based on one or more relevant fracture code(s) found in inpatient, outpatient or emergency department records.

Potential confounders

At study baseline and at all ACT study follow-up visits, information was collected on demographic characteristics (age, sex, race), self-reported medical history, other health-related factors, and measures of functional status. Additionally we adjusted for the cohort participants belonged to (original, replacement, or expansion) to help control for possible differences by calendar year. Medical history included self-reported data on epilepsy, vision problems, stroke, congestive heart failure, and coronary heart disease (CHD), defined as self-report of myocardial infarction, angina, CABG, or angioplasty at this or any prior ACT visit. Pharmacy data were used to characterize treated diabetes or

hypertension based on a history of 2 or more pharmacy fills for antihypertensive medications or fills for insulin or other oral diabetes medications in any 12 month period. Health-related factors included body mass index (BMI) calculated from measured height and weight, self-rated health (fair/poor vs. excellent/very good/good), physical activity frequency (≥3x weekly vs. not; complied and categorized responses to questions probing number of self-reported bouts of exercise of 15 or more minutes), smoking, and Deyo-Charlson (DC) comorbidity index score[18]. We also considered depression status for each participant, calculated using the Center for Epidemiological Studies Depression scale (CESD).[19] We used a modification of this tool and defined a person as depressed if their score was 10 or higher. Cognition was measured using the Cognitive Abilities Screening Instrument (CASI). Interviewers also had the option to refer participants for diagnostic work up for cognitive problems if their observations during the study visit suggested impairment might be present. We defined cognitive impairment as present if a participant received a score of 86 or more out of 100 on the CASI or was referred for detailed evaluation for other reasons.[20] The ACT study also collected information about functional status including difficulty with one or more activities of daily living (ADLs) or with one or more instrumental activities of daily living (IADLs). Additionally, low gait speed, defined based on gait speed of less than 0.6 meters/second, was measured because of its implications as a clinical marker for functional capacity in older adults.[21] Information on concomitant medication use was obtained from linked pharmacy data, focusing on medications that have previously been shown in the literature to influence fracture risk. Medication use variables were created in one of two ways to account for those medications that were suspected to impact fracture risk based on either a) a history of past or sustained use or b) medications suspected to impact fracture risk within a relatively short window after use. Using the first method, a person was defined as a user if they had a history of at least two fills for a given medication class. This method was used for the following medication classes: bisphosphonates, corticosteroids, histamine-2 receptor antagonists (H2RAs), and hormone replacement therapy (HRT).

Using the second method, a person was defined as a user if they had fill for a given medication class within the prior 30 days. This method was used for the following medication classes: prescription nonsteroidal anti-inflammatory drugs (NSAIDs), anxiolytics, antidepressants, thiazide diuretics, opioids, and anticonvulsants.

The following characteristics were included as time-varying variables: medical history factors, health behavior factors, and medication use. Information on ADLs, IADLs, and gait speed came from baseline only as we hypothesized that these may be influenced by PPI use and thus could be in the causal pathway.

Statistical analysis

We descriptively characterized the overall cohort by stratifying according to baseline level of PPI use and presented results as means and standard deviations for continuous variables and numbers and proportions for categorical variables. We additionally examined factors associated with PPI exposure by calculating proportions of person-time based on exposure category and participant characteristics. To analyze the association between PPI exposure and risk of fracture, hazard ratios (HRs) from Cox proportional hazards regression models were calculated using time since ACT entry as the time scale. Participants were followed until the first fracture event or censoring event. Censoring events in this analysis include disenrollment from ACT or GH, dementia onset, 1 year after last ACT visit, death or end of ACT study period (April 13, 2014). Participants were censored 1 year after last ACT visit because this ensured that we had covariate information from a recent ACT visit to include in analysis. Dementia onset was included as a censoring event since we believed PPI medication, the risk of fractures, and the possible relationship between the two might be very different in those with dementia. We selected potential confounders for our models a priori, based on review of the literature and clinical plausibility. In our model we adjusted for age, sex, cohort, epilepsy, treated diabetes, treated hypertension, depression, impaired cognition, vision problems, stroke, CHF, CHD, difficulty with ADLs, difficulty with

