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# Gastric and Duodenal Safety of Daily Alendronate

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**Background:** Isolated case reports of gastric ulcers after alendronate sodium use raised concern about the gastroduodenal safety of daily alendronate. This study was conducted to estimate the excess risk of hospitalizations for gastric or duodenal perforations, ulcers, and bleeding associated with alendronate use.

**Participants and Methods:** Study subjects were 6432 men and women, 35 years or older. The subjects were members of 8 health maintenance organizations who were dispensed alendronate from October 1995 through September 1997. There was also a group of 33 176 age-, sex-, and health maintenance organization–matched unexposed persons. Because of concerns that osteoporosis might confound the association between alendronate use and perforation, ulcer, or bleeding, a second comparison group of 9776 women, 60 years or older, who had osteoporotic fractures was assembled. Hospitalizations for gastroduodenal events were identified by discharge diagnosis codes in automated claims records, and confirmed by manual record review.

**Results:** Based on the 14 confirmed events in the alendronate group and 35 in the unexposed group, the crude incidence rate ratio of gastroduodenal perforation, ulcer, or bleeding for the alendronate cohort was 3.0. The incidence rate ratio was 1.8 (95% confidence interval, 0.8–3.9) after control for prior hospitalizations, comorbidity, and recent exposure to prescription nonsteroidal anti-inflammatory drugs and oral corticosteroids. The crude incidence ratio rate for the age, sex, and health maintenance organizations–restricted cohort of alendronate users relative to the fracture cohort was 1.1 and the adjusted incidence rate ratio was 1.1 (95% confidence interval, 0.6–2.2).

**Conclusions:** Osteoporosis and related factors appear to play an important role in the relationship between alendronate use and confirmed gastroduodenal perforation, ulcer, or bleeding; a substantial fraction of the increased risk we observed for alendronate users in the unadjusted analysis was the result of confounding.

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**T**EN MILLION to 20 million postmenopausal women in the United States have osteoporosis. The enormous medical, social, and economic consequences are due primarily to osteoporotic fractures; in 1995 they were responsible for at least 400 000 hospitalizations, 2.5 million physician visits, and medical expenditures of nearly \$14 billion.<sup>1,2</sup> Several clinical trials have demonstrated the efficacy of alendronate sodium to treat osteoporosis and prevent osteoporotic fractures.<sup>3-8</sup> Although esophageal irritation was recognized as a potential side effect of alendronate, reports to the Food and Drug Administration in 1996 and 1997 raised concern that alendronate may have previously unappreciated potential for gastric and duodenal injury, especially among the elderly.<sup>9-11</sup>

This observational study was designed to compare the incidence of hospitalizations for gastric or duodenal perforations, ulcers, and bleeding among users

of alendronate with that among a randomly selected, unexposed group. However, osteoporosis (the condition for which alendronate is indicated) is associated with excess nontrauma mortality<sup>12-14</sup> and was therefore a potential confounder in the association between alendronate use and gastrointestinal injury. Although the prevalence of osteoporosis among the study population could not be directly measured, we sought to approximate the magnitude of this potential confounding effect by comparing the rates of gastroduodenal perforations, ulcers, and bleeding in a cohort of older women who had nonpathologic fractures with age-matched women exposed to alendronate.

## RESULTS

### STUDY COHORTS

A total of 6549 eligible men and women 35 years and older had 1 or more dispens-

Author affiliations are listed at the end of this article.

## PARTICIPANTS AND METHODS

### STUDY POPULATION

This was a retrospective cohort study of health plan members of 8 health maintenance organizations (HMOs) in geographically diverse locations. The institutional review board of each HMO approved the study protocol. Membership, demographic, drug dispensing, and hospital discharge information were obtained from automated databases at each HMO. Eligible subjects were continuously enrolled in the HMO for at least 1 year after October 1, 1994 (1 year before the initial marketing of alendronate), had prescription drug coverage during the entire observation period, and had hospital records generally accessible to study personnel. Three study cohorts (alendronate, unexposed, and fracture) were identified.

