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Proton Pump Inhibitor Use and the Antifracture Efficacy of Alendronate

Bo Abrahamsen, MD, PhD; Pia Eiken, MD, PhD; Richard Eastell, MD, FRCP

Background: Proton pump inhibitors (PPIs) are widely used in elderly patients and are frequently coadministered in users of oral bisphosphonates. Biologically, PPIs could affect the absorption of calcium, vitamin B_{12}, and bisphosphonates and could affect the osteoclast proton pump, thus interacting with bisphosphonate antifracture efficacy. Moreover, PPIs themselves have been linked to osteoporotic fractures.

Methods: Population-based, national register–based, open cohort study of 38 088 new alendronate sodium users with a mean duration of follow-up of 3.5 years. We related risk of hip fracture to recent pharmacy records of refill of prescriptions for alendronate.

Results: For hip fractures, there was statistically significant interaction with alendronate for PPI use ($P < .05$). The treatment response associated with complete refill compliance to alendronate was a 39% risk reduction (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.52-0.71; $P < .001$) in patients who were not PPI users, while the risk reduction in concurrent PPI users was not significant (19%; HR, 0.81; 95% CI, 0.64-1.01; $P = .06$). The attenuation of the risk reduction was dose and age dependent. In contrast, there was no significant impact of concurrent use of histamine H_2 receptor blockers.

Conclusions: Concurrent PPI use was associated with a dose-dependent loss of protection against hip fracture with alendronate in elderly patients. This is an observational study, so a formal proof of causality cannot be made, but the dose-response relationship and the lack of impact of prior PPI use provides reasonable grounds for discouraging the use of PPIs to control upper gastrointestinal tract complaints in patients treated with oral bisphosphonates.

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Author Affiliations: Odense Patient Data Exploratory Network (OPEN), Institute of Clinical Research, University of Southern Denmark, Odense, and Department of Medicine and Endocrinology F, Copenhagen University Hospital Gentofte, Hellerup, Denmark (Dr Abrahamsen); Department of Cardiology and Endocrinology, Hillerød Hospital, Hillerød, Denmark (Dr Eiken); and Academic Unit of Bone Metabolism, University of Sheffield, Sheffield, England (Dr Eastell).

PROTON PUMP INHIBITORS (PPIs) are very widely used among the elderly population with a considerable overlap with the population that receives antiosteoporotic treatment with bisphosphonates. Thus, as shown herein, 26% of alendronate sodium users in Denmark take PPIs during the first 3 years of alendronate use. A recent editorial in the *Archives*[1] warned that more than half of all PPI prescriptions are for inappropriate indications. Proton pump inhibitors have the potential to interact with the absorption of calcium, vitamin B_{12}, and oral bisphosphonates themselves,[2-4] as well as affecting the osteoclast proton pump. Observational studies have shown that patients receiving PPI treatment make up a high-risk group for osteoporotic fractures.[5-8] Recently, data from the Women's Health Initiative revealed no significant effect of PPI exposure on the risk of hip fracture (hazard ratio [HR], 1.47; 95% confidence interval [CI], 1.18-1.82), but a significant increase in clinical spine, forearm, and total fractures.[9] Several studies suggest a causal relationship[6-8] between PPI use and fractures, while other studies do not[10,11] or have found the effect to be small.[12] Using national health data for Denmark, we therefore undertook a comprehensive analysis that included both the degree of refill compliance for alendronate and the cumulative exposure to PPIs during alendronate therapy for osteoporosis. We hypothesized that PPIs would blunt the antifracture efficacy of alendronate and that this phenomenon would not be reproduced by exposure to histamine H_2 receptor blockers or glucocorticoids, the former identifying a patient group with increased gastrointestinal (GI) tract morbidity and the latter a patient group with strongly increased fracture risk.

See Invited Commentary at end of article

See also page 991

METHODS

Our hypothesis was that concurrent PPI use is associated with a dose-dependent loss of protection against hip fracture with alendronate in elderly patients. We designed a population-based, nationwide open cohort study.