IADLs, low gait speed, exercise, categories of BMI, smoking, self-rated health, DC comorbidity index, and use of the following medications: bisphosphonates, corticosteroids, prescription NSAIDs, anxiolytics, antidepressants, thiazide diuretics, HRT, H2RAs, prescription opioids and anticonvulsants. Additionally, we estimated whether an association between PPI use and fracture incidence was influenced by age or sex by including an interaction for these two variables and PPI use in two separate models. We used complete case analysis methods. All analyses were performed using STATA version 13. The assumption of proportionality of hazards was tested by examining Schoenfeld residuals.

Results

There were a total of 4441 participants with median age of 81.2 years (interquartile range (IQR) 75.7-86.5) at study entry, and 58% of participants were women. Table 1 provides baseline characteristics of all study participants. Additionally, Table 2 provides a breakdown of the proportion of total person-time based on various participant characteristics and PPI exposure category. Since the exposure was time-varying, each participant was able to contribute person-time to multiple exposure categories depending on changes in cumulative dose of PPI exposure during study follow-up. Less than 5% of data was missing for all variables.

Overall, there were 410 participants (9.2%) with a history of PPI exposure at baseline, with 219 (53.4%) of users having light use (defined as ≤ 30 SDD), 62 (15.1%) of users having moderate use (defined as 21-540 SDD), and 129 (31.5%) of users having high levels (defined as ≥ 1080 SDD) of cumulative PPI exposure. At the last study visit for all participants, there were 1,069 exposed participants with 487 (45.6%) having a history of light use (31-541 SDD), 161 (15.1%) having moderate use (541-1080 SDD), and 421 (39.4%) having high cumulative use (>=1080 SDD). Examining results based on follow up time, there were 22,955 person-years of follow-up during which participants had <=30 SDD (reference group), 2,183 person-years of follow-up time during which participants had light

use, 705 person-years of follow-up time during which participants had moderate use, and 1,548 person years of follow-up time during which participants had high use. Compared to those contributing person-time to the reference group, person-years accumulated during periods of light, moderate, or high levels of PPI exposure were associated with greater comorbidity, adverse health characteristics, and higher levels of concomitant medication use.

Over a mean follow-up of 5.9 years, 764 participants (17.2% of the cohort) experienced a fracture of the hip, forearm, humerus, clavicle or scapula, rib or sternum, tibula or fibula, or ankle. The most common fracture type was hip fracture, comprising 25% of all observed events, followed by forearm fracture (24%), rib and sternum fracture (19%), humerus fracture (13%), ankle fracture (10%), tibia and fibula fracture (6%) and clavicle and scapula fracture (3%). No overall association was found between the categories of cumulative PPI use and risk of fracture in this population. The adjusted HR comparing various groups to the reference group was 1.08 (95% CI 0.83-1.42) for those with little use, 1.41 (95% CI 0.94-2.14) for moderate use, and 1.10 (95% CI 0.78-1.55) for heavy use (Table 3). There was no clear evidence of an association between PPI use and fracture in any subgroup defined by age (> 75 years of age compared to ≤75 years of age) or sex with p value= 0.3447, 0.1835, for a difference in the size of the relative risk by age and sex, respectively (data not shown).

