Comparison of Risedronate to Alendronate and Calcitonin for Early Reduction of Nonvertebral Fracture Risk: Results From a Managed Care Administrative Claims Database

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ABSTRACT

OBJECTIVE: Recent randomized clinical trials have shown that risedronate reduces the risk of nonvertebral fractures and clinical vertebral fractures within 6 months of initiating treatment. The objective of the current study was to determine whether this early antifracture effect could be demonstrated in nonvertebral fractures for risedronate and other osteoporosis therapies in an observational administrative claims database.

METHODS: A proprietary administrative claims database was used to identify managed care members who received a new prescription for risedronate, alendronate, or nasal calcitonin from July 1, 2000, to December 31, 2001. Patient records were analyzed for the incidence of nonvertebral fractures (clavicle, humerus, wrist, pelvis, hip, and leg) in the first 6 and 12 months following initiation of treatment. A Cox proportional hazards regression model was used to estimate relative risk (RR) of fracture at 6 and 12 months.

RESULTS: In the 6-month analysis, 774 patients (11%) received calcitonin, 5,307 (75%) received alendronate, and 1,000 (14%) received risedronate. Twelve-month data were available for a subset (71%) of patients (656 calcitonin [13%], 3,716 alendronate [74%], and 652 risedronate [13%]). Most were women (93%); mean age was similar for alendronate and risedronate, and nasal calcitonin patients were about 3 years older, on average. Risedronate and alendronate patients were more likely to have used estrogen, while nasal calcitonin patients were more likely to have been hospitalized and had higher use of concomitant medications and more physician visits. Relative risks were adjusted for these differences. Risedronate and alendronate patients were similar with respect to these indicators of general health status.

In the 6-month analysis, nonvertebral fractures were observed in 2.2% of patients receiving nasal calcitonin, 1.4% of patients receiving alendronate, and 0.6% of patients receiving risedronate. The adjusted RR reduction was 69% for risedronate versus calcitonin (RR = 0.31; 95% CI, 0.12 to 0.81; $P = 0.02$), 54% for risedronate versus alendronate (RR = 0.46; 95% CI, 0.20 to 1.06; $P = 0.07$), and 26% for alendronate versus calcitonin (RR = 0.74; 95% CI, 0.43 to 1.27; $P = 0.28$). In the 12-month analysis, nonvertebral fracture rates were 2.9% for nasal calcitonin, 2.4% for alendronate, and 0.9% for risedronate patients. The adjusted RR reduction was 75% for risedronate versus calcitonin (RR = 0.25; 95% CI, 0.10 to 0.64; $P<0.01$), 59% for risedronate versus alendronate (RR = 0.41; 95% CI, 0.18 to 0.94; $P = 0.04$), and 25% for alendronate versus calcitonin (RR = 0.75; 95% CI, 0.45 to 1.25; $P = 0.27$).

CONCLUSIONS: This analysis of medical and pharmacy claims contained in an administrative database confirms the early fracture reduction with risedronate that was shown in randomized clinical trials. Risedronate was more effective than calcitonin in reducing the risk of nonvertebral fractures within the first 6 months of treatment. Risedronate was more effective than either calcitonin or alendronate in reducing the risk of nonvertebral fractures within 12 months of treatment.

KEYWORDS: Alendronate, Calcitonin, Osteoporosis, Nonvertebral fracture, Risedronate

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Osteoporosis is an increasing concern for older adults as painful fragility fractures can significantly affect overall health and quality of life. In the United States, the lifetime risk of fracture at age 50 is estimated at 40% for women and 12.5% for men.[1]

Bisphosphonates are considered first-line therapy for the prevention and treatment of osteoporosis—both risedronate and alendronate have demonstrated efficacy in the prevention of osteoporotic fractures at a variety of skeletal sites. Multiyear clinical studies of each agent have demonstrated statistically significant reductions in the risk of nonvertebral fractures.[2,3] Reductions in relative risk (RR) of radiographic vertebral fracture were comparable for the 2 drugs, ranging from 41% to 49% over 3 years (3.0% to 10.9% absolute risk reduction [ARR]).[2,4-6]

