Proton Pump Inhibitors and Histamine-2 Receptor Antagonists Are Associated With Hip Fractures Among At-Risk Patients

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BACKGROUND & AIMS: Drugs that inhibit gastric acid might increase the risk of hip fracture. However, little long-term exposure data exist and no large studies have been conducted in the United States. **METHODS:** We conducted a case-control study using data from an integrated health services organization. We evaluated 33,752 patients with incident diagnoses of hip/femur fractures (cases), 130,471 matched members without fractures (controls), prescription data for use of proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) (up to 10 years' cumulative duration), and confounders. **RESULTS:** Patients with hip fractures were more likely than controls to have previously received a ≥2-year supply of PPIs (odds ratio [OR], 1.30; 95% confidence interval [CI], 1.21–1.39) or H2RAs (OR, 1.18; 95% CI, 1.08–1.29). The risk was reduced after discontinuation of medication (OR of 1.30 [95% CI, 1.21–1.41] for current PPI users vs OR of 1.09 [95% CI, 0.64–1.85] for patients who received their last prescription 2–2.9 years ago). Higher dosages (but not increasing cumulative durations) were associated with increased risk (eg, ≥1.5 pills/day: OR, 1.41 [95% CI, 1.21–1.64]; <0.74 pills/day: OR, 1.12 [95% CI, 0.94–1.33]). Excess fracture risk for PPI use was only present among persons with at least one other fracture risk factor. **CONCLUSIONS: Use of drugs that inhibit gastric acid is associated with an increased risk of hip fracture; however, this association was only found among persons with at least one other risk factor for hip fracture. Acid inhibition might therefore be associated with fracture risk in persons already at risk for osteoporosis, although other confounding cannot be excluded.**

Keywords: Calcium; Bone; Medication; Gastroesophageal Reflux.

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Hip fractures are a major cause of morbidity and mortality; more than 329,000 persons are hospitalized annually with hip fractures in the United States.[1] The resultant disease burden is substantial, with a frequent need for invasive interventions (eg, more than 234,000 hip replacement surgeries in 2004 alone), prolonged rehabilitation, and a mortality rate of 5% to 10% within the first month.[1] Thus, identifying modifiable risk factors for hip fractures would be of substantial benefit to the public health.[2]

Acid inhibitors, which are among the most commonly used pharmaceuticals in the United States, may theoretically increase or decrease the risk of hip fractures.[3,4] Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) could diminish bone density by decreasing calcium absorption[5] or by inducing hyperparathyroidism through hypergastrinemia.[6,7] Alternatively, acid inhibitors may modify acid-related enzymes in bones that regulate bone remodeling, which could decrease (or increase) fracture risk.[4,8,9]

Few human studies of the association between acid inhibition and hip fractures exist, the results are discordant (even among 3 studies within the same European data set),[10–12] and no large or long-term studies have been published from the United States. In addition, in prior studies, increased fracture risk was also associated with medications not clearly associated with osteoporosis, such as anticholesterol medications, aspirin, or nonsteroidal anti-inflammatory drugs, raising the possibility of confounding.[10,13]

Thus, we performed a nested case-control study of the association between prescriptions for acid-suppressing medications (for up to 10 years) and the risk of hip fracture within a large, community-based population. We also evaluated whether fracture risk was generally associated with other commonly used medications, which would suggest confounding.

Materials and Methods

Study Population

We conducted a case-control study among the approximately 3.3 million members of the Kaiser Permanente, Northern California (KPNC) integrated health care delivery system, which provides comprehensive inpatient and outpatient services. The KPNC membership

Abbreviations used in this paper: CI, confidence interval; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; ICD-9, International Statistical Classification of Diseases, 9th Revision; KPNC, Kaiser Permanente, Northern California; OR, odds ratio; PPI, proton pump inhibitor.

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demographics closely approximate the underlying census demographics of the region.[14] Prescription drug benefits are utilized by >90% of members; pharmacy databases electronically record all dispensed prescriptions (including amount, directions for use, calculated days supply, and refills), and their performance is validated for both as-needed and daily medications.[15,16] Additional databases include information on membership, medical diagnoses assigned by the provider for each outpatient visit, hospitalization diagnoses, and procedures performed. Outpatient diagnoses are assigned by clinicians and are not linked with clinician compensation. The analyses were approved by the institutional review board.