Discussion

In this prospective cohort study of people aged 65 and older, we did not find an association between cumulative PPI use and risk of non-vertebral fracture. Much of the previous literature lacked information on cumulative dose or duration of use, which based on the BMD mechanism of action, is an important factor to consider in PPI and fracture research. One study by Lewis et al. did measure dose of PPIs in relation to risk of fracture-related hospitalizations, using ICD-9 codes to identify fractures, as we did for the current study. They reported an OR of 2.15 (95% CI: 1.21-3.81) among people who had used

PPIs for 1 year or more. However, when they restricted to new-users only, there was no longer an excess risk of fracture-related hospitalizations (OR 0.88 95%CI: 0.45-1.71) Findings from a different, large cohort study also attempted to consider duration of use and found an increased risk of fracture among PPI users of 2-3 years (HR= 1.36 (1.12-1.65) , 4-5 years (HR=1.42 (1.05-1.93) , and 6-8 years (HR=1.55 (1.03-2.32). The association with PPI use was restricted to persons who smoked cigarettes.[4]

Strengths of the present research include the large community-based sample, the average of approximately 6 years of follow-up, and the availability of extensive information on relevant covariates including measures of functional status, smoking status, concomitant medication use and other important covariates. The large community-based sample is beneficial over other studies that have focused on nursing/retirement homes where the participants tend to be sicker or frailer since these settings may limit the generalizability and may induce bias if comorbid conditions are not adequately controlled for. Additionally, having approximately 6 years of average follow-up time was advantageous because it resulted in inclusion of participants who used PPIs for several years at a time, offering us the potential to detect changes in fracture risk that may take several years to become clinically evident. Nonetheless, our observations should be interpreted in light of potential limitations. Residual confounding may have biased the results. For instance, we lacked information about alcohol use, which has been previously shown to be associated with fracture risk.[27] Additionally, misclassification of outcome could have biased results. We attempted to reduce misclassification of the outcome that may have resulted from relying on ICD-9 codes of fractures by limiting the outcome of interest to a sub-set of codes that has been previously shown to have high positive predictive value based on an unpublished validation study within GH (personal communication, Dr. Delia Scholes). Lastly, the findings here may not be generalizable to populations that are dissimilar from the largely white, insured people residing in the Pacific Northwest who are members of GH and included in the current study.

At present it would be premature to conclude that there is an altered risk of fracture associated with use of PPIs.

Figure 1: Flow chart of selection of population for inclusion in study

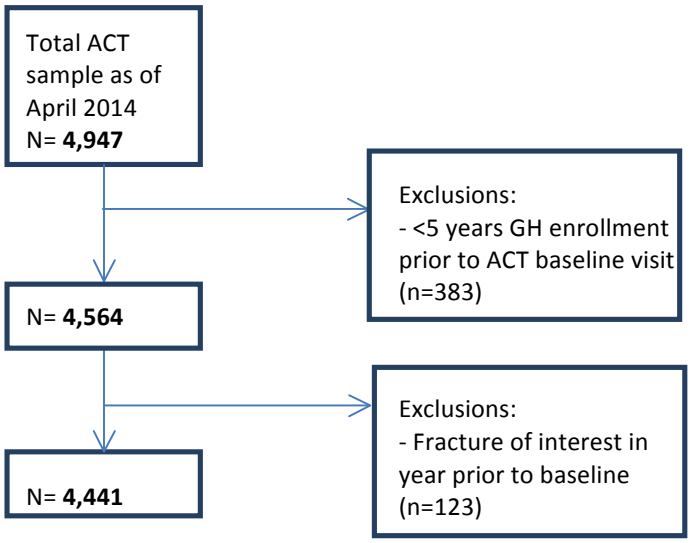

Table 1: Baseline characteristics according to standard daily dose of proton pump inhibitor use before study entry

Characteristic*	**Study participants N= 4,441**
Age, median (25^{th}, 75^{th})	74.0 (69.8, 79.5)
Female	2,578 (58.1)
Race	
White	3,984 (89.8)
Black	168 (3.8)
Asian	138 (3.1)
American Indian/Alaska Native	8 (0.2)
Other, including mixed	138 (3.1)
Cohort	
Original	2,346 (52.8)
Expansion	721 (16.2)
Replacement	1,374 (30.9)
Epilepsy	34 (0.8)
Treated diabetes[†]	390 (8.8)
Treated hypertension[†]	2,437 (54.9)
Depression	424 (9.8)
Impaired cognition	253 (5.7)
Vision problems	658 (15.0)
Stroke	130 (2.9)
Congestive Heart Failure	168 (3.8)
Coronary Artery Disease	797 (18.1)

