Adherence to Bisphosphonate Therapy and Fracture Rates in Osteoporotic Women: Relationship to Vertebral and Nonvertebral Fractures From 2 US Claims Databases

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OBJECTIVE: To characterize the relationships between adherence (compliance and persistence) to bisphosphonate therapy and risk of specific fracture types in postmenopausal women.

PATIENTS AND METHODS: Data were collected from 45 employers and 100 health plans in the continental United States from 2 claims databases during a 5-year period (January 1, 1999, through December 31, 2003). Claims from patients receiving a bisphosphonate prescription (alendronate or risedronate) were evaluated for 6 months before the index prescription and during 24 months of follow-up to determine total, vertebral, and nonvertebral osteoporotic fractures, persistence (no gap in refills for >30 days during 24 months), and refill compliance (medication possession ratio ≥0.80).

RESULTS: The eligible cohort included 35,537 women (age, ≥45 years) who received a bisphosphonate prescription. A subgroup with a specified diagnosis of postmenopausal osteoporosis was also evaluated. Forty-three percent were refill compliant, and 20% persisted with bisphosphonate therapy during the 24-month study period. Total, vertebral, nonvertebral, and hip fractures were significantly lower in refill-compliant and persistent patients, with relative risk reductions of 20% to 45%. The relationship between adherence and fracture risk remained significant after adjustment for baseline age, concomitant medications, and fracture history. There was a progressive relationship between refill compliance and fracture risk reduction, commencing at refill compliance rates of approximately 50% and becoming more pronounced at compliance rates of 75% and higher.

CONCLUSIONS: Adherence to bisphosphonate therapy was associated with significantly fewer fractures at 24 months. Increasing refill compliance levels were associated with progressively lower fracture rates. These findings suggest that incremental changes in medication-taking habits could improve clinical outcomes of osteoporosis treatment. 


BMD = bone mineral density; HR = hazard ratio; ICD-9 = International Classification of Diseases, Ninth Revision; MPR = medication possession ratio; OR = odds ratio; PMO = postmenopausal osteoporosis

The National Osteoporosis Foundation estimates that approximately 10 million people (8 million women and 2 million men) have received a diagnosis of osteoporosis, approximately 1.5 million of whom experience osteoporosis-related fractures annually. In addition, 54% of postmenopausal white women in the United States are believed to have osteopenia (defined as a bone mineral density [BMD] between 1 and 2.5 SDs below the mean BMD of young adult women), which places them at a substantially increased risk of fractures. Menopause accelerates bone loss, thereby increasing the risk of osteoporosis. A 50-year-old white woman in the United States has a 40% overall lifetime risk of fracture. For women older than 50 years, the lifetime risk of hip fracture is estimated at 18%; the risks of spinal and forearm fractures are both estimated at 16%. The growing number of postmenopausal women in the United States substantially increases the at-risk population.

Bisphosphonates are a cornerstone of drug therapy for osteoporosis. Clinical trials indicate that bisphosphonates can reduce the incidence of fractures related to postmenopausal osteoporosis (PMO) by 33% to 60%. Nevertheless, adherence to bisphosphonate therapy remains suboptimal, and researchers have been actively examining relationships between medication-taking behaviors and fracture outcomes. Randomized clinical trials offer the strongest evidence of the efficacy and safety of treatment, but they may not provide the best datasets for assessing real-world patient behaviors regarding treatment adherence. In contrast, clinical databases offer access to large numbers and types of patients, as well as the option of capturing multiple aspects of medical care and services. Database populations are not ideal for evidence of the efficacy and safety of treatment, but they may not provide the best datasets for assessing real-world patient behaviors regarding treatment adherence. In contrast, clinical databases offer access to large numbers and types of patients, as well as the option of capturing multiple aspects of medical care and services.
limited by clinical trial inclusion criteria, and behavior is not
dictated by trial design.\textsuperscript{17} Claims database studies are well
suited to the evaluation of therapeutic outcomes on select
cohorts of patients and subpopulations.\textsuperscript{18}

Clinical and claims databases have been used to evaluate
the impact of adherence to various osteoporosis therapies on
clinical, health care utilization, and cost outcomes.\textsuperscript{15,19,20} Re-
cent research suggests that adherence to bisphosphonate
therapy at 6 months may be less than 50\% for both once-
weekly and daily dosing regimens.\textsuperscript{21} A study that compared
multiple osteoporosis medications reported that 45\% of pa-
tients were noncompliant with therapy at 1 year and that 52\%
of patients were not refilling prescriptions for an osteoporo-
sis medication at 5 years.\textsuperscript{22} In that study, patient-based vari-
ables, such as sex, age, comorbidities, and BMD testing
before and after initiation of therapy, accounted for only 6\%
of the variation seen in compliance levels.