POPULATION

All patients at least 35 years old who began treatment with alendronate (Anatomical Therapeutic Chemical codes M05BA04 and M05BB03) in Denmark from January 1, 1996, through December 31, 2005, and who had not previously filled a prescription for any antiosteoporotic drugs (selective estrogen receptor modulators, bisphosphonates, parathyroid hormone analogs, or strontium ranelate). We excluded from the cohort persons who emigrated before the end of the study period, so that fracture outcomes could not have been identified with certainty, providing a study population of 38 088 persons (**Figure 1**).

The reasons for starting the study in 1996 were that we were using the National Hospital Discharge Register, which started recording outpatient diagnoses in 1995 (although inpatient diagnoses have been recorded since 1977), and we were also using the National Prescription Database, which started collecting prescription information in 1995. The access to anonymized data in the Register was provided by Statistics Denmark, Copenhagen (project reference No. 702538), as approved by the Data Protection Agency, the National Board of Health, and the Danish Medicines Agency. We did not have access to individual patient names, addresses, social security numbers, radiographs, or notes.

INTERVENTIONS

The index date was defined as the date of the first prescription for alendronate. All prescriptions for PPIs, histamine H_2 receptor blockers, and oral glucocorticoids were identified and 2 exposure windows defined: (1) baseline use was defined as any prescription filled in the past 12 months before the index date, and (2) concurrent use was defined as any prescription filled during the first 36 months of alendronate treatment, truncated on the date of fracture or death. Information on death and emigration was obtained from the central civic register; no patients were lost to follow-up. All drug exposures were calculated in defined daily doses (DDDs) as established by the World Health Organization.[13] Ethics committee approval was not needed because the study was not a clinical trial.

OUTCOMES AND ASSESSMENTS

The primary outcome was hip fracture (neck or intertrochanteric femur) and the secondary outcomes fractures of the spine, forearm, or humerus. We identified prior fractures sustained between the date of the 50th birthday and the index date, using hospital discharge information back to 1977. Assessment of comorbid conditions was based on hospital contacts, on an inpatient or outpatient basis, in the past 3 years prior to the index date.

STATISTICAL ANALYSIS

Data are shown as mean (SD). Demographics were compared by *t* tests and χ^2 analysis. We used Cox proportional hazards models with time to fracture, death, or end of the study (December 31, 2006) to obtain crude and adjusted HRs. The statistical analysis consisted of first establishing a base model for fracture outcomes using alendronate refill compliance (medication possession ratio [MPR], calculated in blocks of 365 days as the number of DDDs available per day) as the time-dependent covariate in an analysis adjusted for age, sex, individual comorbidities (**Table 1**), prior fracture, and the number of comedications based on the approach used by Siris et al.[15] Second, interaction terms for concurrent PPI use were then added to the model to test for PPI-by-MPR (alendronate) interaction on the fracture outcome. Only for outcomes with significant interaction were stratified analyses by dose undertaken. For these, we prespecified the following scale: none, 1 to 359 DDDs, 360 to 719 DDDs, and 720 or more DDDs (cutoffs corresponding to 1 vs 2 years of use of 1 DDD). All analyses were performed using SPSS statistical software (version 18.0; SPSS Inc, Chicago, Illinois). $P < .05$ was considered significant. In a sensitivity analysis, users were instead first stratified by refill compliance to alendronate. Their PPI dose intensity was then used as the time-dependent variable.