Case Definition

Cases were KPNC members who met the following criteria: an incident diagnosis of a hip fracture between January 1995 and September 2007, using International Statistical Classification of Diseases, 9th Revision (ICD-9) codes 820.0 to 821.20 (hip or femur fractures, excluding lower femoral condyle); at least 18 years of age at the index date; no prior hip/femur fracture diagnosis; and at least 2 years of membership before the index date. The index date was the fracture date. We evaluated the validity of electronic coding for hip fracture using a manual record review of 60 randomly selected patients from 1998 to 2007; we identified data supporting a fracture diagnosis in 90% of patients, indicating a high level of coding validity.

Control Definition

For each case, up to 4 matched controls (if available) were randomly selected from the KPNC membership using incidence density sampling. With this method, each control was chosen from among all eligible adult members who lacked a diagnosis of a hip fracture at the index date of the matched case and who had at least 2 years of membership before the index date.[17]

Controls were matched by sex, year of birth (3-year age groups), duration of membership (rounded to year), first year of membership, and race/ethnicity.

Exposure Status

Medication exposures used KPNC prescription pharmacy databases. All prescriptions were for before the index date and definitions were created a priori (ie, before the analyses). The databases contain detailed information on dispensed medications since approximately January 1994, the frequency of refills, and directions for use. The primary exposure for the analysis was the cumulative dose, defined as "days supply." The days supply variable used the number of pills dispensed and their directions for use; for example, 60 pills dispensed, with instructions to take one pill twice a day, equaled a 30-day supply. The "exposure duration" was the interval between the first and last prescriptions plus the number of days supplied for the last prescription. For subjects with a single prescription, the duration equaled the days supplied. We evaluated compliance and dose intensity using the "average daily dose" (dispensed pills divided by exposure duration) and 3 dose categories: occasional use (<0.75 pills/day), approximate daily use (0.75–1.49 pills/day), and twice-daily use (≥1.5 pills/day).

For the PPI analyses, exposed subjects had all exposure PPI prescriptions dispensed before their index date; unexposed (reference) subjects had prescriptions for neither PPIs nor H2RAs.

For the H2RA analyses, exposed subjects had all exposure H2RA prescriptions dispensed before their index date; unexposed (reference) subjects had prescriptions for neither PPIs nor H2RAs. We excluded subjects with PPI prescriptions from all H2RA exposure categories.

Confounding and Effect Modification

In addition to the matched factors, we evaluated the following as potential confounders (using ICD coding): arthritis, cerebrovascular disease, hemiplegia, asthma, dementia, psychoses, diabetes mellitus, thyroid disease, ischemic heart disease, epilepsy, gait disorder, peptic ulcer disease, gastroesophageal reflux disease (GERD), visual impairment, and chronic kidney disease. We evaluated smoking (prior or current) and alcohol abuse/counseling using ICD codes and internal KPNC codes for substance use or treatment.

Persons with multiple health problems or health care–seeking behavior may be more likely to receive common diagnoses (such as reflux) and to receive treatment for acid-related conditions (such as with a PPI). Thus, we also evaluated as potential confounders other diagnoses that indicate use of the health system, including essential hypertension and colon polyp (both diagnoses require screening tests), headaches, and diverticulosis (without diverticulitis).

We evaluated whether expected associations were present for other medications known to modify fracture risk (eg, glucocorticoids, estrogen, thiazide diuretics, thyroid supplementation, bisphosphonates, and anxiolytics) and medications not known to be associated with fracture risk (eg, angiotensin-converting enzyme inhibitors, calcium channel blockers, nonnarcotic analgesics).[18] For glucocorticoids or bisphosphonates, which can modify fracture risk with few doses, subjects were "exposed" if they received ≥1 prescriptions. For other medications, patients were "exposed" if they received a ≥365-day supply, unexposed if they received no prescriptions, and not included in these analyses if they had intermediate values.

Finally, we evaluated common indications for antisecretory therapy (ie, GERD).