The exposed cohort consisted of persons who were dispensed 10-mg tablets of alendronate at least once from October 1995 through September 1997 and were 35 years or older at the time of the first alendronate dispensing. Person-time at risk for an individual started on the date alendronate was dispensed and extended for a number of days equal to the number of tablets dispensed, according to the recommended dose of 1 10-mg tablet per day. When dispensings overlapped, the number of tablets dispensed in all such dispensings was summed and time at risk was computed from the first dispensing date. Only the first 15 days of a gap in dispensing were considered alendronate-exposed time. Person-time at risk ended on whichever of the following occurred first: September 30, 1997; first hospitalization for confirmed esophageal, gastric or duodenal perforations, ulcers, or bleeding; disenrollment; or the date that the last dispensed alendronate pills were supposed to be taken, plus 15 days. Since the 40- and 5-mg tablets were infrequently dispensed (52 and 65 persons, respectively), individuals who were given these dosages were not included in the study.

The unexposed cohort was frequency matched to the alendronate cohort with respect to age and sex at a ratio of 5:1 within each HMO. These individuals were not given alendronate and person-time at risk for each was counted from a randomly chosen referent date after October 1, 1995, to whichever the following occurred first: September 30, 1997; first hospitalization for confirmed esophageal, gastric, or duodenal perforations, ulcers, or bleeding; or disenrollment.

The fracture cohort was composed of women older than 60 years as of October 1, 1994, judged to have a high prevalence of osteoporosis. They were from 7 of the 8 participating HMOs, and had at least 1 diagnosis code between October 1994 and September 1997 for fracture of the hip, humerus, distal tibia, vertebrae, or wrist in ambulatory or hospital records. Women who had at least 1 diagnosis code that represented bone cancer, breast cancer, colon cancer, lung cancer, cancer metastasis, multiple myeloma, concurrent major trauma, or pathologic fracture were excluded. As part of a secondary analysis, the fracture cohort was further subdivided into a hip fracture group and a nonhip fracture group. Women who had multiple fractures, one being a hip fracture, were classified as having hip fracture. Diagnosis codes for hip fracture have been reported to have high predictive value positive rates.<sup>15</sup> We reviewed medical records of a random sample of 404 women who fulfilled the selection criteria for nonhip fractures to evaluate the accuracy of the fracture identification algorithm. We calculated the proportion of true positives for each nonhip anatomic site at each HMO and excluded cases of fracture sites from HMOs that had a true-positive rate of less than 60%. Among the remaining fracture groups reviewed, 314 (82%) of 383 women were confirmed to have a nonpathologic fracture. Fracture-exposed person-time started on October 1, 1995, and continued until the earliest of September 30, 1997; disenrollment; first dispensing of alendronate; or first hospitalization for confirmed esophageal, gastric, or duodenal perforations, ulcers, or bleeding.

Continued on next page

ings of alendronate between October 1, 1995, and September 30, 1997. Analysis was restricted to the 6432 persons who were dispensed the 10-mg tablet exclusively. Nearly 60% of the alendronate users were 65 years or older, 3% were younger than 45 years, and 92% were women (**Table 1**). The median number of 10-mg tablets dispensed per person during the study period was 180; the median number of dispensings was 3. The median number of days from October 1, 1995, to the first alendronate dispensing was 362, ranging from 16 to 730.

When comparing the alendronate users with the 33 176 unexposed subjects, the median chronic disease score for persons exposed to alendronate was 39% greater than the unexposed group (Table 1). In 25 of 29 drug categories used to compute the chronic disease score, alendronate users were significantly more likely to have 1 or more dispensings during the year before the first dispensing of alendronate (or the random start date for the unexposed group). Differences were most marked for persons being treated for rheumatoid arthritis, asthma, and gastric acid disorder. Persons dispensed alendronate were

73% more likely to have been hospitalized at least once for any reason during the prior year than their unexposed counterparts.