With respect to the onset of effect, risedronate significantly reduced the RR of radiographic vertebral fractures by 61% to 65% within one year (4.0% to 7.4% ARR),[2,4] and recent post hoc analyses of data from the risedronate trials demonstrated protection against clinical vertebral fractures and nonvertebral fractures within the first 6 months of treatment as well.[7,8] Similar data have not been reported for other bisphosphonates or for nasal calcitonin. Unlike the bisphosphonates, for which substantial evidence of vertebral and nonvertebral fracture efficacy is available, the single large clinical trial of nasal calcitonin showed only an effect on vertebral fracture risk and no statistically significant effect on nonvertebral fractures.[9]

Osteoporosis is considered to be a "silent" disease, and patients may fail to be compliant with therapy due to multiple

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factors, including side effects, not recognizing the long-term benefit, not perceiving that the treatment is necessary, or the development of nontreatment-related health problems.[10,11] Most of the agents for treating osteoporosis were approved based on 3-year clinical trial data.[2,3,5] Although significant fracture protection can be achieved within the first 3 years of initiating therapy, this can seem quite long from the perspective of the patient and managed care organization (MCO). Patient adherence might be improved by use of an agent that provides an early benefit (e.g., fracture protection within 6 months to 1 year). While a reduction in fracture risk at 6 months of treatment has been shown in clinical trials for risedronate,[7,8] there appear to be no published studies that have shown an early beneficial effect on fracture risk for alendronate or nasal calcitonin.

Evaluating osteoporotic fractures in a claims-based setting is limited by the fact that only those patients who seek medical attention and have the fracture appropriately diagnosed will be counted as fracture cases. While most nonvertebral fractures are painful and result in immediate treatment, vertebral fractures are often underdiagnosed due to lack of reporting by the patient or physician. Vertebral fractures are often not diagnosed at the time they occur and, when brought to medical attention, are sometimes coded solely as "osteoporosis." Studies in both the hospital and primary care setting have demonstrated that even among women with fractures evident on radiographs, fewer than 20% receive a discharge diagnosis of vertebral fracture[12] and only one third receive prescription medications for osteoporosis.[13] For these reasons, the present study assessed only nonvertebral fractures, thus minimizing the problem associated with capturing vertebral fractures in an administrative claims database.

Observational studies provide the opportunity to assess the early effects of treatment in real-world patients, outside of the controlled environment of clinical trials. Currently, there is scant epidemiologic literature on the antifracture effectiveness of calcitonin, alendronate, and risedronate. In this analysis of a large medical and pharmacy claims database, we sought to assess the incidence of nonvertebral fractures at sites evaluated in previous risedronate clinical trials,[2] (i.e., fractures of clavicle, humerus, wrist, pelvis, hip, and leg), in the first 6 and 12 months after initiation of osteoporosis treatment with risedronate, alendronate, or calcitonin.

Methods

A retrospective cohort study was conducted among patients with medical and pharmacy claims contained in a proprietary administrative claims database.[14] This database contains longitudinal data, representing health care services from professional, facility, and outpatient pharmacy claims and enrollment data. These services are provided through health maintenance organization (HMO), preferred provider organization (PPO), and specialty products to approximately 3 million members

FIGURE 1A Flowchart of Patients Selection Criteria and Process, 6-month analysis

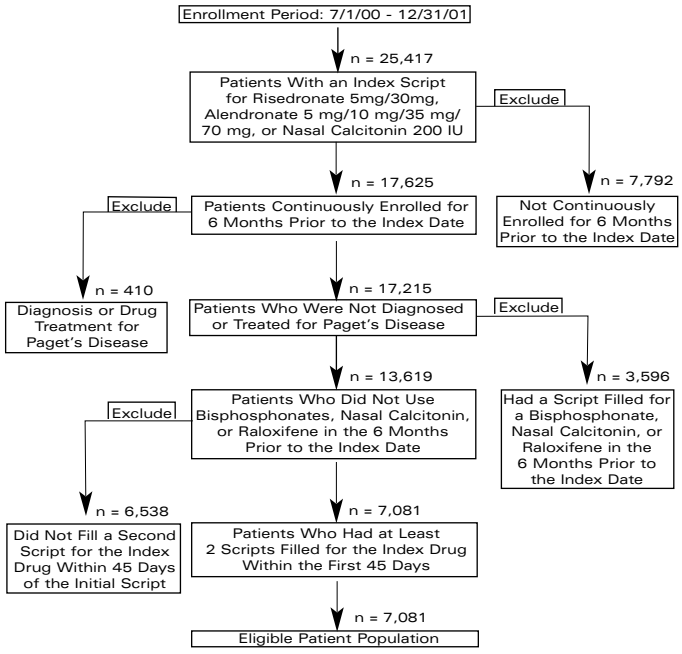


FIGURE 1B Flowchart of Patients Selection Criteria and Process, 12-month analysis