Primary Statistical Analysis

The study utilized standard analytic techniques for evaluating case-control studies and conditional logistic regression.[17,19–21] All definitions and modeling strategies were planned a priori (ie, before analysis). We evaluated confounding by contrasting odds ratios (ORs) between models with and without potential confounders; using a priori criteria, the final model included factors that altered the OR by approximately ≥10%.[17] Of all the risk factors and medications, only smoking met these criteria; thus, the final model included the outcome, the exposure, and smoking. The "saturated" model contained all variables listed in the confounding section. Effect modification (eg, differences in PPI effect across age strata) was evaluated using cross product terms in the logistic regression model and by evaluating stratum-specific ratios.[21] Comparable results were found for both conditional and unconditional logistic regression models; all main results used the conditional regression models. The attributable fraction calculations used maximum likelihood estimates from the unconditional logistic regression models.[22]

Results

We identified 33,864 members with a diagnosis of hip fracture between 1995 and September 2007. Of these, we excluded 112 cases (mainly elderly members) lacking controls who fulfilled all the matching criteria, leaving 33,752 cases and 130,471 controls for the main analyses. The cases were predominantly women (65.7%), subjects 70 years of age or older (69.4%), and non-Hispanic white subjects (79.6%) (Table 1). Of the cases, 20,498 (60.7%) had not received any prescriptions for PPIs or H2RAs. Among PPI users, 1558 (4.6%) were dispensed a ≥2-year supply. Among H2RA users (without any PPI use), 875 (2.6%) were dispensed a ≥2-year supply.

Table 1. Demographic Characteristics

	Controls	Cases
Total subjects	130,471	33,752
Female sex	84,550 (64.8)	22,183 (65.7)
Age at index date (*y*)		
18–29	5230 (4.0)	1302 (3.9)
30–39	4369 (3.4)	1075 (3.2)
40–49	6109 (4.7)	1531 (4.5)
50–59	9880 (7.6)	2452 (7.3)
60–69	16,026 (12.3)	3963 (11.7)
70–79	35,316 (27.1)	8890 (26.3)
80–89	43,322 (33.2)	11,332 (33.6)
Older than 89	10,219 (7.8)	3207 (9.5)
Smoking[a]	29,473 (22.6)	9940 (29.5)
Alcohol abuse	4883 (3.7)	2261 (6.7)
Diabetes	19,607 (15.0)	6102 (18.1)
Arthritis	44,104 (33.8)	13,462 (39.9)
Kidney disease	2966 (2.3)	1399 (4.1)
Ethnicity		
Non-Hispanic white	103,962 (79.7)	26,879 (79.6)
Hispanic white	8395 (6.4)	2183 (6.5)
Black	5952 (4.6)	1526 (4.5)
Asian/Pacific Islander	5522 (4.2)	1424 (4.2)
Other	3902 (3.0)	1051 (3.1)
Unknown	2738 (2.1)	689 (2.0)
Medication days supply		
PPI use[b]		
None	84,913 (65.1)	20,498 (60.7)
≥2 years	4806 (3.7)	1558 (4.6)
H2RA use[b]		
None	84,913 (65.1)	20,498 (60.7)
≥2 years	3061 (2.4)	875 (2.6)

NOTE. All values are expressed as number of subjects (%) unless otherwise noted. Cases and controls were matched for sex, age, duration of membership, first year of membership, and race/ethnicity.
[a]Prior or current smoking diagnosis.
[b]"None" designates members with no PPI or H2RA use. Among users of acid suppression, H2RA users had no PPI use; PPI users could use H2RAs.

Analyses

Antisecretory medication and fracture risk. We defined long-term users as those with a ≥2-year supply of medication. The risk of fracture was 30% higher among persons with a ≥2-year supply of PPIs compared with nonusers (OR, 1.30; 95% confidence interval [CI], 1.21–1.39). Fracture risk was also higher among persons with ≥2-year use of H2RAs (OR, 1.18; 95% CI, 1.08–1.29).

Dose intensity and fracture risk. There was a general trend for increased fracture risk among subjects taking higher average daily doses (Tables 2 and 3). The fracture risk was not significantly elevated among persons who used <0.75 PPI pills/day for ≥2 years compared with nonusers (OR, 1.12; 95% CI, 0.94–1.33). In contrast, risk was increased among persons taking 0.75 to 1.49 pills/day (OR, 1.30; 95% CI, 1.19–1.42) and ≥1.5 pills/day (OR, 1.41; 95% CI, 1.21–1.64; vs nonusers).

Dose duration and fracture risk. Fracture risk did not substantially increase with longer durations of use (Tables 2 and 3). Although there was a statistically significant increase in risk with longer durations (*P* value trend <.01 for both duration of PPI therapy and duration of H2RA therapy), this was mainly due to the increase between nonusers and any use.

Fracture risk after discontinuation. The strength of the association between PPI use and hip fracture was strongest among current users and diminished after discontinuation of PPI use (Table 4). Among current users (a ≥2-year supply of PPIs before the index date and at least one PPI prescription in the year before the index date), the fracture risk associated with PPI use was an OR of 1.30 (95% CI, 1.21–1.41). The risk trended lower for persons whose most recent prescription was 1 to 1.9 years before the index date (OR, 1.24; 95% CI, 0.90–1.72) and 2 to 2.9 years before the index date (OR, 1.09; 95% CI, 0.64–1.85).