There were 9776 women, 60 years or older, in the fracture group and 3863 women in the corresponding subset of age-sex-HMO-restricted alendronate users. These 2 groups had similar median chronic disease scores and proportions of subjects who had at least 1 nonfracture hospitalization during the previous year (Table 1).

### INCIDENCE OF GASTRODUODENAL PERFORATIONS, ULCERS, AND BLEEDING

From the HMO databases, 1376 hospitalizations with 1 or more diagnoses of interest were identified from the 3 study cohorts. The hospitalizations were approximately uniformly distributed during the study period. Hospital records were reviewed for 1041 (76%) of the 1376 potential perforations, ulcers, or bleeding episodes; study personnel were denied access to most of those that were not reviewed. The proportion of charts unavailable for review was

## ASCERTAINMENT OF OUTCOMES

Persons with upper gastrointestinal events of interest were identified in each HMO by a 3-step procedure: (1) computerized search of claims files; (2) abstraction of hospital records; and (3) confirmation of perforations, ulcers, or bleeding. Hospital claims files were searched with *International Classification of Diseases, Ninth Revision, Clinical Modification* codes from October 1995 through September 1997 for the discharge diagnoses of gastric ulcer (531.xx), duodenal ulcer (532.xx), peptic ulcer (533.xx), gastrojejunal ulcer (534.xx), gastrointestinal hemorrhage (578.xx), or esophageal ulcer (530.2). Full-text hospital records from hospitalizations with any one of these codes were reviewed to abstract additional information to confirm or reject the diagnosis and to determine the time of onset of signs and symptoms (before or after admission to the hospital). Three investigators (J.G.D., K.A.C., and R.P.) who were blinded to alendronate exposure status, reviewed the anonymized abstraction forms. The second reviews were conducted for all individuals except those for whom the primary review clearly indicated that there was no perforation, ulcer, or bleeding. Final arbitration of the small number of indeterminate records that remained was performed in a blinded manner by a gastroenterologist (T.R.L.).

Persons were classified as cases if they were hospitalized for esophageal, gastric, or duodenal ulcer as confirmed by surgery, endoscopy, radiology, or autopsy. In addition, cases included persons with upper gastrointestinal hemorrhage determined by surgery, endoscopy, radiology, or autopsy to originate from esophageal, gastric, or duodenal ulcer; hemorrhagic gastritis; or duodenitis. Excluded from both the case and comparison groups were persons with esophageal, gastric, or duodenal events with onset during hospitalization or other specified pathological conditions (eg, neoplasm). Cases of duodenal and pyloric ulcer were classified as "duodenal ulcer." Cases of gastric, gastrojejunal, and gastric or duodenal ulcer occurring simultaneously were classified as "gastric ulcer."<sup>16</sup>

Persons with nonprimary esophageal ulcers concurrent with gastric or duodenal ulcers were also classified by either gastric or duodenal ulcer as noted above.

## ADJUSTMENT FOR COMORBIDITY

Comorbidity was assessed through the chronic disease score, which is based on age, sex, and dispensings of prescription drugs used to treat specific chronic diseases during the previous 12 months.<sup>17,18</sup> The scores are directly related to and predictive of utilization of health care resources; higher scores reflect higher health care costs.<sup>17-19</sup>

## DATA ANALYSIS

We used the method of Breslow to estimate the incidence rate ratios (IRRs) and 95% confidence intervals (CIs).<sup>20</sup> The protocol-defined primary analysis was to compare the incidence of gastric or duodenal perforations, ulcers, and bleeding among the alendronate cohort, the unexposed cohort, and the fracture cohort. Secondary analyses included the evaluation of event rates among the hip and nonhip fracture groups and comparisons with the age-sex-HMO-restricted alendronate cohort. The impact of potential effect modification and confounding by oral corticosteroids and prescription nonsteroidal anti-inflammatory drugs (NSAIDs) was assessed by stratification and regression modeling. Individuals with a confirmed event were classified as exposed to prescription NSAIDs if they were dispensed a prescription NSAID during the 45 days of eligible person-time before onset of the event. Persons without an event were classified as exposed if a prescription NSAID was dispensed during the 45 days preceding a randomly chosen date during eligible person-time. A similar strategy was used to classify oral corticosteroid exposure. We used Poisson regression to obtain the hazard rate estimates under a censored exponential event-time model.<sup>21</sup> Confidence intervals were formed with model-robust SEs that are consistent regardless of the adequacy of the exponential model for the process under consideration.<sup>22</sup>