The current study used 2 large pharmaceutical claims
databases to evaluate the relationship between adherence to
bisphosphonate therapy (specifically, alendronate and rised-
ronate) and osteoporotic fractures among postmenopausal
women. Analyses presented herein expand on previous re-
search by examining the risk of specific fracture types (ie,
vertebral, nonvertebral, hip, and wrist) as a function of 2
measures associated with adherence to therapy, specifically,
refill compliance and persistence (based on gaps between re-
fills). Claims data were examined from a large cohort of women
selected by age and compared with data from a subpopulation
for which a specific diagnosis of PMO was required.

To our knowledge, this is the first study to analyze
fracture probability across the full range of possible compli-
ance values expressed as a medication possession ratio
(MPR) (full MPR range, 0.0-1.0). Original health outcomes
studies evaluated compliance as a study end point and typi-
cally compared compliance levels for 2 different agents or
changes in compliance after clinical interventions. The prac-
tice of defining a specific value (commonly MPR \(\geq 0.80\) or
\(\geq 80\%\)) allowed for a dichotomous measure of compliance
and was used in the current study. However, because this
distinction is arbitrary and may not be readily applicable to
evaluating the spectrum of medication-taking behaviors as
they relate to clinical outcomes, fracture probability across
the full spectrum of MPR values was also analyzed. This
 type of information may be more relevant for daily clinical
practice because it provides an assessment of the benefits of
medications across the range of possible adherence rates.

\textbf{PATIENTS AND METHODS}

\textbf{STUDY DESIGN}

A retrospective cohort design was used to evaluate phar-
macy and medical claims data. The study population was
drawn from geographically diverse populations in the
Medstat MarketScan Commercial Claims and Encounters
and Medicare databases. Adjudicated claims from a 5-year
period (January 1, 1999, through December 31, 2003),
drawn from 45 employers and 100 health plans in the
continental United States, were included in the analysis.

The Commercial Claims and Encounters database con-
tains the health care claims history of approximately 5 mil-
lion individuals aged 0 to 64 years. The health care services
are provided under a variety of fee-for-service and capitated
plans, including comprehensive plans (17\%), exclusive pro-
vider organizations (4\%), preferred provider organizations
(37\%), point-of-service plans (13\%), point-of-service plans
with capitation (13\%), and health maintenance organizations
(16\%). The Medicare supplemental and coordination of ben-
efits database contains the health care claims records of
approximately 1 million individuals. This database of retir-
es includes comprehensive services plans (69\%), preferred
provider organizations (28\%), and point-of-service plans
(3\%).

\textbf{POPULATIONS}

Records were eligible for inclusion in the study if the
patients were 45 years and older and had submitted a claim
for an index prescription for either alendronate or risedronate
during a 30-month patient selection period (July 1, 1999, through December 31, 2001). A 6-month
baseline period before the index prescription was used to
identify previous medical diagnoses and medication use.
Inclusion into the study required continuous enrollment in
a covered health care plan during the 6-month baseline
period and a 24-month follow-up period. The establish-
ment of an index prescription required that the patient had
no evidence of a previous claim for alendronate or
risedronate during the 6-month baseline period. At the
earliest time of possible baseline data collection (January 1,
1999), only daily regimens of alendronate (5 mg/d and 10
mg/d) and risedronate (5 mg/d) were available. Two differ-
ent weekly regimens of alendronate (35 mg/wk and 70
mg/wk) became available in October 2000; a weekly regi-
men of risedronate (35 mg/wk) became available in April
2001. Dose regimens for Paget disease (alendronate, 40
mg; risedronate, 30 mg) were also introduced during this
time and occasionally were used for osteoporosis treat-
ment. However, women were excluded only if they re-
ceived a diagnosis of Paget disease of bone at any time
during the 5-year patient selection and follow-up periods,
not based on dosing regimen. Women were also excluded if
they had a medical claim for a malignant neoplasm during
the 6-month baseline period. Individuals were to be ex-
cluded if they had a medical claim for human immunodefi-
ciency virus during the 6-month baseline period; however,
no individuals met this exclusion criterion. A subset of claims were identified from women (n=6391; 18% of the total population) who met all these inclusion criteria and additionally received a diagnosis of PMO during the 5 study years. Results from this cohort were compared with the full study population to evaluate consistency of effect in a group of women with the specific diagnosis of PMO.

**STUDY VARIABLES**

Refill compliance was defined by MPR for the percentage of time that medication was available for use. The MPR was calculated as the sum of the days’ supply divided by the follow-up time. Therefore, if a patient was given a prescription for 3 months of medication and sought 2 additional 3-month refills, this patient would be considered 75% compliant with her medication during a 1-year period. During the 24-month period, patients were classified as refill compliant if their MPR was 0.80 or higher, a value traditionally used in most database studies. Persistence was defined as the length of time a patient received continuous therapy without a gap in refills that exceeded 30 days during the 24-month follow-up period.