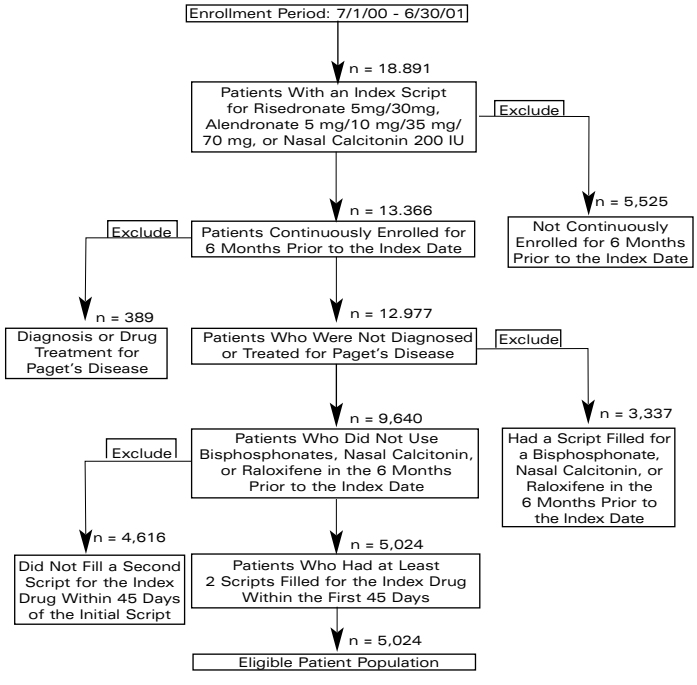


TABLE 1 *Dosing Regimens and Approval Dates by Indication for Risedronate and Alendronate*

	Dose Strength	Dosing Regimen	Date of FDA Approval
Risedronate			
Paget's disease	30 mg	One tablet per day for 2 months	April 1998
***PMO—prevention/treatment**			
Daily dosing	5 mg	One tablet per day	April 2000
Weekly dosing	35 mg	One tablet per week	April 2002
Alendronate			
Paget's disease	40 mg	One tablet per day for 6 months	June 1999
PMO—prevention			
Daily dosing	5 mg	One tablet per day	September 1995
Weekly dosing	35 mg	One tablet per week	October 2000
PMO—treatment			
Daily dosing	10 mg	One tablet per day	September 1995
Weekly dosing	70 mg	One tablet per week	October 2000

** PMO = postmenopausal osteoporosis. Both risedronate and alendronate also have indications for glucocorticoid-induced osteoporosis. Those indications are not presented in this chart since they are not within the scope of this study.*

annually. The plans cover a wide geographic distribution, with members residing predominantly in more than 20 states. These health insurance products are marketed to employer and other commercial groups and Medicare-eligible individuals.

The commercial group HMO plans provide health care services to their members through primary care and specialty physicians employed by the HMO at facilities owned by the MCO or through a network of independent primary care and specialty physicians and other health care providers who contract with the MCO to provide these services. The commercial group PPO plans are similar to the HMO plans in that, through financial incentives, a member is encouraged to use preferred health providers who have contracted with the MCO to provide services at favorable rates. Approximately 72% of the members belong to commercial HMO or PPO plans.