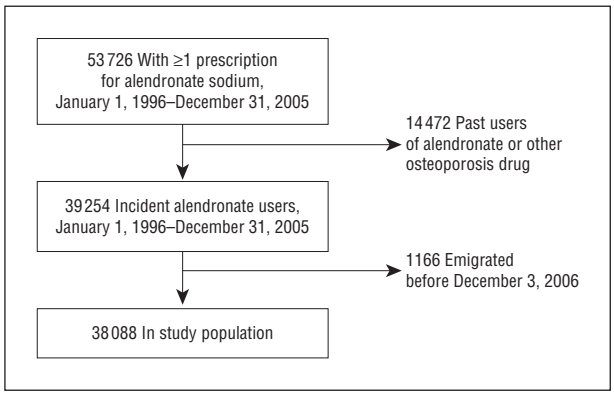

Figure 1. Study flowchart. Population-based, national register–based, open cohort study of 38 088 new alendronate sodium users, with a mean duration of follow-up of 3.5 years. Information on exposures and outcomes was retrieved from the National Board of Health and the Danish Medicines Agency (Statistics Denmark, Copenhagen).

Based on an expected hip fracture incidence of 5% and an expected combined incidence of humerus, forearm, and spine fractures of 3% while assuming a 40% reduction in fracture risk with complete refill compliance, the study had 99.7% power to detect a 50% increased risk with PPI coadministration and 71% power to detect a 25% increased risk. For nonhip fractures, the corresponding power was 91.5% and 44%, respectively. The calculation assumed that 25% of alendronate users would be concurrent users of PPIs.

RESULTS

DEMOGRAPHICS AND EXPOSURES

The study population consisted of 6431 men and 31 657 women (mean age, 70.4 years [range, 35-101 years]) (Table 1), with 30% having prior hospital-treated fractures. Ulcer disease had been recorded in 2.5%. In the 12 months prior to the index date, 26% had filled prescriptions for oral glucocorticoids, 5.5% for histamine H_2 receptor blockers, and 18.1% for PPIs. The most commonly used PPIs during treatment with alendronate were esomeprazole magnesium and omeprazole sodium (**Table 2**).

BASE MODELS TESTING THE EFFECT OF ALENDRONATE

Hip fractures were sustained by 2071 persons while 1110 persons experienced a major osteoporotic nonhip frac-

Table 1. Baseline Demographics[a]

Characteristic	Total Study Population (n=38 088)	Concurrent Use of PPIs?[b] No (n=27 911)	Concurrent Use of PPIs?[b] Yes (n=10 177)	*P* Value
Age at first Rx, mean (SD) [range], y	70.4 (10.9) [35-101]	70.0 (10.7) [35-100]	71.6 (10.9) [35-101]	<.001
Male sex	16.9	16.0	19.4	<.001
History of fracture after age 50 y	29.9	29.2	31.6	<.001
Myocardial infarction	2.6	2.0	4.2	<.001
Chronic heart failure	10.3	8.8	14.5	<.001
Peripheral vascular disease	2.6	2.2	3.6	<.001
Cerebrovascular disease	4.0	3.5	5.3	<.001
Dementia	0.9	0.9	1.0	.20
Pulmonary disease	12.6	10.5	18.5	<.001
Collagen disease	7.5	6.4	10.7	<.001
Ulcer disease	2.5	1.2	6.0	<.001
Hemiplegia	0.3	0.3	0.3	.78
Renal failure	0.4	0.3	0.8	<.001
DM, no complications	3.2	2.6	4.8	<.001
DM complications	0.8	0.6	1.2	<.001
Mild liver disease	1.1	0.8	1.8	<.001
Severe liver disease	0.2	0.1	0.5	<.001
Malignant disease	5.7	5.1	7.3	<.001
Solid metastatic tumor	0.6	0.5	0.9	<.001
AIDS or HIV	0	0	0	.58
Charlson index, mean (SD) [range][c]	0.8 (1.4) [0-15]	0.7 (1.4) [0-15]	1.2 (1.7) [0-13]	<.001
Comedications, mean (SD), No.	8.6 (6.1)	7.5 (5.5)	11.8 (6.6)	<.001
Any prednisolone, past 12 mo	26.1	22.5	35.4	<.001
Cumulative prednisolone, mg, past 12 mo, mean (SD)	794.0 (1772.0)	666.7 (1628.2)	1145.2 (2078.7)	<.001
Any PPI Rx, past 12 mo	18.1	6.2	50.7	<.001
Any H2RA Rx, past 12 mo	5.5	4.2	8.9	<.001
Length of follow-up, mean (SD), y	3.3 (2.3)	3.4 (2.3)	3.3 (2.1)	.75