Occurrence and types of osteoporotic fracture(s) were defined by *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic codes. Osteoporotic fractures included those at traditional osteoporotic fracture sites (vertebrae, humerus, radius, ulna, clavicle, pelvis, femoral neck, and femur), as well as the patella, tibia, fibula, and ankle. Fractures that were most likely the result of serious trauma were excluded, including compound or open fractures, multiple fractures, and vertebral fractures with spinal cord injury. Analyses were based on determination of the first claim for an osteoporotic fracture in the 24-month follow-up period, as documented by a medical claim that contained an appropriate ICD-9 code.

**STATISTICAL ANALYSES**

A power analysis was performed to determine the sample sizes required to detect clinically meaningful differences. A sample size of more than 30,000 compliant and noncompliant individuals was estimated as the population needed to produce a power of greater than 90% to detect a difference in the 2-year fracture rates of 10% vs 8.5% using the 2-sided Fisher exact test (*P*=.05).

Unadjusted fracture risks (proportion of individuals with at least 1 fracture) during the 24-month follow-up period were calculated for 4 groups defined by adherence status (ie, compliant, noncompliant, persistent, and nonpersistent). Absolute risk differences and relative risk reductions were obtained comparing compliant with noncompliant patients and persistent with nonpersistent patients. The relationship between fracture rates and adherence (as measured by compliance and persistence) was analyzed using the 2-sided Fisher exact test. A difference in the fracture risk (proportion of patients with fracture) between compliant patients and noncompliant patients (or persistent and nonpersistent patients) was deemed statistically significant if *P*≤.05. This analysis was stratified for 5 nested categories of fracture types: overall osteoporotic, vertebral, nonvertebral, hip, and wrist. Patients could have fractures in more than 1 category (a total of 2979 fractures occurred in 2856 patients).

Logistic regression was used to estimate an adjusted relative risk of fracture, comparing adherent and nonadherent groups. Since this is an observational study, randomization to adherent or nonadherent groups was not possible. To assess and control for potential confounders, an extensive analysis of the possible effect of measured covariates was undertaken, including demographics, previous fracture history, disease status, comorbid conditions, and co-pay levels. More than 30 candidate variables were examined using logistic regression analysis to evaluate their possible influence on the probability of fracture, including use of medications in the baseline period (anticonvulsants, benzodiazepines, β-blockers, calcitonin, estrogens or estrogen combinations, oral glucocorticoids, selective estrogen-receptor modulators, statins, or thyroid hormones) and diagnoses in the baseline period (diabetes, hyperlipidemia, smoking habit, alcoholism, obesity, bulimia or anorexia, hyperthyroidism, hypothyroidism, primary hyperparathyroidism, secondary hyperparathyroidism, chronic renal insufficiency, postmenopausal symptoms, vitamin D deficiency, and neurologic disorders). Clinical review was used to identify the most relevant variables for the initial models (eg, smoking habit was eliminated because it was infrequently coded).

Independent variables, based on clinical relevance, availability, and level of significance in the univariate analysis, were identified and subjected to the stepwise multivariate logistic regression. Analyses were performed using PROC LOGISTIC software (version 9.1; SAS Institute Inc, Cary, NC). The logistic regression generates an odds ratio (OR), which was used as the estimate of the adjusted relative risk of fracture comparing compliant with noncompliant (and persistent with nonpersistent), adjusted for the baseline covariates in the model. Goodness-of-fit statistics examined included the percentage of concordant pairs and the c statistic, a measure of the area under the receiver operating characteristic curve. A discussion of these statistics is found in the article by El-Soh et al.23

Time-to-fracture (survival) analysis using Cox proportional hazards regression with time-varying covariates was used to estimate the relative risk (hazard) of fracture, comparing adherent with nonadherent patients and adjusting
ADHERENCE TO BISPHOSPHONATE THERAPY AND FRACTURE RATES IN OSTEOPOROSIS

Patients who filled at least 1 bisphosphonate prescription between January 1, 1999, and December 31, 2003 (N=302,771)

Women ≥45 y (n=267,961)

30 mo continuous enrollment (6 mo baseline plus 24 mo follow-up) (n=42,901)

Filled the bisphosphonate prescription(s) in the subject selection period of July 1, 1999, to December 31, 2001 (n=39,772)

Patients excluded
Cancer (n=4129)
Paget disease (n=106)

Final treated cohort (n=35,537)

Patients who filled at least 1 bisphosphonate prescription between January 1, 1999, and December 31, 2003 (N=302,771)

Patients excluded
Men (n=25,746)
Women <45 y (n=6330)
Data issues (n=2734)

Women ≥45 y (n=267,961)

30 mo continuous enrollment (6 mo baseline plus 24 mo follow-up) (n=42,901)

Filled the bisphosphonate prescription(s) in the subject selection period of July 1, 1999, to December 31, 2001 (n=39,772)

Patients with PMO diagnosis on medical claim between January 1, 1999, and December 31, 2003 (n=7778)

Filled the bisphosphonate prescription(s) in the subject selection period of July 1, 1999, to December 31, 2001 (n=7232)

Patients excluded
Cancer (n=4129)
Paget disease (n=106)

Final treated cohort (n=35,537)

Final PMO cohort (n=6391)

FIGURE 1. Patient selection flowchart. PMO = postmenopausal osteoporosis.