Medicare plans include both Medicare risk and Medicare supplement products. The Medicare risk product is marketed to Medicare-eligible individuals and provides HMO-based managed care services that include all required Medicare benefits and, in some circumstances, additional managed care services not among those required (e.g., vision care or pharmacy benefits). The Medicare supplement plans provide indemnity insurance policies that supplement Medicare benefits. Approximately 17% of the members belong to a Medicare risk plan; an additional 4% belong to a Medicare supplement plan. The remaining membership (7%) is enrolled in a variety of specialty and administrative-services-only (ASO) products. This database has been used extensively for more than 10 years to conduct retrospective studies.[15-19]

Study Population

The subset of patients used for the present study consisted of men and women, aged 45 years or older. All were required to have a new ("index") prescription for nasal calcitonin, alendronate (5 mg, 10 mg, 35 mg, or 70 mg), or risedronate (5 mg or 30 mg) between July 1, 2000, and December 31, 2001 (Figure 1A). In an attempt to assure that patients were included only if they actually took their medication, only those who filled a second prescription within 45 days of the index prescription were included. This 45-day criterion was selected arbitrarily, based on the most common quantity dispensed (30-day supply) plus 15 days to account for a late refill or gaps in therapy.

Patients were excluded if there was evidence of a previous prescription for a bisphosphonate, raloxifene, or nasal calcitonin in the 6 months prior to the index prescription. Patients with a diagnosis of Paget's disease according to the International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM) code of 731.0 were also excluded from the analysis.

Risedronate patients with an index prescription for 30 mg tablets were considered to be Paget's disease patients if they filled at least 2 risedronate 30 mg prescriptions where the days supply equaled the number of tablets dispensed, suggesting a pattern of daily dosing.[20] Other patients receiving 30 mg of risedronate with appropriate quantities dispensed (i.e., where the number of pills was sufficient for weekly rather than daily dosing) were included in the analysis since it was inferred that they were taking this (off-label) dose once per week. The approved weekly 35 mg dose form of risedronate was not commercially available during this study period (see Table 1 for available dose strengths by indication).

Because alendronate had an approved weekly 70 mg dose for postmenopausal osteoporosis available throughout most of the study period, all patients receiving the alendronate 40 mg dose were considered to be taking the drug for Paget's disease, and thus excluded from the study.[21] Figures 1A and 1B provide a graphic illustration of the inclusion/exclusion steps and the number of patients excluded based on each criterion.

Patients contributed follow-up (exposure) time to the end point of the study until the occurrence of the outcome event (nonvertebral fracture), the date of cessation of drug or medical coverage, or the end of the follow-up period, whichever occurred first. Patients who discontinued their index therapy were "censored" (no longer permitted to contribute follow-up time to the study) if, at any point, they did not fill another prescription for the index product (or another dose strength/regimen of the index product) within 30 days of the completion of the supply of their previous prescription. In addition, patients who switched from their index therapy to another osteoporosis

therapy were censored on the date that the switch occurred. Changing dose strengths and regimens of the same product (e.g., alendronate 10 mg per day to alendronate 70 mg per week and vice versa) was not considered to be a switch.

Study Period

The present study consisted of 2 separate analyses: a 6-month analysis and a 12-month subset analysis for patients who were observed for up to 12 months of drug therapy. Patients in the 6-month analysis were selected for inclusion based on a new prescription for nasal calcitonin, alendronate, or risedronate during the 18-month enrollment period of July 1, 2000, to December 31, 2001. These patients had up to 6 months of observation following the index prescription. Not all patients were required to have a full 6 months of therapy so as not to exclude patients who fractured early and subsequently discontinued therapy. The 12-month analysis used a shorter enrollment period of July 1, 2000, to June 30, 2001, thereby including a subset of patients with up to 12 months of observation following the index prescription. The enrollment periods were different for the 2 analyses because the last date of follow-up at the time of the study was fixed (claims data were not available beyond June 2002). For both the 6-month analysis and the 12-month subset, a 6-month period prior to initiating therapy, defined as the "pretreatment period," was used to assess underlying characteristics of the study populations, including prescription use and medical histories.

Baseline Clinical Characteristics

For the 6-month pretreatment period, general background characteristics of the patients were assessed in several areas. Individual fracture histories were evaluated, and patients with one or more closed fractures of the hip, spine, or wrist were considered to have a "prior fragility fracture." To address possible concerns that physicians might routinely treat more-severe patients with a particular therapy (selection bias) and that those patients would also be more likely to fracture after initiating therapy (a confounding factor), the overall health status of the patients was estimated (not actually determined) from the average number of physician visits, hospitalizations, a diagnosis of rheumatoid arthritis (ICD-9-CM 714 or 714.0), having (versus not having) a prescription for an oral glucocorticoid, and use of concomitant medications (quantified by the number of therapeutic classes[22] represented by prescriptions in the pretreatment period).