Abbreviations: DM, diabetes mellitus; HIV, human immunodeficiency virus; H2RA, histamine type 2 receptor antagonist; PPI, proton pump inhibitor; Rx, prescription.
[a] Categorical variables are shown as percentages while continuous variables are given as mean (SD). Data are given as percentages except where noted.
[b] Concurrent users of PPI was defined as at least 1 prescription filled in the first 3 years after beginning treatment with alendronate sodium.
[c] See Quan et al.[14]

Table 2. Details of Proton Pump Inhibitor (PPI) Exposure Within the Analysis

ATC Code	Name	DDD, mg	DDDs in Analysis	Total PPI DDDs, %
A02BC01	Omeprazole sodium	20	1 024 000	31.8
A02BC02	Pantoprazole sodium	40	582 500	18.1
A02BC03	Lansoprazole	30	595 000	18.5
A02BC04	Rabeprazole sodium	20	27 500	0.9
A02BC05	Esomeprazole magnesium	30	994 000	30.8
Total			**3 223 000**	100

Abbreviations: ATC, Anatomical Therapeutic Chemical; DDD, defined daily dose (World Health Organization[13]).

ture (spine, forearm, humerus) (**Table 3**). The base models used in the following contained MPR as a time-dependent covariate with age, sex, prior fracture, comorbid conditions, and the number of comedications used entered as fixed covariates according to status at baseline. The risk reduction was more pronounced in younger patients, but there was no treatment-by-sex interaction. For hip fracture (**Figure 2**), the HR for hip fracture decreased below 1.0 for MPR values of 70% and higher, with a mean HR of 0.71 (95% CI, 0.56-0.85) at 100% MPR. In patients younger than 70 years, the HR was 0.53 (95% CI, 0.41-0.70) compared with 0.71 (95% CI, 0.62-0.82) in those 70 years or older. The HR for major osteoporotic nonhip fracture risk at 100% MPR was 0.44 ($P<.001$; data not shown).

BLUNTING OF ANTIFRACTURE EFFICACY BY PPI

For hip fractures, interaction terms for concurrent PPI use were statistically significant when added to the base models ($P<.05$). The treatment response associated with complete refill compliance was a 39% risk reduction (HR, 0.61; 95% CI, 0.52-0.71; $P<.001$) in patients who were not PPI users, while the risk reduction in PPI users was not significant (19%; HR, 0.81; 95% CI, 0.64-1.01; $P=.06$). The attenuation of the risk reduction depended on the cumulative PPI dose, with a cumulative PPI dose of 1 to 359 DDDs having no impact on the treatment response at the hip but with a progressive impact of larger exposures

Table 3. Fracture Numbers and Incidence Rates by Age and Proton Pump Inhibitor (PPI) Exposure[a]

Age, y	Patients, No.	Fractures, No. (%)				Incidence per 1000 Patient-years			
		Hip	Spine	Humerus	Forearm	Hip	Spine	Humerus	Forearm
<70									
None	13 116	300 (2.3)	45 (0.3)	65 (0.5)	160 (1.2)	6.5	1.0	1.4	3.4
PPI	4089	126 (3.1)	29 (0.7)	36 (0.9)	61 (1.5)	8.5	2.0	2.4	4.1
≥70									
None	14 795	1177 (8.0)	80 (0.5)	169 (1.1)	245 (1.7)	25.2	1.7	3.6	5.2
PPI	6088	468 (7.7)	63 (1.0)	64 (1.1)	93 (1.5)	24.4	3.3	3.3	4.8
All									
None	27 911	1477 (5.3)	125 (0.4)	234 (0.8)	405 (1.5)	15.8	1.3	2.5	4.3
PPI	10 177	594 (5.8)	92 (0.9)	100 (1.0)	154 (1.5)	17.4	2.7	2.9	4.5
Total	**38 088**	**2071** (5.4)	**217** (0.6)	**334** (0.9)	**559** (1.5)	16.2	1.7	2.6	4.4

[a]Refer to the "Results" section for hypothesis tests and interactions.