For baseline covariates. Patients were followed up after their index prescription until a fracture occurred, until the end of the study, or until they were lost to follow-up—rather than for the fixed 24-month period, as was done in the logistic regression analyses. A time-dependent covariate was created for compliance for every patient. For every fracture event, the compliance variable (compliant or noncompliant) was created based on whether the patient had drug supply coverage for 80% or more of the time before fracture. The hazard ratio for compliance using this approach is based on the actual compliance of each patient at the time of fracture. Additional covariates that were included in the analysis were age group (≥65 years compared with <65 years), previous fracture history, baseline estrogen use, and baseline oral glucocorticoid use. Analyses were performed using SAS’s PROC PHREG.

For each of the predictor variables, statistical tests were performed to determine if the Cox proportional hazards assumption of a constant hazard rate over time was valid. Variables that failed the test had nonproportional hazard ratios. In those cases, a stratified Cox proportional hazards analysis was performed. To explore the relationship between the full range of compliance values and fracture probability, logistic regression was used to model the probability of fracture as a function of MPR.

RESULTS

BASELINE CHARACTERISTICS

The databases included 302,771 patients (Figure 1) who filled a bisphosphonate prescription between January 1, 1999, and December 31, 2003. Of these, 42,901 met the
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inclusion criteria, and 35,537 remained in the bisphosphonate cohort after exclusion criteria were applied. The mean patient age at the time the index prescription was filled was 65.3 years, and 59% of the women were between 55 and 74 years of age at index prescription (Table 1). Most women (85%; n=30,175) received an index prescription for alendronate, and the remainder (15%; n=5362) received risedronate.

Logistic regression analysis demonstrated a number of covariates to compliance and persistence that were significantly associated with the rate of fracture (Table 2). The variable most strongly associated with fracture for compliant and persistent patients was history of previous fracture. Other significant covariates included age older than 65 years and factors related to risk of falls (ie, neurologic disorders, benzodiazepine use). Diabetes, oral glucocorticoids, smoking, calcitonin use, and chronic renal insufficiency were also associated with increased fracture risk.

ADHERENCE AND FRACTURE RATES

Refill Compliance. Overall, 43% of women (n=15,348) in the bisphosphonate cohort had an MPR of 0.80 or higher during a period of 24 months; 57% of women were considered noncompliant based on MPR (Table 1). Women who achieved compliance with therapy had a 21% reduction in fractures overall compared with those who were not compliant (P<.001; Table 3). New nonvertebral fractures occurred in 2856 women; 702 were fractures of the hip and 687 were fractures of the wrist. The adjusted relative risk for nonvertebral fractures was lower in women who were refill compliant than in those who were not (20%; P<.001). When the analysis was limited to hip fractures, the adjusted risk was 37% lower for compliant compared with noncompliant women (P<.001). Although

### TABLE 1. Baseline Characteristics of Total Bisphosphonate Cohort in 24-Month Study*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (N=35,537)</th>
<th>Compliant (n=15,348 [43%])</th>
<th>Noncompliant (n=20,189 [57%])</th>
<th>Persistent (n=7164 [20%])</th>
<th>Nonpersistent (n=28,373 [80%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>65.3</td>
<td>65.6</td>
<td>65.1†</td>
<td>65.8</td>
<td>65.2†</td>
</tr>
<tr>
<td>Age group (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>6495 (18)</td>
<td>2548 (17)</td>
<td>3947 (20)</td>
<td>1150 (16)</td>
<td>5345 (19)†</td>
</tr>
<tr>
<td>55-64</td>
<td>11,338 (32)</td>
<td>4889 (32)</td>
<td>6449 (32)</td>
<td>2204 (31)</td>
<td>9134 (32)</td>
</tr>
<tr>
<td>65-74</td>
<td>9638 (27)</td>
<td>4466 (29)</td>
<td>5172 (26)</td>
<td>2199 (31)</td>
<td>7439 (26)</td>
</tr>
<tr>
<td>≥75</td>
<td>8066 (23)</td>
<td>3445 (22)</td>
<td>4621 (23)</td>
<td>1611 (22)</td>
<td>6455 (23)</td>
</tr>
<tr>
<td>Fracture in prior 6 mo</td>
<td>1565 (4.4)</td>
<td>637 (4.2)</td>
<td>928 (4.6)‡</td>
<td>313 (4.4)</td>
<td>1252 (4.4)</td>
</tr>
<tr>
<td>Medical history in prior 6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2242 (6.3)</td>
<td>792 (5.2)</td>
<td>1450 (7.2)†</td>
<td>350 (4.9)</td>
<td>1892 (6.7)†</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6633 (19)</td>
<td>2903 (19)</td>
<td>3730 (18)</td>
<td>1339 (19)</td>
<td>5294 (19)</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>107 (0.3)</td>
<td>28 (0.2)</td>
<td>79 (0.4)†</td>
<td>9 (0.1)</td>
<td>98 (0.3)§</td>
</tr>
<tr>
<td>Medications in prior 6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogens or estrogen combination</td>
<td>4306 (12)</td>
<td>2148 (14)</td>
<td>2158 (11)†</td>
<td>982 (14)</td>
<td>3324 (12)†</td>
</tr>
<tr>
<td>Oral glucocorticoids</td>
<td>2072 (5.8)</td>
<td>759 (5.0)</td>
<td>1312 (6.5)†</td>
<td>302 (4.2)</td>
<td>1770 (6.2)†</td>
</tr>
</tbody>
</table>