Table 2. PPIs and the Risk of Hip Fracture by Increasing Daily Dose and Cumulative Duration of Use

	Cumulative duration (*y*)							
	No use	<1	1–1.9	2–3.9	4–5.9	6–7.9	8–9.9	≥10
Pills/day	Adjusted ORs and 95% CIs[a]							
0.01–0.74	Reference	1.08 (0.90–1.29)	1.21 (1.03–1.41)	1.23 (1.08–1.39)	1.10 (0.95–1.28)	1.35 (1.13–1.62)	0.99 (0.75–1.32)	2.07 (1.30–3.28)
0.75–1.49	Reference	1.30 (1.22–1.39)	1.36 (1.20–1.53)	1.43 (1.28–1.60)	1.18 (1.03–1.36)	1.18 (0.99–1.41)	1.36 (1.05–1.75)	1.64 (1.07–2.52)
≥1.5	Reference	1.21 (1.13–1.29)	1.51 (1.24–1.85)	1.23 (1.01–1.51)	1.59 (1.21–2.10)	1.59 (1.08–2.32)	2.39 (1.40–4.08)	1.39 (0.61–3.16)
All doses	Reference	1.25 (1.19–1.31)	1.31 (1.20–1.42)	1.34 (1.24–1.44)	1.21 (1.10–1.33)	1.33 (1.19–1.49)	1.33 (1.12–1.57)	1.85 (1.41–2.43)
	Total no. of cases and controls by duration category[b]							
Cases	20,498	3359	863	1114	696	465	212	86
Controls	84,913	10,868	2591	3484	2317	1423	658	216

NOTE. Reference group for all comparisons consists of members with no PPI or H2RA use. Members in PPI user categories could also use H2RAs.
[a]Cases and controls were individually matched for sex, age, duration of membership, first year of membership, and race/ethnicity; models were adjusted for a smoking diagnosis.
[b]No. of subjects for each cumulative duration category.

Attributable fraction and population incidence. Approximately 1.78% (95% CI, 1.39–2.17) of fractures in the population were theoretically independently attributable to ≥1 year of PPI use, if we assume the association was causal.

We calculated the crude fracture incidence rates for 2 groups matched by birth year, sex, health plan enrollment date, and duration of KPNC membership. For persons not exposed to PPIs, the incidence of hip fractures was 2.14 per 1000 person-years. For persons with at least a 365-day supply of PPIs, the fracture incidence after this exposure period was 3.24 per 1000 person-years. These estimates are within the range of prior population-based reports of fracture incidence.[10,23,24]

Presence of other risk factors for hip fracture. The association between ≥2 years of PPI use and hip fracture was only present among subjects with at least one other risk factor for hip fracture (≥1 risk factor present: OR, 1.25; 95% CI, 1.16–1.35; no risk factors present: OR, 0.66; 95% CI, 0.38–1.12; *P* value interaction = .02; individual risk factors listed in Table 5 and Materials and Methods). At least one risk factor was present among 73% of persons 50 years of age or older and 36% of persons younger than 50 years of age. Most of the 6364 members with ≥2 years of PPI use had at least one other risk factor for hip fracture (6006 subjects; 94.4%); in contrast, relatively few of the 112,437 subjects with ≥1 risk factor had ≥2 years of PPI use (6006 subjects; 5.3%).

We provide the fracture risk for ≥2 years of PPI use versus nonusers for each risk factor, although the study is underpowered to evaluate each risk factor individually (Table 5). The risk associated with PPI use trended higher among persons with alcohol abuse, arthritis, diabetes, kidney disease, and glucocorticoid use than among persons without these risk factors (Table 6). The trends for increased risk were most notable for fracture risk factors associated with decreased bone density (eg, diabetes,[3] renal insufficiency,[25] and glucocorticoid use).

Age, sex, and indication for antisecretory treatment. The association between ≥2 years of PPI use and fracture risk differed by age (*P* value interaction term <.01). Risk was significantly increased for all decades between ages 40 and 89 years; however, an association was still only present for persons with other fracture risk factors and the excess risk associated with PPI use trended stronger for younger age groups (eg, for ages 50 years or older with ≥1 risk factor present: OR, 1.25 [95% CI, 1.16–1.35]; for ages 50 years or older with risk factors absent: OR, 0.75 [95% CI, 0.43–1.31]; for persons younger than 50 years with ≥1 risk factor: OR, 1.71 [95% CI, 1.00–2.93]).