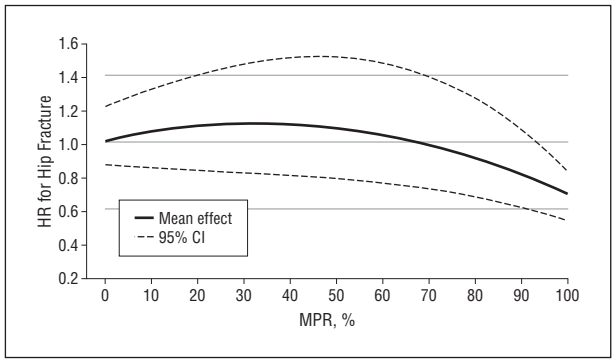

Figure 2. Base model. This illustrates the model fitted to fracture outcomes (exemplified by hip fracture) using alendronate sodium refill compliance (medication possession ratio [MPR]) as the time-dependent covariate. The analysis was adjusted for age, sex, comorbid conditions, prior fracture, and the number of comedications. Data are given as mean effect and 95% confidence interval (CI). The number of patients was 38 088 (MPR <25%, N=7905; MPR 25%-49%, N=3045; MPR 50%-74%, N=3419; and MPR >75%, N=23 719). The x-axis shows fracture risk as a function of alendronate refill compliance from 0% to 100% and is not a time axis. HR indicates hazard ratio.

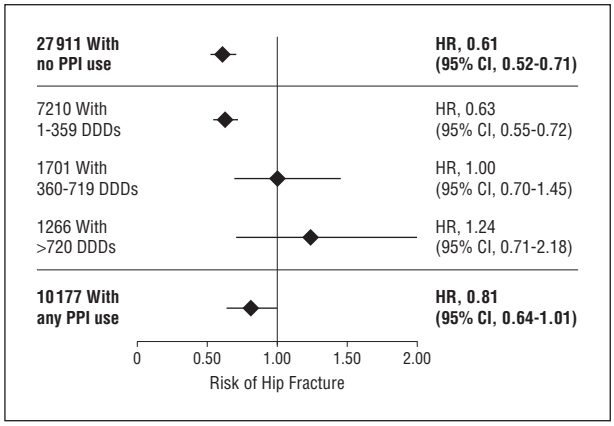

Figure 3. Proton pump inhibitor (PPI) use and fracture risk. Hazard ratios (HRs) (diamonds) and 95% confidence intervals (CIs) illustrating the hip fracture risk reduction theoretically associated with 100% refill compliance for alendronate sodium, with and without concurrent use of PPI. Refer to the "Results" section for interaction tests. Note attenuation of antifracture efficacy associated with increasing exposure to PPI. DDD indicates defined daily dose.

(**Figure 3**). We could demonstrate no risk reduction with alendronate in patients exposed to more than 360 DDDs of a PPI. By contrast, there was no significant interaction between PPI use and the treatment response to alendronate for fracture of the spine, humerus, or forearm. In addition, there was no interaction between the hip fracture risk reduction driven by the degree of alendronate refill compliance (MPR) and prior PPI use ($P=.31$). As for the interaction between alendronate and concurrent PPI use on hip fracture risk, this was statistically significant only in patients older than 70 years (**Figure 4**), whereas the difference between hip fracture rates in PPI users vs nonusers among persons younger than 70 years (Table 3) was accounted for by differences in baseline characteristics and in refill compliance.