Therapeutic class was selected because it categorizes the drug therapies into distinct groupings that represent the treatment of specific conditions or diseases. While more general comorbidity indices, such as the Charlson Index,[23] have been validated in studies with mortality as the primary outcome, they are not sensitive enough to differentiate a relatively healthy population (such as osteoporosis patients) based on health status. (A preliminary check of the Charlson Index for the present dataset showed that nearly all patients score a "0" or "1," which fails to provide sufficient variability for creating a useful comorbidity variable.) Patients were also evaluated for one or more prescriptions for hormone therapy (HT), including estrogenic agents and progestational agents (e.g., estradiol, conjugated estrogen, esterified estrogen, and medroxyprogesterone) in either the pretreatment or treatment periods, and categorized as "prior," "current," or "non-" users of HT.

TABLE 2 ICD-9-CM Codes Selected for Nonvertebral Fractures

	Fracture Site	ICD-9-CM
Clavicle (closed)	Closed	810.0x*
	Closed/open not indicated	810
Femur, other/unspecified (closed)	Pathologic	733.15
	Shaft/unspecified	821.0x
	Lower end	821.2x
	Closed/open not indicated	821
Forearm/wrist (closed)	Pathologic	733.12
	Upper end	813.0x
	Shaft	813.2x
	Lower end	813.4x
	Unspecified	813.8x
	Closed/open not indicated	813
Hip (closed)	Pathologic	733.14
	Transcervical	820.0x
	Pertrochanteric	820.2x
	Unspecified	820.8x
	Closed/open not indicated	820
Humerus (closed)	Pathologic	733.11
	Upper end	812.0x
	Shaft/unspecified	812.2x
	Lower end	812.4x
	Closed/open not indicated	812
Pelvis (closed)	Acetabulum	808.0x
	Pubis	808.2x
	Other specified	808.4x
	Unspecified	808.8x
	Closed/open not indicated	808
Tibia/fibula (closed)	Pathologic	733.16
	Upper end	823.0x
	Shaft	823.2x
	Unspecified	823.8x
	Closed/open not indicated	823

**The ICD-9-CM code given reflects the specific 3- to 5-digit descriptor evaluated in the dataset. An "x" indicates that both the 4-digit code and all associated 5-digit subcodes were included.*

Outcome Assessments

Nonvertebral fractures. In order to maximize the probability of selecting osteoporotic (fragility) fractures, only closed, nonvertebral fractures were examined in this analysis (see Table 2 for relevant ICD-9-CM codes). Open-wound fractures were assumed to be traumatic and were not included. (While some

closed fractures may be traumatic, such fractures would not be related to therapy and therefore would be expected to occur with comparable frequency among the 3 treatment groups). In an effort to avoid counting diagnostic x-ray (radiographic) procedures as actual fractures, any nonvertebral fracture (except pelvis) that was captured in a single claim that was based on a radiographic procedure was not considered for analysis. Additionally, any fracture that was initially identified by a pathologic fracture diagnosis (ICD-9-CM 733.1X) accompanied by an ICD-9-CM code for a malignant neoplasm (ICD-9-CM 140.0–208.9) was excluded.

Persistence with therapy. The nasal calcitonin, alendronate, and risedronate populations were also assessed for persistence with treatment to explore possible differences in length of treatment for the 3 study groups. Nasal calcitonin patients were included in this analysis, although it should be noted that the days supply of the multiple-dose nasal spray may not be directly comparable to the tablet form of the bisphosphonates. While each dispensed amount of the bisphosphonates contains a distinct number of pills, the calcitonin nasal spray may be used differently by each individual patient. For example, some patients may waste more spray in priming, while others judiciously dispense limited quantities. This individual variability in nasal calcitonin use creates a measurement bias that makes comparison with the bisphosphonates difficult. Continuation with therapy was defined as having no gaps in therapy that exceeded 30 days, while still taking the index therapy at the end of the study period.