Table 3. H2RAs and the Risk of Hip Fracture by Increasing Daily Dose and Cumulative Duration of Use

	Cumulative duration (*y*)							
	No use	<1	1–1.9	2–3.9	4–5.9	6–7.9	8–9.9	≥10
Pills/day	Adjusted ORs and 95% CIs[a]							
0.01–0.74	Reference	1.17 (1.02–1.35)	1.09 (0.98–1.21)	1.12 (1.02–1.22)	1.03 (0.93–1.14)	1.06 (0.94–1.19)	1.32 (1.14–1.53)	1.29 (1.02–1.62)
0.75–1.49	Reference	1.18 (1.10–1.27)	1.19 (1.06–1.34)	1.14 (1.03–1.27)	1.21 (1.05–1.39)	1.23 (1.04–1.47)	0.95 (0.76–1.19)	1.20 (0.89–1.62)
≥1.5	Reference	1.14 (1.09–1.19)	1.27 (1.12–1.45)	1.34 (1.18–1.51)	1.15 (0.97–1.36)	1.25 (1.01–1.55)	1.10 (0.83–1.46)	1.53 (1.09–2.14)
All doses	Reference	1.11 (1.06–1.15)	1.14 (1.04–1.24)	1.15 (1.06–1.24)	1.10 (0.99–1.22)	1.02 (0.89–1.18)	1.03 (0.86–1.24)	1.31 (1.03–1.66)
	Total no. of cases and controls by duration category[b]							
Cases	20,498	3695	761	924	517	286	169	107
Controls	84,913	13,720	2747	3352	1913	1221	715	333

NOTE. Reference group for all comparisons consists of members with no PPI or H2RA use. PPI user categories could also use H2RAs.
[a]Cases and controls were individually matched for sex, age, duration of membership, first year of membership, and race/ethnicity; models were adjusted for a smoking diagnosis.
[b]No. of subjects for each cumulative duration category.

Table 4. Association Between a ≥2-Year Supply of PPIs and the Risk of Hip Fracture, Stratified by Time Since Most Recent Prescription

	User status	Interval since last prescription[a]	Cases	Controls	Adjusted OR (95% CI)[b]
No use			84,913	20,498	Reference
≥2-year supply	All users	All persons with a ≥2-year supply	1558	4806	1.30 (1.21–1.39)
Current vs former users[c]	Current user	Prescription in last year	1288	3958	1.30 (1.21–1.41)
	Recent user	Last prescription 1–1.9 years prior	73	220	1.24 (0.90–1.72)
	Former user	Last prescription 2–2.9 years prior	23	84	1.09 (0.64–1.85)
	Former user	Last prescription 3–5.9 years prior	15	87	0.69 (0.37–1.28)

[a]Time between index date and last PPI prescription among persons with a ≥2-year supply of PPIs before their index date. A current user, for example, would have received at least one prescription in the year before hip fracture (or the comparable index date for controls).
[b]Cases and controls were individually matched for sex, age, duration of membership, first year of membership, and race/ethnicity; models were adjusted for a smoking diagnosis.
[c]Among subjects with a ≥2-year supply.

The association between ≥2 years of PPI use and hip fracture was comparable between men (OR, 1.34; 95% CI, 1.18–1.51) and women (OR, 1.28; 95% CI, 1.17–1.39; *P* value interaction = .55). There was no significant interaction by race/ethnicity (*P* = .38).

The association between ≥2 years of PPI use and hip fracture was somewhat greater among the 103,123 persons without a diagnosis of GERD (OR, 1.66; 95% CI, 1.41–1.96) than among the 8652 persons with a diagnosis of GERD (OR, 1.38; 95% CI, 1.05–1.82; *P* value interaction term <.01). For ≥2 years of H2RA use, an increased risk was found among patients without GERD (OR, 1.22; 95% CI, 1.08–1.38) but not for persons with GERD (OR, 0.89; 95% CI, 0.55–1.44).