*Data are number (percentage) of patients unless otherwise indicated. All P values are compared with corresponding compliant or persistent subpopulation.
†P<.001.
‡P<.05.
§P<.01.
fewer compliant women experienced a wrist fracture, this reduction in risk was not statistically significant (Table 3).

**Persistence.** Using a refill gap of more than 30 days to denote nonpersistence, 80% of women in this study were not persistent with bisphosphonate therapy during a period of 24 months. In the remaining 20% of women who persisted with therapy, the overall fracture rate was 29% lower ($P<.001$), and the vertebral fracture rate was 40% lower ($P<.001$; Table 3). Persistence was associated with a 29% reduction in the risk of nonvertebral fractures and a 45% reduction in the risk of hip fractures alone ($P<.001$ for both). The risk of fractures to the wrist was also significantly reduced (23%; $P=.02$) in patients who persisted with therapy during the 24-month evaluation period.

**TABLE 3. Refill Compliance or Persistence and Fracture Rates for the Total Bisphosphonate Cohort***

<table>
<thead>
<tr>
<th>Compliant cohort</th>
<th>Total bisphosphonate cohort (N=35,537)</th>
<th>No. (%) compliant or persistent</th>
<th>No. (%) noncompliant or nonpersistent</th>
<th>$P$ value</th>
<th>RR</th>
<th>Adjusted OR ($P$ value)</th>
<th>RR reduction in adjusted OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant cohort</td>
<td>Total fractures</td>
<td>15,348 (43)</td>
<td>20,189 (57)</td>
<td>&lt;.001</td>
<td>0.795</td>
<td>0.789 ($&lt;.001$)</td>
<td>21.1</td>
</tr>
<tr>
<td></td>
<td>Vertebral fractures</td>
<td>1309 (8.5)</td>
<td>2165 (11)</td>
<td>&lt;.001</td>
<td>0.630</td>
<td>0.628 ($&lt;.001$)</td>
<td>37.2</td>
</tr>
<tr>
<td></td>
<td>Nonvertebral fractures</td>
<td>276 (1.8)</td>
<td>576 (2.8)</td>
<td>&lt;.001</td>
<td>0.808</td>
<td>0.799 ($&lt;.001$)</td>
<td>20.1</td>
</tr>
<tr>
<td></td>
<td>Hip fractures</td>
<td>1087 (7.1)</td>
<td>1769 (8.8)</td>
<td>&lt;.001</td>
<td>0.683</td>
<td>0.627 ($&lt;.001$)</td>
<td>37.3</td>
</tr>
<tr>
<td></td>
<td>Wrist fractures</td>
<td>240 (1.6)</td>
<td>462 (2.3)</td>
<td>&lt;.001</td>
<td>0.873</td>
<td>0.908 (.24)</td>
<td>9.2</td>
</tr>
<tr>
<td>Persistent cohort</td>
<td>Total bisphosphonate cohort (N=35,537)</td>
<td>7164 (20)</td>
<td>28,373 (80)</td>
<td>&lt;.001</td>
<td>0.748</td>
<td>0.707 ($&lt;.001$)</td>
<td>29.3</td>
</tr>
<tr>
<td></td>
<td>Total fractures</td>
<td>552 (7.7)</td>
<td>2922 (10)</td>
<td>&lt;.001</td>
<td>0.643</td>
<td>0.600 ($&lt;.001$)</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Vertebral fractures</td>
<td>119 (1.7)</td>
<td>733 (2.6)</td>
<td>&lt;.001</td>
<td>0.747</td>
<td>0.713 ($&lt;.001$)</td>
<td>28.7</td>
</tr>
<tr>
<td></td>
<td>Nonvertebral fractures</td>
<td>453 (6.3)</td>
<td>2403 (8.5)</td>
<td>&lt;.001</td>
<td>0.612</td>
<td>0.555 ($&lt;.001$)</td>
<td>44.5</td>
</tr>
<tr>
<td></td>
<td>Hip fractures</td>
<td>94 (1.3)</td>
<td>608 (2.1)</td>
<td>&lt;.001</td>
<td>0.796</td>
<td>0.775 (.02)</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>Wrist fractures</td>
<td>115 (1.6)</td>
<td>572 (2.0)</td>
<td>.08</td>
<td>0.873</td>
<td>0.908 (.24)</td>
<td>9.2</td>
</tr>
</tbody>
</table>