similar between alendronate users (28%) and unexposed individuals (30%), but lower for the fracture cohort (18%).

### Alendronate Users vs Unexposed Cohort

Among the alendronate and unexposed cohorts, 167 (28%) cases of upper gastrointestinal perforation, ulcer, or bleeding were confirmed by record review; 155 were gastroduodenal and 12 were esophageal. Of the 155 persons with gastroduodenal perforation, ulcer, or bleeding, 49 (32%) had their event during at-risk person-time; 14 were alendronate users and 35 were from the unexposed group. No person had more than 1 confirmed event. For most cases among the alendronate users, the perforation, ulcer, or bleeding event occurred at a time relatively distant from their initial alendronate dispensing (median, 198 days). The incidence rates of gastroduodenal perforation, ulcer, or bleeding at various durations of alendronate therapy were not significantly different ( $P = .59$ ; **Table 2**).

The crude incidence rate of gastroduodenal perforation, ulcer, or bleeding for the alendronate cohort (3.4 per

1000 person-years) was 3 times (95% CI, 1.6-5.5) greater than the crude rate for the unexposed group (1.1 per 1000 person-years). The IRR was 1.8 (95% CI, 0.8-3.9) after adjustment for age, sex, chronic disease score, recent exposure to prescription NSAIDs and oral corticosteroids, and the number of hospitalizations in the year before the first dispensing of alendronate (or the referent date for the unexposed group; **Table 3**). When terms for the interaction of alendronate exposure with prescription NSAIDs and oral corticosteroids were included in the full model, only the term for corticosteroids significantly improved the fit of the model ( $P < .03$ ). Stratified regression analysis showed an adjusted IRR of 2.8 (95% CI, 1.4-5.8) for those without recent use of oral corticosteroids and an adjusted IRR of 2.6 (95% CI, 1.1-6.3) for those with no recent NSAID use. The IRR was less than 1, with wide CIs, for those with recent use of drugs from either category, but there were few patients in these strata and the estimates were unstable (data not shown).

The event rate among alendronate users during time not exposed to alendronate was not significantly differ-

**Table 1. Baseline Characteristics of the Study Cohorts**

Characteristic	Alendronate (Full) (n = 6432)	Unexposed (n = 33 176)	Alendronate (Women Aged ≥60 y) (n = 3865)	Fracture (n = 9776)
Age, median (range), y	67 (35-97)	67 (35-105)	72 (60-97)	75 (60-104)
Women, %	92	91	100	100
Chronic disease score, median	3829	2756	5573	5495
Hospitalized during year prior to index date, %*	19	11	19	19
Chronic disease score categories†				
Rheumatoid arthritis	26.3	8.9	30.1	16.2
Gastric acid disorder	24.2	16.0	37.0	29.2
Malignancies	9.8	2.9	11.9	3.6
Asthma/respiratory illness	28.6	19.5	41.7	39.2

\*Index date was date of first alendronate sodium dispensing for the alendronate cohort, the randomly selected reference date for the comparison cohort, and October 1, 1995, for the fracture cohort. Only nonfracture hospitalizations were counted for the fracture group.

†Percentage of persons with 1 or more dispensings of drugs used to treat selected chronic diseases during the year before the index date. The chronic disease score categories shown are the most directly relevant to upper gastrointestinal tract disease.