Table 5. PPI Use ≥2 Years and the Risk of Hip Fracture, Stratified by Presence or Absence of Other Specific Risk Factors for Hip Fracture

Risk factor	Risk factor absent	Risk factor present
Fracture risk increased among PPI users with risk factor		
Alcohol abuse	1.29 (1.20–1.39)	1.45 (0.71–2.96)
Arthritis	1.26 (1.10–1.45)	1.37 (1.22–1.54)
Diabetes	1.22 (1.12–1.33)	1.43 (1.12–1.82)
Kidney disease	1.26 (1.17–1.36)	2.02 (0.80–5.06)
Glucocorticoids	1.11 (1.00–1.24)	1.51 (1.28–1.78)
Fracture risk similar or lower among PPI users with risk factor		
Cerebrovascular disease	1.32 (1.20–1.44)	1.06 (0.85–1.33)
Dementia	1.36 (1.26–1.48)	0.81 (0.58–1.14)
Epilepsy	1.30 (1.21–1.40)	Not available[a]
Gait disorder	1.18 (1.08–1.30)	0.90 (0.32–2.49)
Hemiplegia	1.30 (1.21–1.40)	1.04 (0.33–3.27)
Psychoses	1.30 (1.18–1.42)	1.06 (0.86–1.31)
Smoking	1.32 (1.19–1.47)	1.16 (1.00–1.35)
Visual impairment	1.29 (1.20–1.39)	Not available[a]
Anxiolytics	1.29 (1.14–1.44)	0.79 (0.39–1.60)
≥1 Risk factor[b]	0.66 (0.38–1.12)	1.25 (1.16–1.35)

NOTE. All values are expressed as OR (95% CI). ORs contrast risk of hip fracture among persons with ≥2 years of PPI use vs reference group. Reference group for all comparisons consists of members with no PPI or H2RA use. For example, for the diabetes strata, the OR evaluates the association between PPI use and fracture risk among persons with a diagnosis of diabetes (risk factor present) and the same association among persons without a diagnosis of diabetes (risk factor absent). The fracture risk associated with PPI use was 21% greater among diabetic subjects than among nondiabetic subjects.
[a]Too few matched cells available for calculation.
[b]*P* value interaction = .02.

Other Medications and Risk of Hip Fracture

The associations between other medication classes and the risk of hip fracture were generally in accordance with expected values (Table 6). For medications not known to be mechanistically linked with fracture risk (angiotensin-converting enzyme inhibitors, calcium channel blockers, nonnarcotic analgesics), we found no significant associations. For medications/conditions with known associations (anxiolytics, bisphosphonates, estrogen, glucocorticoids, thiazide diuretics, thyroid supplementation),[26] associations were in the expected direction, although not all were statistically significant.

Confounding

The magnitude of the associations between ≥2 years of PPI use (vs no use) and fracture risk were comparable between a saturated model containing all the listed risk factors and medications (OR, 1.22; 95% CI, 0.96–1.54), a simple bivariate model with only PPI use and case status (OR, 1.36; 95% CI, 1.27–1.46), and the final model with PPI use, case status, and smoking (OR, 1.30; 95% CI, 1.21–1.39). Similar findings were present for ≥1 year of use (final model with only smoking: OR, 1.34; 95% CI, 1.27–1.42). We did not include serum vitamin D levels or prescriptions for vitamin D as potential confounders because levels are often obtained after a diagnosis of osteoporosis has been made; however, inclusion of these variables also did not change the estimates (data not shown).

Discussion

The use of acid-suppressing medications (H2RAs or PPIs) was associated with an increased risk of hip fracture in a large, general population. The risk was higher among subjects taking the more potent PPIs