OTHER DRUG EXPOSURES

In contrast to what was observed in PPI users, concurrent histamine H_2 receptor blocker use did not modify the treatment response to alendronate (interaction term with alendronate MPR, $P=.06$; alendronate effect: HR, 0.66; 95% CI, 0.58-0.75 in nonusers and HR, 0.69; 95% CI, 0.45-1.05 in users of histamine H_2 receptor blockers). However, a significant interaction ($P=.02$) was observed with oral glucocorticoid use. The direction of this interaction was the opposite of that seen with PPIs, indicating a slightly greater benefit in patients who were exposed to oral glucocorticoids. In nonusers of oral glucocorticoids the alendronate effect yielded an HR of 0.67 (95% CI, 0.58-0.78) and in patients exposed to oral glucocorticoids, an HR of 0.65 (95% CI, 0.51-0.83).

SENSITIVITY ANALYSIS

We confirmed the results on PPI coadministration using an alternative approach, in which PPI dose was entered as a time-dependent covariate after first stratifying the study population for alendronate refill compliance over the observation period. In this analysis, MPR for coadministered PPIs was time dependently associated with an increased risk of hip fractures in users who were highly refill compliant with alendronate (MPR >75%: HR, 1.28; 95% CI, 1.05-1.56) and moderately refill compliant (MPR 50%-75%: HR, 1.53; 95% CI, 1.02-2.29), but not in patients with low refill compliance for alendronate (MPR <50%: HR, 0.97; 95% CI, 0.76-1.24).

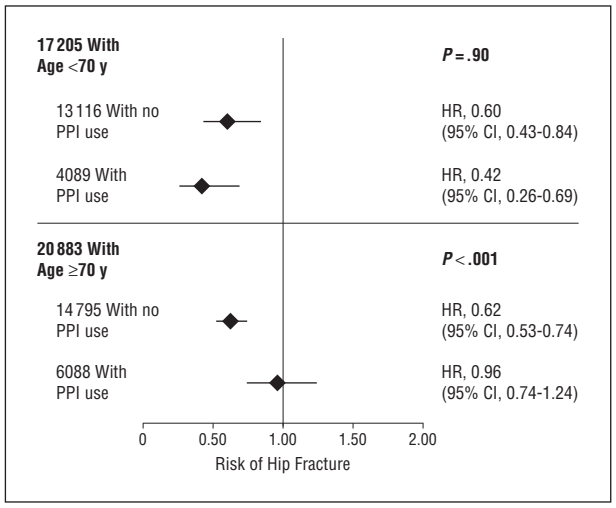

Figure 4. Proton pump inhibitor (PPI) use and fracture risk. Hazard ratios (HRs) (diamonds) and 95% confidence intervals (CIs) illustrating the hip fracture risk reduction theoretically associated with 100% refill compliance for alendronate sodium, shown separately for patients younger than 70 years and those 70 years or older. Refer to the "Results" section for interaction tests.

COMMENT

Proton pump inhibitors are often prescribed inappropriately,[1] and the present observational study using national prescription and health outcomes data for Denmark suggests a pronounced blunting of the antifracture efficacy of alendronate, with loss of half the effect against hip fractures in patients who take PPIs. This is a major concern because PPIs are now taken by a large proportion of elderly individuals, with 18% of alendronate users being baseline PPI users and 26% having taken PPIs at some point within the first 3 years of their treatment with alendronate in the present study. The association was dose dependent, with very minor impact of using PPIs for less than 1 dose-year (ie, 360 DDDs) but apparent complete loss of antifracture efficacy at the hip in users of more than 720 DDDs. On average, PPI users had only half the hip fracture risk reduction with alendronate seen in PPI nonusers. Although significant in the total study population, the effect was driven by the patients 70 years or older with no attenuation of antifracture efficacy in the younger age group. No such effects were seen with histamine H_2 receptor blockers that would be targeted to a similar group of patients but which have a different mechanism of action.