**Table 2. Rate of Confirmed Gastroduodenal Perforation, Ulcers, and Bleeding by Duration of Alendronate Therapy**

	Duration of Alendronate Therapy, d			Total
	1-30	31-90	≥91	
No. of confirmed events*	2	1	11	14
Person-time at risk, y	515	868	2755	4138
Incidence rate (95% CI)†	3.9 (0.5-14.0)	1.1 (0.0-6.4)	4.0 (2.0-7.1)	3.4 (1.8-5.7)

\*Restricted to gastroduodenal events that occurred during alendronate sodium–exposed time.

†Unadjusted incidence rate (per 1000 years).  $\chi^2$  Test for trend = 0.29,  $P = .59$ . CI indicates confidence interval.

**Table 3. Adjusted Incidence Rate Ratios for Gastroduodenal Perforation, Ulcers, and Bleeding Derived From Poisson Regression Models\***

	Incidence Rate Ratio (95% CI)	
	Alendronate Users (n = 6432) vs Unexposed Cohort (n = 33 176)	Age-Sex-HMO–Restricted Alendronate Users (n = 3865) vs Fracture Cohort (n = 9776)
Alendronate sodium	1.81 (0.83-3.94)	1.11 (0.56-2.19)
Female	0.39 (0.19-0.81)	Not applicable
Hospitalizations during previous year†	1.11 (0.88-1.40)	1.14 (0.88-1.47)
Chronic disease score (per 1000)	1.06 (1.02-1.11)	1.06 (1.04-1.08)
Corticosteroid exposure‡	4.50 (1.92-10.55)	1.33 (0.52-3.39)
Prescription NSAID exposure‡	3.28 (1.70-6.33)	3.33 (1.94-5.72)

\*CI indicates confidence interval; HMO, health maintenance organization; and NSAID, nonsteroidal anti-inflammatory drug. Age was controlled for as indicator variables in 10-year age groups.

†Only nonfracture hospitalizations were counted for the age-sex-HMO–restricted alendronate users and the fracture cohort.

‡Exposure to corticosteroids and prescription NSAIDs was defined as a dispensing within 45 days before the date for a confirmed gastroduodenal event and within 45 days before a random date for subjects without confirmed gastroduodenal event.

ent from the rate during alendronate-exposed time (2.4 vs 3.4 per 1000 person-years;  $P = .25$ ), but it was greater than the rate among the unexposed cohort (1.1 per 1000 person-years;  $P < .001$ ).

#### Alendronate Users vs Fracture Cohort

Ten of the 14 gastroduodenal perforations, ulcers, or bleeding events among alendronate users described above were among the 3863 women of the age-sex-HMO–restricted cohort. There were 58 confirmed gastroduodenal perforations, ulcers, or bleeding events in the fracture cohort. Crude IRR for age-sex-HMO–restricted alendronate users rela-

tive to the fracture cohort was 1.1 (95% CI, 0.6-2.3). The IRR was unchanged after controlling for age, chronic disease score, recent exposure to prescription NSAIDs and oral corticosteroids, and the number of nonfracture related hospitalizations during the previous year (IRR, 1.1; 95% CI, 0.6-2.2; Table 3). Interaction terms between alendronate use and NSAID exposure and alendronate use and oral corticosteroid exposure were not significant.

When the fracture cohort was further stratified into the hip fracture group and the nonhip fracture group, the adjusted IRR of gastroduodenal perforations, ulcers, and bleeding for alendronate users relative to the hip fracture group (IRR, 0.6; 95% CI, 0.3-1.2) was substantially differ-

ent from that for alendronate users relative to the nonhip fracture group (IRR, 1.6; 95% CI, 0.7-3.3). Women with hip fractures represented only 29% of the fracture cohort, but they generated more than 50% of the confirmed perforations, ulcers, or bleeding events in the fracture group.

#### ESOPHAGEAL PERFORATIONS, ULCERS, AND BLEEDING

There were 20 confirmed esophageal perforations, ulcers, or bleeding events without gastric or duodenal ulcers; 1 occurred during exposure to alendronate, 5 after the referent date in the unexposed group, 7 among the fracture group, and the rest occurred during ineligible person-time. No further analysis was performed for esophageal lesions because of the small number of events.