Low gait speed[§#]	393 (8.9)
Difficulty with ≥1 ADL[¶#]	954 (21.6)
Difficulty with ≥1 IADL[¶#]	655 (14.8)
Regular exercise[x]	3,136 (70.8)
BMI	
<18.5 (underweight)	46 (1.1)
18.5-24.9 (normal)	1,424 (32.5)
25.0-29.9 (overweight)	1,770 (40.4)
≥30.0 (obese)	1,146 (26.1)
Smoking	
Never	2,141 (48.3)
Former	2,068 (46.7)
Current	220 (5.0)
Fair or poor self-rated health	677 (15.3)
Charlson comorbidity index	
0	2,904 (65.4)
1	760 (17.1)
2	494 (11.1)
3+	283 (6.4)
Medication use	
Recent or current use	
Opioids[‡]	194 (4.4)
Anticonvulsants[‡]	47 (1.1)

Anxiolytics[‡]	124 (2.8)
Prescription NSAIDs[‡]	217 (4.9)
Antidepressants[‡]	254 (5.7)
Thiazide diuretics[‡]	302 (6.8)
Sustained use	
Bisphosphonates[†]	235 (5.3)
Corticosteroids[†]	2,268 (51.1)
H2RAs[†]	869 (19.6)
Hormone therapy (limited to women)[†]	925 (20.8)

Abbreviations: BMI, body mass index; ADL, activities of daily living; IADL, instrumental activities of daily living, H2RA, histamine type2 receptor antagonist, NSAID, nonsteroidal anti-inflammatory drug

*Results are provided as n (%) unless otherwise stated. Less than 5% of people had missing values for all characteristics

[§]Based on walk speed of <0.6 meters/second

[¶]Defined as having trouble with ≥1 ADL or IADL

[x] Defined as ≥15min of activity 3x/week

[‡]Defined from computerized pharmacy data as having a fill within the prior 30 days

[†]Defined from computerized pharmacy data as filling at least 2 prescriptions for a medication in this class

Table 2: Characteristics associated with varying levels of PPI exposure: proportion of accumulated person time

Characteristic*	≤ 30 SDD (n=22,955 person-years)	31-540 SDD (n=2,183 person-years)	541-1080 SDD (n= 705 person-years)	≥ 1080 SDD (n= 1,548 person-years)
Age (years)				
65-69	7.7	5.0	3.3	4.6
70-74	23.5	17.8	15.9	16.0
75-79	28.4	26.9	26.5	21.9
80-84	22.9	26.9	30.6	27.8
≥ 85	17.5	25.6	24.0	29.5
Female	57.7	64.6	55.0	57.6
Race				
White	90.0	88.1	89.2	88.3
Black	4.0	3.5	4.8	6.1
Asian	3.5	2.9	2.7	2.5
American Indian/Alaska Native	0.1	0.3	0.3	0.5
Other, including mixed	2.4	5.2	2.3	2.7
Cohort				
Original	68.0	50.4	52.5	41.3
Expansion	16.5	23.0	19.3	23.7
Replacement	15.5	26.6	28.4	35.0
Epilepsy	0.6	0.7	0.0	0.0
Treated diabetes[†]	9.8	12.1	12.9	12.3
Treated hypertension[†]	63.5	78.2	79.2	84.8