Bone remodeling is a coupled process, during the early stages of which an acidic environment is created underneath the ruffled border of the osteoclast through the action of vacuolar H^+-ATPase (V-ATPase), the osteoclast proton pump. Formation of this acidic enclosure is a *sine qua non* for osteoclastic bone resorption. Although this proton pump, like that of gastric cells, is inhibited by omeprazole, in vitro studies[16] indicate that much higher concentrations are required to inhibit osteoclast resorbing activity than acid production in gastric glands. Therefore, while PPIs could theoretically maintain skeletal integrity through acting as antiresorptives, this would seem to require doses several-fold larger than those needed to treat gastroesophageal reflux or ulcer disease. By contrast, through their desired action toward raising gastric pH via inhibition of the gastric H^+/K^+ ATPase, PPIs may reduce the absorption of calcium[2] and vitamin B_{12}.[3] Deficiency states for vitamin B_{12} have been linked to osteoporosis in elderly patients in several studies,[17-20] as has genetic variation in vitamin B_{12} metabolism.[21-24] *Helicobacter* infection itself—which would be much more prevalent in PPI users than in the general population—has also been linked to osteoporosis.[25] Data from the Study of Osteoporotic Fractures indicate that reduced calcium absorption is a strong predictor for hip fracture in elderly women,[26] but 30 days of continuous PPI use was recently shown not to affect fractional calcium absorption in postmenopausal women.[27] Proton pump inhibitors are not likely to impair absorption of alendronate itself. Like other oral bisphosphonates, alendronate is poorly absorbed, but raising gastric pH increases rather than decreases the bioavailability of alendronate.[4]

One prior study[7] has examined the possibility that patients receiving acid suppressing medications may benefit less from oral bisphosphonates. Using cohort data from the General Practice Research Database (http://www.gprd.com/products/database.asp), de Vries et al[7] found that patients who were exposed to PPI at a daily dose higher than 1 DDD were at increased risk of hip fracture while taking bisphosphonates compared with patients receiving bisphosphonates alone. However, this effect could not be shown to persist with longer durations of PPI treatment, but most patients were coadministered PPIs for less than 12 months.

There is some evidence that PPI use is associated with hip fracture risk,[4-6] but this is not supported in all studies.[9,10] There is also evidence that PPI use is associated with risk of vertebral fracture[6,7] or all fractures. However, causality is difficult to ascribe because the effect is not always related to duration of use,[6,7,11] and women may be affected more than men.[28] Some important limitations should be borne in mind. This is an observational study. Because there is no placebo group, the effect of alendronate is captured through the relationship between refill compliance and the reduction in fracture risk. While this produced a risk estimate that is remarkably similar to that reported in phase 3 trials with alendronate,[29,30] as was also the case in other observational studies,[15] patients with low refill compliance may differ in unmeasured confounders from patients with high refill compliance, and this may produce an additional risk reduction that is not due to the drug. This can bias the interaction estimate. Owing to the nonrandomized nature of PPI exposure, as illustrated in Table 1, patients with osteoporosis who take PPIs differ in comorbidity from patients with osteoporosis who do not. In our study, PPI users benefited less from alendronate in terms of hip fracture risk than did nonusers. We included both comorbidity and comedication terms in the base models, but because the 2 groups may differ in other, unmeasured confounders it remains possible that the difference in alendronate response is driven not by PPIs themselves but by differences in nonskeletal risk factors for osteoporosis that would not respond to bisphosphonates. However, support for causality is provided by the finding of a pronounced dose-response relationship, by the impact of current but not past PPI use, and also to some ex-

tent by the absence of similar effects by histamine H_2 receptor blockers when addressed in the same way. Furthermore, when we applied the same analytical approach to a known strong risk factor for osteoporotic fractures—oral glucocorticoids—the analyses did not result in a spurious blunting of alendronate effect due to use of glucocorticoids preferentially by high-risk patients but to the method correctly identifying a pronounced treatment effect for alendronate under these circumstances, which remains a key indication for oral bisphosphonates and one which has been verified in clinical trials.[31]

Additional limitations to the study include lack of information about nonprescription histamine H_2 receptor blocker use, which could mask a relationship between histamine H_2 receptor blockers and the response to alendronate. Also, patients may have filled prescriptions for drugs that they did not subsequently take. Finally, it is not possible to capture individual drug exposures during hospital stays, but this is unlikely to significantly affect the findings.