Statistical Methods

In examining the baseline demographic and clinical characteristics of the study subjects, the chi-square test was used to compare the 3 drug groups on dichotomous variables, including rates of prior fracture, HT use, oral glucocorticoid use, and diagnosis of rheumatoid arthritis. The Wilcoxon rank sum test was used to compare age, sex, number of concomitant medications, number of hospitalizations, and physician visits across the groups since the variables were continuous (and not normally distributed).

Estimates of RR for nonvertebral fractures were generated for each drug group through survival analysis with a Cox proportional hazards regression model (as the assumption of proportional hazards was appropriately met). Risedronate, nasal calcitonin, and alendronate were compared in crude and adjusted models. Age, sex, and prior fragility fracture were included in all adjusted models; although the treatment groups did not differ significantly with respect to all of these variables in the univariate models, including these terms reduces bias that can be introduced in the multivariate models. Additional variables were then selected only if they significantly added to the multivariate model ($P<0.05$). A 95% confidence interval and P value were computed for each measure of RR, and Kaplan-Meier curves (with accompanying log rank tests for differences between the curves) were constructed to graphically illustrate time-to-fracture for each therapy.

As a measure of persistence with therapy, overall continuation rates were calculated for the nasal calcitonin, alendronate, and risedronate groups. Because nasal calcitonin is administered via a multiple-dose intranasal spray, the days supply is not necessarily constant for each patient (e.g., priming, waste, and overfill). For the purpose of comparing persistence of nasal calcitonin with the bisphosphonates, each calcitonin prescription was assigned a days supply of 22. This calculation is based on the fact that the multiple-dose bottle contains 2 ml of the drug, and the recommended dose is 1 spray, or 200 IU/0.09 ml, per day in alternating nostrils.[24] In the current study, a preliminary examination of refill patterns for long-term nasal calcitonin users (those with at least 15 prescriptions per year) supported this calculation, with an average time between refills of 22.4 days. When assessing the persistence of nasal calcitonin, alendronate, and risedronate patients, chi-square tests were used to compare the percentage of patients continuing (persisting) on therapy at the end of the study period. All statistical tests were calculated using SAS version 8 statistical software.[25]

Results

The 6-month analysis included 7,081 patients: 774 (10.9%) treated with nasal calcitonin, 5,307 (75.0%) treated with alendronate, and 1,000 (14.1%) treated with risedronate (Table 3). The 12-month subset included 5,024 patients (71% of the 6-month cohort): 656 (13.1%) treated with nasal calcitonin, 3,716 (74.0%) treated with alendronate, and 652 (12.9%) treated with risedronate. Approximately 93% of the patients in each group were women, with no statistically significant differences for any of the pair-wise comparisons of the 3 treatment groups. The mean age of subjects was similar for the risedronate and alendronate groups, while the nasal calcitonin patients were, on average, a few years older ($P<0.01$ versus both risedronate and alendronate).

For patients in the 6-month analysis, fracture rates (hip, wrist, and vertebra) in the 6-month pretreatment period were similar for risedronate (6.0%) and alendronate patients (4.9%) and lower than the pretreatment fracture rate for the nasal calcitonin patients (10.7%, $P<0.01$ for both risedronate and alendronate versus nasal calcitonin; Table 3). The pattern was similar for the 12-month subset analysis, in which pretreatment fractures occurred in 10.7% of nasal calcitonin patients versus 5.3% for alendronate and 7.2% for risedronate patients ($P = 0.03$ for risedronate and $P<0.01$ for alendronate versus nasal calcitonin).

In the pretreatment period, there were some differences in health status based on resource utilization parameters for the 3 treatment groups. While the risedronate and alendronate groups were similar, the nasal calcitonin patients had a slightly higher average number of concomitant medications, hospitalizations, and physician visits in both the 6-month and

TABLE 3 *Demographic, Clinical, and Utilization Characteristics of Study Subjects in the 6-Month Pretreatment Period*