#### COMMENT

We conducted a retrospective cohort study of nearly 50 000 persons to investigate a possible association between alendronate and confirmed gastroduodenal perforation, ulcer, or bleeding resulting in hospitalization. Because of the potential for confounding by indication (ie, osteoporosis), estimates of the effect of alendronate were computed with 2 separate comparison groups. Although neither estimate was statistically significant, they were substantially different, with a smaller (nonsignificant) excess risk when the fracture cohort was used as the comparison group. Not surprisingly, the fracture group was heterogeneous with respect to the risk of these gastroduodenal events; the adjusted rate ratios were markedly different when the alendronate group was separately compared with those with hip fracture and those with nonhip fracture.

We considered osteoporosis a potential confounder of the alendronate and gastroduodenal perforations, ulcers, and bleeding relationship because of the increased morbidity and mortality in persons with osteoporosis.<sup>12-14</sup> The excess morbidity can be attributed to underlying diseases and osteoporotic fractures, especially fractures of the hip and vertebrae<sup>23</sup>; the consequences of nonhip fractures such as wrist and humerus are substantially less.<sup>12,24</sup> The relationship between alendronate use and upper gastrointestinal adverse events is further complicated by the increased prevalence of gastrointestinal symptoms in the elderly.<sup>25</sup> Persons dispensed alendronate in the present study appeared to have greater morbidity than the unexposed group; they were more likely to have been hospitalized in the preceding 12 months and their chronic disease scores were higher. Moreover, they were substantially more likely to have been dispensed drugs that either predispose to peptic ulcers (eg, prescription NSAIDs and oral corticosteroids) or are used to treat conditions that may progress to peptic ulcers (eg, histamine<sub>2</sub> antagonists). Taken together, it appears that persons using alendronate may have had a greater underlying risk of a gastroduodenal adverse event than persons not using alendronate, and this may have accounted for the decrease in observed risk after control for potential confounders. Alendronate recipients' nearly equal rate of perforation, ulcer, or bleeding during periods when they were not exposed to alendronate and periods when they were exposed lends further support to this possibility.

The ideal group with which to compare alendronate-exposed persons would have osteoporosis at the same rate and intensity but without exposure to alendronate. However, coded diagnoses of osteoporosis were not uniformly available in the automated databases of the HMOs participating in this study, and the misclassification inherent in the diagnosis of osteoporosis would result in a biased sample of persons with osteoporosis. We postulated that a comparison group consisting of older women (men were excluded from the fracture cohort) with osteoporotic fractures would be subject to less misclassification, and although not representative of all persons with osteoporosis, they would be more likely to have osteoporosis than a randomly selected comparison group. In fact, the general risk profile of the fracture cohort closely approximated the profile of the corresponding alendronate cohort; the 2 groups had comparable chronic disease scores and nonfracture hospitalization rates in the preceding 12 months. It should be noted, however, that the fracture cohort was not homogeneous with respect to the risk of gastroduodenal adverse events. Compared with women with nonhip fractures, those with hip fractures accounted for a disproportionate number of gastroduodenal perforations, ulcers, and bleeding. We do not know whether this difference is a reflection of more severe osteoporosis in women with hip fracture or whether such women have a greater prevalence of other unmeasured risk factors for these adverse events.

