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 B₁₂, 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 H₂ 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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PROTON PUMP INHIBITORS (PPIs) are very widely used among the elderly population with a considerable overlap with the population that receives antosteoporotic 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 Archives¹ 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 B₁₂, 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.⁵⁻⁶ 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.⁷ Several studies suggest a causal relationship⁸⁻¹⁰ between PPI use and fractures, while other studies do not¹⁰,¹¹ 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 H₂ 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.

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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 antosteoporotic 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 1993 (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 H2 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 on the date of fracture or death. Information on death during the first 36 months of alendronate treatment, truncate.

The calculation assumed that 25% of alendronate users would be concurrent users of PPIs. The most commonly used PPIs during treatment with alendronate were esomeprazole (41.6%) and (2) concurrent use was defined as any prescription filled in the past 12 months before the index date, 26% had filled prescriptions. 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 H2 receptor blockers, and 18.1% for PPIs. The most commonly used PPIs during treatment with alendronate were esomeprazole magnesium and omeprazole sodium.

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 χ2 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 comediations 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.

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 30% 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

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 H2 receptor blockers, and 18.1% for PPIs. The most commonly used PPIs during treatment with alendronate were esomeprazole magnesium and omeprazole sodium.

BASE MODELS TESTING THE EFFECT OF ALENDRONATE

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

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 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Study Population (n=38 088)</th>
<th>No (n=27 911)</th>
<th>Yes (n=10 177)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first Rx, mean (SD) [range], y</td>
<td>70.4 (10.9) [35-101]</td>
<td>70.0 (10.7) [35-100]</td>
<td>71.6 (10.9) [35-101]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>16.9</td>
<td>16.0</td>
<td>19.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of fracture after age 50 y</td>
<td>29.9</td>
<td>29.2</td>
<td>31.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.6</td>
<td>2.0</td>
<td>4.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.6</td>
<td>2.2</td>
<td>3.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4.0</td>
<td>3.5</td>
<td>5.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.9</td>
<td>0.9</td>
<td>1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>12.6</td>
<td>10.5</td>
<td>18.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Collagen disease</td>
<td>7.5</td>
<td>6.4</td>
<td>10.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Uler disease</td>
<td>2.5</td>
<td>1.2</td>
<td>6.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>.78</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.4</td>
<td>0.3</td>
<td>0.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DM, no complications</td>
<td>3.2</td>
<td>2.6</td>
<td>4.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DM complications</td>
<td>0.8</td>
<td>0.6</td>
<td>1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1.1</td>
<td>0.8</td>
<td>1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>0.2</td>
<td>0.1</td>
<td>0.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>5.7</td>
<td>5.1</td>
<td>7.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Solid metastatic tumor</td>
<td>0.6</td>
<td>0.5</td>
<td>0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AIDS or HIV</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>.58</td>
</tr>
<tr>
<td>Charlson index, mean (SD) [range]c</td>
<td>0.8 (1.4) [0-15]</td>
<td>0.7 (1.4) [0-15]</td>
<td>1.2 (1.7) [0-13]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comedications, mean (SD), No.</td>
<td>8.6 (6.1)</td>
<td>7.5 (5.5)</td>
<td>11.8 (6.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any prednisolone, past 12 mo</td>
<td>26.1</td>
<td>22.5</td>
<td>35.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cumulative prednisolone, mg, past 12 mo, mean (SD)</td>
<td>794.0 (1772.0)</td>
<td>666.7 (1628.2)</td>
<td>1145.2 (2078.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any PPI Rx, past 12 mo</td>
<td>18.1</td>
<td>6.2</td>
<td>50.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any H2RA Rx, past 12 mo</td>
<td>5.5</td>
<td>4.2</td>
<td>8.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of follow-up, mean (SD)</td>
<td>3.3 (2.3)</td>
<td>3.4 (2.3)</td>
<td>3.3 (2.1)</td>
<td>&lt;.75</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Name</th>
<th>DDD, mg</th>
<th>DDDs in Analysis</th>
<th>Total PPI DDDs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A02BC01</td>
<td>Omeprazole sodium</td>
<td>20</td>
<td>1 024 000</td>
<td>31.8</td>
</tr>
<tr>
<td>A02BC02</td>
<td>Pantoprazole sodium</td>
<td>40</td>
<td>562 500</td>
<td>18.1</td>
</tr>
<tr>
<td>A02BC03</td>
<td>Lansoprazole</td>
<td>30</td>
<td>595 000</td>
<td>18.5</td>
</tr>
<tr>
<td>A02BC04</td>
<td>Rabeprazole sodium</td>
<td>29</td>
<td>27 500</td>
<td>0.9</td>
</tr>
<tr>
<td>A02BC05</td>
<td>Esomeprazole magnesium</td>
<td>30</td>
<td>994 000</td>
<td>30.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>3 223 000</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: ATC, Anatomical Therapeutic Chemical; DDD, defined daily dose (World Health Organization13).
(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 H2 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 H2 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).
Proton pump inhibitors are often prescribed inappropriately, 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 at-tenuation of antifracture efficacy in the younger age group. No such effects were seen with histamine H2 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+/K+-ATPase (V-ATPase), the osteoclast proton pump. Formation of this acidic enclosure is a sine qua non for osteoclastic bone resorption. Althou...
tent by the absence of similar effects by histamine H2 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 H2 receptor blocker use, which could mask a relationship between histamine H2 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 H2 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 H2 receptor blockers or by changing to parenteral or other therapy.

Accepted for Publication: December 3, 2010. Published Online: February 14, 2011. doi:10.1001/archinternmed.2011.20. This article was corrected for typographical errors on June 13, 2011.

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Author Contributions: Study concept and design: Abrahamsen. Acquisition of data: Abrahamsen. Analysis and interpretation of data: Abrahamsen, Eiken, and Eastell. Drafting of the manuscript: Abrahamsen, Eiken, and Eastell. Critical revision of the manuscript for important intellectual content: Abrahamsen, Eiken, and Eastell. Statistical analysis: Abrahamsen. Obtained funding: Abrahamsen. Administrative, technical, and material support: Abrahamsen.

Financial Disclosure: Dr Abrahamsen has received consultancy fees from Nycomed, Amgen, and Novartis; research grants from Roche; and speakers’ fees from Servier, Eli Lilly, and MSD. Dr Eiken has received consultancy fees from Nycomed and Amgen and speakers’ fees from Novartis and Eli Lilly. Dr Eastell has received consulting or advisory board fees from Amgen, Novartis, Procter & Gamble, Servier, Ono Pharmaceutical, and GlaxoSmithKline; lecture fees from Eli Lilly; and grant support from AstraZeneca, Procter & Gamble, and Novartis.

Funding/Support: This study was made possible through grant support from Kaptajnlejntarm Harald Jensen og Hustrus Fond, Denmark. Dr Eastell was partly funded by the National Institute for Health Research (NIHR) via its Biomedical Research Units funding scheme for musculoskeletal health (April 2008–March 2012).

Role of the Sponsors: The funding sources had no role in any part of the design, execution, interpretation, or presentation of this study.

Disclaimer: The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service, United Kingdom, the NIHR, or the Department of Health.

REFERENCES


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 showed that PPIs were associated with an increase in the rate of spine, lower arm, and total fractures; Howell et al showed that PPIs increased the risk of *Clostridium difficile* infection; and Linsky et al showed that PPIs also increased the recurrence of *Clostridium 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

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We were pleased that just after publication of these articles the US Food and Drug Administration7 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 on risk of fracture in women with existing vertebral fractures. Lancet. 1996;348(9041):1535-1541.


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