	Overall 6-Month Population (N = 7,081)			12-Month Subset (N = 5,024)		
	Calcitonin N = 774 (10.9%)	Alendronate N = 5,307 (74.9%)	Risedronate N = 1,000 (14.1%)	Calcitonin N = 656 (13.1%)	Alendronate N = 3,716 (73.9%)	Risedronate N = 652 13.0%)
Sex, n (%)						
Females	709 (92)	4,946 (93)	938 (94)	603 (92)	3,463 (93)	610 (94)
Males	65 (8)	361 (7)	62 (6)	53 (8)	253 (7)	42 (6)
Age in years, mean (SD)	71.1 (10.8)	68.1 (10.6)*	68.2 (10.5)*	71.1 (10.6)	68.8 (10.3)*	68.5 (10.6)*
Median (i.q. range)†	72 (65-79)	69 (60-76)	69 (60-76)	72 (65-79)	70 (62-76)	69 (61-77)
Prior fragility fracture (hip, wrist, or vertebra)	10.7%	4.9%*	6.0%*	10.7%	5.3%*	7.2%‡
HT§ use (prior or current)	23.6%	29.4%*	31.0%*	24.4%	29.6%*	32.5%*
No. of concomitant medications, mean (SD)	7.4 (4.3)	6.1 (3.6)*	6.1 (3.5)*	7.4 (4.3)	6.1 (3.7)*	6.3 (3.4)*
Median (i.q. range)	7 (4-10)	5 (3-8)	5 (4-8)	6 (4-10)	5 (3-8)	5 (4-8)
Oral glucocorticoid use	14.3%	11.4%‡	13.9%‖	15.4%	12.7%	16.6%¶
No. of hospitalizations, mean (SD)	0.3 (0.8)	0.1 (0.6)*	0.1 (0.5)*	0.3 (0.8)	0.1 (0.5)*	0.1 (0.5)*
Median (i.q. range)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
No. of physician visits, mean (SD)	5.6 (5.8)	5.1 (5.3)‡	5.0 (5.3)‡	5.6 (5.8)	5.0 (5.1)	4.7 (4.9)*
Median (i.q. range)	4 (2-7)	4 (2-7)	4 (1-7)	4 (2-7)	4 (2-7)	4 (1-7)
Diagnosis of rheumatoid arthritis	2.5%	3.6%	4.2%	2.9%	3.9%	5.2%‡

** Statistically significant compared with calcitonin, P<0.01.*
† i.q. range = inter-quartile range.
‡ Statistically significant compared with calcitonin, P<0.05
§ HT = hormone therapy.
// Statistically significant compared with alendronate, P<0.05.
¶ Statistically significant compared with alendronate, P<0.01.

12-month analyses (Table 3). Even though the absolute number of events was relatively small for each therapy, the individual comparisons yielded statistically significant differences. However, only concomitant medications significantly contributed to the multivariate model. Once the variable for concomitant medications was included in the model, adding other variables failed to explain additional variability. While the treatment groups exhibited significant differences with respect to rheumatoid arthritis and oral glucocorticoid use (Table 3), neither variable significantly added to the multivariate analysis and therefore were not included in the final model.

In the 6-month population analysis, both risedronate and alendronate patients were significantly more likely to have used HT prior to or following the index therapy (31.0% and 29.4%, respectively) than were nasal calcitonin patients (23.6%, $P<0.01$ for both comparisons). Prevalence of HT use in the 12-month subset was similar to that seen in the 6-month analysis (Table 3).

Nonvertebral Fractures

In the overall population (6-month analysis), the incidence of nonvertebral fractures was 2.2% for nasal calcitonin patients, 1.4% for alendronate patients, and 0.6% for risedronate patients (Table 4), or an ARR of 1.6% for risedronate compared with calcitonin and 0.8% for risedronate compared with alendronate; the ARR for alendronate compared with nasal calcitonin was 0.8%. For the 12-month subset, nonvertebral fractures occurred in 2.9% of nasal calcitonin patients, 2.4% of alendronate patients, and 0.9% of risedronate patients (Table 5), or statistically lower fracture risks for risedronate compared with nasal calcitonin, risedronate compared with alendronate, and alendronate compared with nasal calcitonin. The Kaplan-Meier cumulative distribution functions illustrate the time to first nonvertebral fracture for each treatment group (Figures 2A and 2B).