Although gastric and duodenal adverse events were reported in some of the alendronate clinical trials, their occurrence was no greater in those treated with alendronate than in the placebo groups.<sup>4,8,26</sup> Nor were there significant differences between the treatment groups in the overall incidence of adverse events leading to discontinuation of study medication. Bauer et al<sup>26</sup> combined the 2 study arms of the Fracture Intervention Trial and determined that the rate of gastroduodenal adverse events among over 6400 women with osteoporosis was nearly equal in the alendronate and placebo treatment groups. Although there are important methodological differences between the Bauer et al study and ours that limit comparisons (eg, their cases included hospitalized as well as nonhospitalized cases), the risks of gastroduodenal adverse events appear to be similar. For example, the event rates among alendronate-exposed women (55-64, 65-74, and 75-84 years old) in the present study were 1.1, 4.9, and 4.4 per 1000 person-years, respectively. These rates approximate the age-specific rates reported by Bauer et al.<sup>26</sup>

Nitrogen-containing bisphosphonates, including alendronate, have the potential to cause mucosal irritation. Studies in laboratory animals have demonstrated that alendronate is a topical irritant capable of inflicting erosions and enhancing indomethacin-induced ulceration of the esophagus and stomach.<sup>27,28</sup> In addition, a number of case reports have described esophagitis and esophageal ulcers subsequent to ingestion of alendronate.<sup>9,10,29-31</sup> Less common and conflicting have been reports of alendronate-associated gastroduodenal ulcers.<sup>11,32</sup> A retrospective cohort study determined that older women taking alendronate were more likely to experience acid-related disorders of the upper gastrointestinal tract than a group of nonalendronate users not selected for osteoporosis.<sup>33</sup>

Our study had approximately 65% power to detect a 2-fold increase in risk of gastroduodenal perforations, ulcers, and bleeding for the comparison between the alendronate and the unexposed cohorts. Additional limitations pertain to the type and level of detail in automated medical records. We had no data on risk factors such as alcohol use, smoking, *Helicobacter pylori* infection, or family history of osteoporosis and peptic ulcer disease. Perhaps more important, we had no information on over-the-counter medications, such as nonprescription NSAIDs, that are known to promote gastrointestinal ulcers.<sup>16</sup> If the alendronate-exposed individuals in our study, who were significantly more likely to have filled prescriptions for NSAIDs, were also more likely to use over-the-counter NSAIDs than those not exposed to alendronate, then we may have overestimated the relative risk of gastroduodenal perforations, ulcers, and bleeding. We probably overestimated exposure since we assumed that all dispensed alendronate tablets were taken, and we have no method to evaluate compliance using automated data. This type of misclassification of exposure would bias the effect measure toward an apparent null effect. Although the fracture types that defined the fracture cohort were known to be associated with osteoporosis,<sup>1,34</sup> it is likely that some individuals in the fracture cohort did not have osteoporosis. Although we were not able to review all potential cases of outcomes of interest, the very specific confirmation criteria that we used for gastroduodenal perforations, ulcers, and bleeding make it unlikely that this would have biased the estimate of the relative risk.<sup>35</sup>

The choice of an appropriate comparison group is crucial to the understanding of the association between alendronate and gastroduodenal perforations, ulcers, and bleeding. To the extent that osteoporosis is a risk factor for these adverse events, the observed relative risk derived by comparing alendronate users with a group with less morbidity and lower prevalence of osteoporosis (randomly selected, not exposed to alendronate) is probably an overestimate. To the extent that nonpathologic fractures are good markers for osteoporosis in older women, the measure of effect derived by comparing alendronate users with those with selected fractures may be more accurate. It is also possible that the fracture cohort, nearly 30% of which had a hip fracture, had a greater level of morbidity, and the rate ratio would be biased toward the null. These results underscore the need to consider the severity of osteoporosis and comorbidity to properly interpret the risk of gastroduodenal adverse events in patients being treated for osteoporosis.

Although the crude analysis demonstrated a 3-fold increase in the risk of gastroduodenal perforations, ulcers, and bleeding among patients dispensed alendronate, a substantial fraction of this association was attributable to comorbid conditions and other factors. The role of osteoporosis as inferred from fractures is both important and complex; countervailing risks of gastroduodenal adverse events depended on the presence of hip fractures in the comparison group. A clearer understanding of the morbidity associated with osteoporosis would more completely elucidate the relationship between alendronate use and gastroduodenal perforations, ulcers, and bleeding.

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