*Refill compliant is defined as a medication possession ratio (MPR) of ≥0.80; persistence, no refill gap for >30 days; noncompliant, an MPR <0.80; and nonpersistent, refill gap of >30 days. OR = odds ratio using logistic regression to adjust for baseline covariates; RR = relative risk.

**FIGURE 2. Probability of fracture in 24 months in the bisphosphonate-treated patients. MPR = medication possession ratio.**

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TABLE 4. Cox Regression Analysis of Total Treated Cohort for Various Fracture Types

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Osteoporotic</th>
<th>Nonvertebral</th>
<th>Hip</th>
<th>Vertebral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance (high vs low)</td>
<td>0.751 (&lt;.001)</td>
<td>0.763 (&lt;.001)</td>
<td>0.557 (&lt;.001)</td>
<td>0.626 (&lt;.001)</td>
</tr>
<tr>
<td>Estrogen use in baseline (yes vs no)</td>
<td>0.896 (&lt;.001)</td>
<td>0.904 (.001)</td>
<td>0.874 (.05)</td>
<td>0.866 (.01)</td>
</tr>
<tr>
<td>Oral glucocorticoid use in baseline (yes vs no)</td>
<td>1.189 (&lt;.001)</td>
<td>1.151 (&lt;.001)</td>
<td>1.157 (.01)</td>
<td>1.314 (&lt;.001)</td>
</tr>
</tbody>
</table>

*There was a nonproportional hazard for age and history of fracture. Stratified analysis was performed.

TABLE 5. Refill Compliance and Persistence and Fracture Rates for the PMO Cohort*

<table>
<thead>
<tr>
<th></th>
<th>Compliant cohort</th>
<th>Persistent cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) compliant or persistent</td>
<td>No. (%) noncompliant or nonpersistent</td>
</tr>
<tr>
<td>Total PMO subset (n=6391)</td>
<td>3019 (47)</td>
<td>3372 (53)</td>
</tr>
<tr>
<td>Total fractures</td>
<td>284 (9.4)</td>
<td>423 (13)</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>67 (2.2)</td>
<td>141 (4.2)</td>
</tr>
<tr>
<td>Nonvertebral fractures (total)</td>
<td>236 (7.8)</td>
<td>326 (9.7)</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>52 (1.7)</td>
<td>96 (2.8)</td>
</tr>
<tr>
<td>Wrist fractures</td>
<td>55 (1.8)</td>
<td>73 (2.2)</td>
</tr>
</tbody>
</table>

*Refill compliant is defined as a medication possession ratio (MPR) of 0.8 or greater; persistence, no refill gap for >30 days; noncompliant, an MPR <0.8; and nonpersistent, refill gap of >30 days. OR = odds ratio using logistic regression to adjust for baseline covariates; PMO = postmenopausal osteoporosis; RR = relative risk.

The Cox regression model of time to fractures for the total population as a function of fracture types and compliance. Since the assumption of proportional hazards was not met for age and baseline history of fracture, a stratified analysis was performed. The relative risk reduction for all osteoporotic fractures was 25% (hazard ratio [HR], 0.751; \( P < .001 \)) for refill-compliant compared with noncompliant subgroups. Similar analyses were repeated for nonvertebral, hip, and vertebral fractures. The relative risk reduction associated with compliance was highly significant and greatest for hip (HR, 0.557) and vertebral (HR, 0.626) fractures, whereas the effect was least, and not significant, for wrist fractures (HR, 0.895) (data not shown).

PMO COHORT

A total of 6391 women (18%) had a specified diagnosis of PMO, and the mean age at index prescription for this cohort was 66.4 years. The percentage of patients adherent to therapy was similar for this cohort and the full population. Forty-seven percent of patients in the PMO cohort were refill compliant (compared with 43% in the full population) and 23% were persistent (compared with 20%) (Tables 3 and 5). Age distribution, percentage of patients taking alendronate vs risedronate, and percentage of patients receiving daily vs weekly therapy were similar for both groups. The reduction in total fracture risk was 22% in the PMO cohort (\( P < .001 \)) for compliant vs noncompliant patients. There was a 29% risk reduction for all osteoporotic fractures among persistent patients in the full population (adjusted OR, 0.707; \( P < .001 \)). Similarly, in the PMO cohort, persistent patients experienced a 25% reduction in fracture risk (OR, 0.752; \( P = .009 \)).
DISCUSSION

This retrospective analysis of a large population of bisphosphonate users followed up for 2 years demonstrated a significant association between adherence to bisphosphonate therapy and risk of osteoporotic fractures. Compared with patients who persisted with therapy, those with gaps in medication coverage had significantly more vertebral and nonvertebral fractures. Similar results were found when the records of those who were compliant and noncompliant were examined.