The Danish National Hospital Discharge Register has very good validity for hip fractures,[32] but it has not been thoroughly evaluated for other fractures, and there is little doubt that many mild or moderate osteoporotic spine fractures are treated by family physicians or other health care providers outside a hospital setting.

The study has important strengths. It is a large population-based study that used national health care data for all incident alendronate users in the country, including patients with comorbid conditions who would not have been included in phase 3 trials but who are a major part of the treated population in the real-world scenario. The data source is not insurance claim based but includes all residents in the country irrespective of employment conditions or age. Also, complete information on death and emigration is available, ensuring that participants are not lost to follow-up. Because use of PPIs during bisphosphonate therapy could be an indicator of upper GI tract tolerability problems and consequently poor adherence to therapy, we did not simply compare the fracture rates between PPI users and nonusers but instead examined if PPI users differed from nonusers in terms of their refill compliance-driven fracture risk reduction. It is important to perform the analysis in this way rather than simply use the overall fracture rates, because this makes allowance for the possibility that patients who experience upper GI tract symptoms may skip more doses than do patients without such complaints. In conclusion, these findings suggest that PPIs in commonly used doses may lead to major attenuation of the antifracture efficacy of alendronate against hip fracture in a real-world setting. This is a concern given the widespread use of both oral bisphosphonates and PPIs in elderly patients.[1] We were also able to examine prescriptions for histamine H_2 receptor blockers and found no blunting of the response to alendronate with this class of drugs. Additional research is needed to verify the interaction with PPI use and to further explain the mechanisms. Pending such studies, GI tract complaints during treatment with oral bisphosphonates should not be managed by addition of a PPI but by using histamine H_2 receptor blockers or by changing to parenteral or other therapy.

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Correspondence: Bo Abrahamsen, MD, PhD, Department of Medicine F, Copenhagen University Hospital Gentofte, DK-2900 Hellerup, Denmark (b.abrahamsen@physician.dk).
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INVITED COMMENTARY

ONLINE FIRST

Opportunities to Decrease Inappropriate Uses of Proton Pump Inhibitors

The May 2010 issue of the *Archives* included 3 articles on the harms of PPIs: Gray et al[1] showed that PPIs were associated with an increase in the rate of spine, lower arm, and total fractures; Howell et al[2] showed that PPIs increased the risk of *Clostridium difficile* infection; and Linsky et al[3] showed that PPIs also increased the recurrence of *C difficile* infection. We deliberately grouped these articles together because we wanted to draw attention to the adverse effects of these drugs given data showing that 53% to 69% of PPI prescriptions are for inappropriate indications.[4-6]

See also page 991

We were pleased that just after publication of these articles the US Food and Drug Administration[7] issued a warning about the increased risk of hip, wrist, and spine fractures with high or long-term use of PPIs. For over-the-counter administration, for which patients may not have a physician guiding their use of PPI treatment, the agency advised patients to limit the length of course of treatment to 14 days and no more than three 14-day courses per year. We hope that adding fractures to the warning label of PPIs will help to stem the overuse of these agents.

Two articles in this issue of the *Archives* offer 2 more opportunities to decrease the use of PPIs. Abrahamsen et al show that concurrent use of PPIs decreased the effectiveness of alendronate sodium in preventing hip fracture. There was no similar reduction in the effectiveness of alendronate among patients taking histamine H2 receptor blockers, suggesting that the effect was not confounded by the tendency to prescribe or take acid-reduction medications. Although the mechanism by which PPIs decreased the effectiveness of alendronate is not known, patients taking alendronate represent a group for whom alternatives to PPIs should be sought.

Herzig et al[8] conducted a careful pharmacoepidemiologic analysis of patients admitted to an academic medical center. They found that even though acid-suppression prophylaxis is not recommended for hospitalized patients unless they are in the intensive care unit, 59% of the admitted patients were prescribed an acid-suppressive regimen. Using a propensity score analysis, the authors found that acid-suppressive regimens decreased nosocomial GI tract