Depression	7.8	10.9	11.2	11.8
Impaired cognition	4.8	6.0	5.8	6.3
Vision problems	26.3	31.5	36.3	32.6
Stroke	3.2	6.4	6.5	3.6
Congestive Heart Failure	4.7	7.4	8.4	13.1
Coronary Artery Disease	19.9	33.1	33.9	37.1
Low gait speed[§#]	6.2	8.7	9.1	8.1
Difficulty with ≥1 ADL[¶#]	17.5	24.8	24.7	28.6
Difficulty with ≥1 IADL[¶#]	11.1	14.9	15.5	16.0
Regular exercise[x]	66.1	60.7	57.7	58.5
BMI				
<18.5 (underweight)	1.0	0.7	1.1	0.2
18.5-24.9 (normal)	33.2	29.5	29.2	25.9
25.0-29.9 (overweight)	41.0	42.3	42.0	46.1
≥30.0 (obese)	24.5	27.3	27.1	26.2
Smoking				
Never	49.0	48.4	40.6	47.2
Former	46.4	48.6	57.2	50.5
Current	4.1	1.7	1.3	1.4
Fair or poor self-rated health	14.0	20.9	25.7	21.6
Charlson comorbidity index				
0	63.6	45.6	44.0	41.5
1	17.6	22.5	22.4	22.0

2	11.3	15.6	14.3	15.4
3+	7.4	16.3	19.3	21.1
Medication use				
Recent or current use				
Opioids[‡]	2.8	6.6	6.0	8.2
Anticonvulsants[‡]	0.7	0.9	0.4	1.1
Anxiolytics[‡]	2.0	3.8	2.8	2.5
Prescription NSAIDs[‡]	5.2	5.9	6.1	9.2
Antidepressants[‡]	4.2	7.9	7.7	9.7
Thiazide diuretics[‡]	6.0	5.8	6.0	8.5
Sustained use				
Bisphosphonates[†]	8.0	17.0	18.3	19.8
Corticosteroids[†]	64.7	81.3	83.4	86.0
H2RAs[†]	21.7	61.3	71.2	67.6
Hormone therapy (limited to women)[†]	26.3	33.9	31.6	33.1

Abbreviations: BMI, body mass index; ADL, activities of daily living; IADL, instrumental activities of daily living, H2RA, histamine type2 receptor antagonist, NSAID, nonsteroidal anti-inflammatory drug

*Results are provided as n (%) unless otherwise stated. Less than 5% of people had missing values for all characteristics

[§]Based on walk speed of <0.6 meters/second

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[‡]Defined from computerized pharmacy data as having a fill within the prior 30 days

[†]Defined from computerized pharmacy data as filling at least 2 prescriptions for a medication in this class

[#] Ascertained at baseline

Table 3: Risk of fractures associated with PPI exposure

Total cumulative use, SDDs	Follow-up time (person-years)	Number of Events	Incidence (per 1000 person-years)	Hazard ratio (95% confidence interval)	
				Age - adjusted	Fully adjusted[‡]
No use, ≤30	22,955	609	26.5	1.00 (Ref.)	1.00 (Ref.)
Light use, 31-540	2,183	73	33.4	1.18 (0.92-1.51)	1.08 (0.83-1.42)
Moderate use, 541-1080	705	30	42.6	1.52 (1.05-2.20)	1.41 (0.94-2.14)
High use, ≥1081	1,548	52	33.6	1.18 (0.89-1.57)	1.02 (0.72-1.44)

[‡]adjusted for age, sex, ACT study cohort, epilepsy, treated diabetes, treated hypertension, depression, impaired cognition, vision problems, stroke, CHF, CAD, low gait speed, difficulty with ADLs, difficulty with IADLs, exercise, BMI, smoking, self-rated health, Charlson comorbidity index, and use of prescription opioids, anticonvulsants, anxiolytics, NSAIDs, antidepressants, thiazide diuretics, bisphosphonates, corticosteroids, H2RAs and HRT.

Supplemental Table: Proton pump inhibitor medications and their standardized daily dose equivalences [16]

	Total standard daily doses (mg)	Date became available over the counter	Over the counter dose (mg)
Omeprazole	20	6-20-2003	20
Pantoprozole	40		
Esomeprazole	20	3-28-2014	20
Lansoprazole	30	5-18-2009	15
Rabeprazole	20		
Dexlansoprazole	30		

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