The current analyses were designed to extend existing database studies on adherence to osteoporosis medications in several ways. First, both refill compliance and persistence were measured in the same population of women. Second, specific analyses with respect to fracture type were also performed. Third, compliance was examined across the full range of possible MPR values to explore the relationship with fracture risk on a continuum. Finally, adherence was evaluated in a population of women defined by age of 45 years or older; this age group was believed to be a better reflection of the women at risk of osteoporosis and fracture routinely seen in clinical practice. Results from this population were compared to the cohort of women with a specific diagnosis of PMO as a method of validating the results of the larger analysis. Results using time-to-event analyses, which were not restricted to a fixed period of 24 months, confirmed comparable reductions in fracture rates for persistent and compliant patients.

Although the MPR has become a popular metric, it does not capture the pattern of medication use—multiple small gaps in refill compliance can yield the same MPR as 1 or 2 large gaps. Refill compliance based on MPR and gap monitoring describe different aspects of medication-taking behavior, and multiple measures may provide a more accurate picture of adherence than can be obtained with a single measure.

The MPR was introduced by Sclar et al. who defined it as the number of days’ supply of a once-daily antihypertensive medication during a study period of 180 days. In addition, the MPR calculation depends on the length of the follow-up period, and this should be taken into account when evaluating the extended follow-up periods (1-2 years) of interest for antosteoporosis medications.

Our findings regarding MPR and fracture probability suggest that women who are refill compliant up to 50% of the time gain only marginal benefit from bisphosphonate therapy. In contrast, once a threshold value of approximately 50% was achieved, benefit from compliance with bisphosphonate therapy progressively increased. The benefits of compliance did not plateau but rather continued up to the maximum level of compliance allowed (100%).

As part of the full analysis, an MPR of 0.75 was examined. This value would roughly correspond with medication use 3 of 4 weeks every month (75% of the time), making it a clinically relevant cutoff point. The examination of fracture rates using an MPR greater than 0.75 revealed values similar to those observed using the traditional cutoff point of 0.80. Osteoporotic fractures occurred in 8.6% of patients with an MPR greater than 0.75 and in 8.5% of those with an MPR greater than or equal to 0.80. Findings were comparable for vertebral fractures (1.8% vs 1.8%), nonvertebral fractures (7.2% vs 7.1%), and hip fractures (1.6% vs 1.6%) for patients with an MPR greater than or equal to 0.75 and greater than or equal to 0.80, respectively.

Less than half of the women in this population were found to be compliant with bisphosphonate therapy (MPR ≥0.80), and approximately 1 in 6 persisted with treatment for 24 months without a substantial gap in therapy. Extrapolating the results of this study to the entire US population (approximately 8 million women and 2 million men are diagnosed as having osteoporosis in whom 1.5 million osteoporotic fractures occur annually), assuming a 25% reduction in fractures through better adherence to therapy as estimated herein, could result in more than 300,000 fewer fractures each year.

The low adherence levels observed in our study are consistent with rates found in other retrospective analyses that used claims data. A retrospective longitudinal analysis of postmenopausal women found a high rate of noncompliance (54%; MPR ≤0.75) with hormone replacement therapy. A recent analysis of the NDCHealth database, which comprises more than 200,000 bisphosphonate users, found that 65% of women receiving daily therapy and 45% of women receiving weekly therapy maintained medication supply for fewer than 271 of a possible 365 days. A 1-year analysis of the Integrated Healthcare Information Services claims database found that 40% of patients receiving daily therapy and 55% of patients receiving weekly therapy achieved an MPR of 80% or higher; this difference was statistically significant (P<0.001). Investigators from a single osteoporosis clinic followed up 349 patients with osteopenia or osteoporosis in whom daily bisphosphonate treatment was initiated and reported that after 1 year 51% of patients had discontinued therapy and after 2 years 70% had discontinued therapy.