Table 6. Diagnoses, Other Medication Use, and Fracture Risk

	No. of controls (%)	No. of cases (%)	OR (95% CI)[a]
Diagnoses[b]			
Alcohol abuse	4883 (3.7)	2261 (6.7)	1.70 (1.48–1.96)
Arthritis	44,104 (33.8)	13,462 (39.9)	1.49 (1.38–1.60)
Cerebrovascular disease	18,643 (14.3)	6579 (19.5)	1.26 (1.12–1.41)
Dementia	10,431 (8.0)	4780 (14.2)	1.58 (1.35–1.85)
Diabetes	19,607 (15.0)	6102 (18.1)	1.18 (1.03–1.34)
Epilepsy	375 (0.3)	169 (0.5)	2.03 (1.45–2.84)
Gait disorder	3210 (2.5)	1421 (4.2)	1.32 (1.02–1.71)
Hemiplegia	3264 (2.5)	1372 (4.1)	1.63 (1.29–2.06)
Kidney disease	2966 (2.3)	1399 (4.1)	1.41 (1.04–1.92)
Psychoses	18,381 (14.1)	7969 (23.6)	1.42 (1.25–1.61)
Smoking	29,444 (22.6)	9936 (29.4)	1.45 (1.34–1.56)
Visual impairment	1990 (1.5)	730 (2.2)	1.51 (1.15–1.98)
Medications[c]			
Angiotensin-converting enzyme inhibitors	25,223 (19.3)	7132 (21.1)	1.05 (0.94–1.16)
Anxiolytics	5234 (4.0)	1997 (5.9)	1.22 (1.02–1.45)
Bisphosphonates[c,d]	10,910 (8.4)	4277 (12.7)	1.46 (1.27–1.68)
Calcium channel blockers	19,672 (15.1)	5561 (16.5)	1.04 (0.93–1.17)
Estrogen	20,602 (15.8)	4613 (13.7)	0.68 (0.61–0.76)
Glucocorticoids[c]	29,144 (22.3)	8800 (26.1)	1.16 (1.06–1.27)
Nonnarcotic analgesics	2390 (1.8)	853 (2.5)	1.22 (0.95–1.57)
Thiazide diuretics	17,478 (13.4)	4251 (12.6)	0.97 (0.86–1.09)
Thyroid supplementation	16,775 (12.9)	4557 (13.5)	1.11 (0.94–1.31)

[a]ORs from saturated model, adjusted for use of other medications and risk factors (see Materials and Methods for details).
[b]Listed diagnoses are those associated with increased risk in the saturated regression model (see Materials and Methods for details). All listed diagnoses were included as risk factors in analyses of other risk factors for hip fracture.
[c]Medications are ≥1 year supply except for glucocorticoids and bisphosphonates, which are for any use (see methods). Glucocorticoids and anxiolytics were included as risk factors in analyses of other risk factors for hip fracture.
[d]Expected direction is increased risk because bisphosphonates are prescribed for persons with an increased fracture risk.

(compared with H2RAs), decreased after medication discontinuation, and increased with increasing dose but not necessarily with longer durations. The increased risk was confined to persons with certain other risk factors for hip fracture.

These findings extend those of prior studies that evaluated acid inhibition and fracture risk, most of which found some association. A case-control study in the UK General Practice Database found an increased fracture risk among persons taking acid inhibitors (for both PPIs and H2RAs) for more than 1 year, even after adjustment for multiple confounders and increased risk with a longer duration of use.[10] A Canadian study, in contrast, found no increased risk for up to 6 years of use but an association for more than 6 years of use.[13] However, both studies also found increased risk for other drugs not clearly associated with fracture risk, such as aspirin, nonsteroidal anti-inflammatory drugs, and antidepressants, raising concerns about confounding. In addition, another study in the same UK database, restricted to persons without risk factors for hip fracture, found no association between PPIs and fracture risk (relative risk, 0.9; 95% CI, 0.7–1.1) and no escalations of risk with increased PPI use.[11] The authors suggested the differences between the studies may have been from "residual confounding or effect modification" in the former study. A Danish study found a small increase in fracture risk associated with PPI use in the year before fracture, but, paradoxically, a significantly decreased risk among H2RA users.[27]

There are several mechanisms through which acid inhibition could theoretically alter fracture risk.[28] First, acid inhibition may directly impair calcium absorption, with a resultant decrease in bone density and increase in fracture risk.[5] A randomized trial in 18 subjects indicated that omeprazole decreased the absorption of radiolabeled calcium pills by 61% compared with placebo.[5] Other studies of acid secretion, dietary calcium, and calcium supplements have disparate results.[29–33] Second, acid inhibition may induce hyperparathyroidism, which directly decreases bone mineral density, through hypergastrinemia, although this is controversial.[6,7] For either of these mechanisms, it is unclear whether brief periods of acid inhibition can change calcium balance sufficiently to

increase the risk of fracture. A third potential mechanism is through an alteration of bone remodeling.[8,9] Proton pumps locally acidify bone at the level of the osteoclast;[34] this local acidification is used in bone remodeling. Bone strength is influenced by a careful balance between bone formation and bone resorption. If PPIs modify this acidity, fracture risk could change in unpredictable ways: fracture risk could decrease (by decreasing resorption) or increase (by altering density without increasing strength).[8,9,35] Of note, none of these mechanisms are proven, minimal mechanistic data are extant, human studies have evaluated only selected populations,[36,37] and animal models suggest that osteoporosis may be induced after surgical removal of the acid-secreting portions of the stomach through a mechanism independent from calcium absorption and parathyroid hormone levels and that is not reproducible with PPIs.[38,39]

We found an increased risk of fracture associated with even short durations of acid inhibitor use (<1 year). Possibilities for this finding include a true association (with even short intervals causing decreased bone density or altered bone remodeling) or confounding. The short-term results could be confounded by indication; indications for short-term treatment (eg, after periods of hospitalization or illness from other disorders) may differ from those for long-term treatment. Such persons may have different risk fracture profiles from longer-term users that are difficult to delineate.

These results raise the following question: do acid inhibitors directly increase the risk of hip fractures? A causal association is supported by the presence of increased risk with greater acid suppression (PPI vs H2RA), elevated risk with higher daily doses, decreased risk with discontinuation of acid suppression, and the presence of increased risk among persons with other risk factors for osteoporosis (if acid suppression decreases calcium absorption, it would be expected to increase fracture risk the most among persons with already diminished bone densities).[17] The main result not supporting a causative association is the absence of a clear trend for increased risk with longer durations of use.

There are several potential limitations of this study. The databases started recording dispensed medications in approximately 1995; thus, more remote exposures were not evaluable. This might underestimate the exposure in both cases and controls, particularly for the first few years of the database. However, analyses confined to fractures diagnosed after January 1, 2000, provided similar results to those from the full data set (data not shown). Second, spurious associations may be seen with variables related to the utilization of medical services. Patients using medical services for other reasons may be more likely to have conditions recognized (such as GERD) that result in treatment with acid inhibitors. However, adjustment for other common medical conditions and inclusion only of persons without a diagnosis of GERD still demonstrated persistent positive associations. In addition, the finding that other frequently prescribed medications were not associated with fracture risk decreases the possibility that the associations between acid inhibitors and fracture risk were solely due to confounding from contacts with the health system. Third, a case-control design cannot completely control for unknown confounders and detailed data on some confounders (eg, lifetime alcohol use, diet, body mass index for all persons, lifetime smoking histories, and so on) were not available. However, prior large surveys in the KPNC population provided smoking and alcohol abuse rates within a reasonable range of those detected by the current study, analyses suggested little evidence for confounding even among those with alcohol abuse and tobacco use diagnoses (who likely represent heavier users), and analyses confined to persons with data on body mass index provided similar results (data not shown). We did not include bone density data. Falls are the most common mechanism for hip fractures; however, only some persons have falls and, among those with falls, only some have fractures. Osteoporosis may contribute to the risk of fracture among those with falls, but individual measurements of bone mineral density measurements are not generally available in large populations and are not randomly distributed, potentially biasing analyses using density data. Finally, misclassification of exposure status may influence the results. One type of PPI became available over the counter in 2003, and H2RAs were available over the counter before that time, although members could receive both PPIs and H2RAs by prescription after that date (at reduced cost compared with over-the-counter medications).[40] Thus, some members who took over-the-counter PPIs or H2RAs may have been classified as "unexposed"; if present, this would be expected to decrease the strength of the association: a "bias toward the null."

The strengths of this study include its large size (approximately 5 times more cases with ≥1 year of PPI use than the UK study), access to care for all members, more than 10 years of exposure data, the ascertainment of all recorded diagnoses of hip fractures arising within a general population (thereby minimizing referral bias), detailed electronic data for dispensed medications (eliminating recall bias), data for multiple confounders, and the use of a control group that approximates the underlying general population base of the region.[14] The large size permitted evaluation for small intervals of use and multiple potential confounders (including use of other medications, such as bisphosphonates).

In conclusion, this study found an association between the use of PPIs and H2RAs and the risk of hip fracture. The risk was higher among PPI users than among H2RA users; however, the increased risk was confined to persons with at least one other fracture risk factor. If the association is causal, the overall increase in risk is small and the

risk attributable to acid inhibition in the general population is low, although the exposed population is fairly large for a medication exposure. These findings do not recommend against acid suppression for persons with clear indications for treatment, but they do advise appropriate vigilance in prescribing these medications to persons with defined indications and at the lowest effective dose. The mechanism for the association is unknown; although diminished calcium absorption from acid inhibition is an intuitive explanation supported by a small trial, it is not a proven mechanism. Additional mechanistic information is needed regarding the effects of acid inhibition on calcium absorption, bone metabolism, and bone strength and whether interventions such as calcium and vitamin D supplements modify the associations between acid inhibition and fracture risk.

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Conflicts of interest

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