Two previously published retrospective studies of claims databases showed a correlation between fractures and poor adherence with various antiresorptive agents, although neither was specific to bisphosphonates. Caro et al analyzed data from 11,252 women with osteoporosis older than 45 years who received bisphosphonates, hormone replacement therapy, or calcitonin (salmon) nasal
spray. In that study, women who were compliant (MPR ≥0.80) for the 24-month follow-up period had a 16% lower fracture rate than noncompliant women.\textsuperscript{19} Similar findings were reported from these investigators using database claims from a larger cohort (>38,000) of women with osteoporosis. Low refill compliance, noted in three quarters of participants, was associated with a 17% increase in fracture rates during the follow-up period of 1.7 years.\textsuperscript{29} McCombs et al\textsuperscript{15} used paid claims data from a large health insurance company to examine the relationship between adherence to treatment regimens (hormone replacement therapy, the selective estrogen receptor modulator raloxifene, or bisphosphonate therapy) and the rate of fracture in 58,109 women older than 55 years with diagnosed osteoporosis. They demonstrated that persistence (no interruption in drug purchases for >14 days during a 1-year period) significantly reduced the rate of hip fractures (OR, 0.382; \textit{P}<.01) and vertebral fractures (OR, 0.601; \textit{P}<.05).\textsuperscript{35} As in other studies, the rate of persistence in that study was poor, with less than 25% of patients maintaining therapy without interruption for 1 year.\textsuperscript{35} Results of our study, although somewhat more comprehensive in scope, are consistent with these previous findings.

Several investigators have examined strategies for improving adherence to osteoporosis medication, including clinical interventions (educational materials, referral for bone densitometry, and consultation),\textsuperscript{30} bone marker and staff monitoring,\textsuperscript{31} and new dosing options.\textsuperscript{32-34} In a recent study that involved patient recall of BMD values, correct understanding of densitometry readings was found to be associated with better adherence to therapy in patients with low BMD.\textsuperscript{35} A database analysis of retail pharmacy prescriptions revealed that patients new to bisphosphonates had the worst medication compliance (based on MPR), suggesting that physicians may need to focus on strategies to encourage adherence in these new users.\textsuperscript{20} Other physician-centered strategies for improving medication adherence for osteoporosis treatment include a development of consensual and consistent practice guidelines and a redesign of clinical processes around osteoporosis care.\textsuperscript{36,37}

In contrast to a prospective randomized trial, our study is limited by its retrospective and observational nature.\textsuperscript{28} Identification of women with PMO is indirect in that it is based on the submission of a claim with a specific \textit{ICD-9} code rather than on hormone levels, documented cessation of menses, or BMD test results. To our knowledge, no studies have validated the osteoporosis diagnosis or identification of fractures in clinical and claims databases with subsequent medical record reviews. Medicare data demonstrated that claims for hip fracture from physician offices match those from hospitals in 89% to 99% of cases for site of fracture (neck vs other) and type of treatment (internal fixation vs arthroplasty).\textsuperscript{39} The number of patients with a fracture could be overestimated by counting the first occurrence of a fracture diagnosis code (approximately 16% of patients had only 1 such code). However, a stricter algorithm (requiring 2 diagnosis codes within 30 days or a diagnosis plus a procedure code within 30 days) found no differential bias in the fracture estimates between adherent and nonadherent groups. Nontraumatic (fragility) fractures cannot be directly identified (eg, via E-codes), but rather they are identified as subsets of \textit{ICD-9} diagnosis codes (excluding multiple and open or compound fractures most likely resulting from trauma). Important demographic data that might affect the risk of fracture, such as family history of osteoporosis, body mass index, heavy alcohol use, smoking, and dietary habits, are not available in databases.\textsuperscript{3,40} However, many factors known to affect fracture risk were confirmed in this study using \textit{ICD-9} codes, even though poorly coded (eg, smoking).

Despite extensive evaluation of potential confounding factors, other unmeasured variables that influence compliance may not have been accounted for within the current analysis. The submission of a claim for, or receiving a supply of, a bisphosphonate is not a guarantee that the drug will be taken—and could misclassify nonadherent patients as being adherent. Patients who receive samples could potentially be misclassified as nonadherent if the refill gap is exceeded. In both cases, the misclassifications would tend to produce conservative results (ie, show no association between adherence and fracture). Women who received a prescription for a bisphosphonate but never filled it would not be included in the analysis. Although this may underestimate the overall extent of nonadherence to therapy, it should not have a systematic effect on the measurement of association of treatment adherence and fracture outcomes, as operationally defined in the current study.

**CONCLUSIONS**

The current study is among the largest observational studies to examine bisphosphonate therapy and fracture rates in osteoporotic women at least 45 years of age in the United States. This study also included 2 years of follow-up. Furthermore, the results contribute meaningful information by corroborating findings in earlier studies and extending them by examining site-specific fracture outcomes. Indeed, we observed a consistent and even greater reduction in fracture risk among compliant patients vs noncompliant patients. The reduced fracture rate became more pronounced with an increase in refill compliance rates.

The availability of safe and effective osteoporosis therapies has the potential to reduce the burden of fragility...
fractures currently being experienced by an aging population of postmenopausal women in a clinically meaningful way. However, the appropriate prescription of these agents will fail to achieve this goal unless we gain greater insight into the reasons for the poor compliance and associated poorer outcomes documented in studies such as this one and determine ways to alter this medication-taking behavior. Additional research is needed to examine these critical issues.

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REFERENCES