The final adjusted model contained parameter estimates including age, sex, prior fragility fracture, HT use ("prior or current HT use" versus "nonuse") and number of concomitant medications. After adjustment, in the 6-month population, risedronate compared with nasal calcitonin demonstrated a statistically significant 69% relative reduction ($P = 0.02$, Table 4) in fracture risk and a 75% relative reduction ($P<0.01$, Table 5) in the 12-month subset. Compared with alendronate, the risedronate patients had a 54% lower RR of fracture at 6 months ($P = 0.07$), a risk reduction that did not achieve statistical significance until 12 months (59%, $P = 0.04$). The unadjusted risk estimates for the 6-month population showed a 48% lower risk of fracture ($P = 0.02$) for alendronate patients compared with nasal calcitonin patients and a 41% lower risk ($P = 0.04$) for the 12-month subset, although these RRs were no longer significant in the final adjusted model at 6 months (RR = 0.74, $P = 0.28$) or 12 months (RR = 0.75, $P = 0.27$).

TABLE 4 Estimated Risk of a Nonvertebral Fracture After Initiation of Osteoporosis Therapy for the Overall 6-Month Population

	All Patients	Patients With at Least 1 Nonvertebral Fracture		Crude Risk			Adjusted Risk*		
Treatment	Total	n	%	RR	95% CI	*P* value	RR	95% CI	*P* value
Nasal calcitonin	774	17	2.2	1.00	–		1.00	–	
Risedronate	1,000	6	0.6	0.25	(0.10,0.63)	<0.01	0.31	(0.12,0.81)	0.02
Alendronate	5,307	72	1.4	1.00	–		1.00	–	
Risedronate	1,000	6	0.6	0.46	(0.20,1.06)	0.07	0.46	(0.20,1.06)	0.07
Nasal calcitonin	774	17	2.2	1.00	–		1.00	–	
Alendronate	5,307	72	1.4	0.52	(0.31,0.89)	0.02	0.74	(0.43,1.27)	0.28

** Adjusted for age, sex, hormone therapy use, prior fragility fracture, and number of concomitant medications in the 6-month pretreatment period.*

TABLE 5 Estimated Risk of a Nonvertebral Fracture After Initiation of Osteoporosis Therapy for the 12-Month Subset

	All Patients	Patients With at Least 1 Nonvertebral Fracture		Crude Risk			Adjusted Risk*		
Treatment	Total	n	%	RR	95% CI	*P* value	RR	95% CI	*P* value
Nasal calcitonin	656	19	2.9	1.00	–		1.00	–	
Risedronate	652	6	0.9	0.24	(0.10,0.61)	<0.01	0.25	(0.10,0.64)	<0.01
Alendronate	3,716	88	2.4	1.00	–		1.00	–	
Risedronate	652	6	0.9	0.42	(0.18,0.96)	0.04	0.41	(0.18,0.94)	0.04
Nasal calcitonin	656	19	2.9	1.00	–		1.00	–	
Alendronate	3,716	88	2.4	0.59	(0.36,0.97)	0.04	0.75	(0.45,1.25)	0.27

** Adjusted for age, sex, hormone therapy use, prior fragility fracture, and number of concomitant medications in the 6-month pretreatment period.*

Persistence With Therapy

In the 6-month analysis, the rate of continuation with therapy was comparable for patients taking risedronate (77.2%) and alendronate (77.5%), with a nonsignificant difference between the 2 groups ($P = 0.85$). However, the nasal calcitonin patients had a slightly lower percentage of patients continuing (68%), which was significantly different compared with both alendronate and risedronate ($P<0.01$). In the 12-month subset, the gap between mean persistence rates for patients receiving nasal calcitonin and the 2 bisphosphonates was narrower, 66.8% of the nasal calcitonin patients remained on therapy until they were censored versus 72.9% of the risedronate patients and 70.9% of the alendronate patients. The only statistically significant difference in the rate of persistence with therapy was between the risedronate and nasal calcitonin patients ($P = 0.03$).

Discussion

In this analysis of treatment to prevent osteoporotic fracture in a real-world population, risedronate was shown to reduce the risk of nonvertebral fractures at 6 months compared with calcitonin and at 12 months compared with both calcitonin and alendronate. While risedronate has been shown to reduce the risk of clinical vertebral fractures and nonvertebral fractures versus placebo within the first 6 months of treatment in clinical trials,[7,8] these effects have not been quantified previously in an observational setting.

The generalizability of clinical trial results to clinical practice may be limited, and the magnitude of effects observed in clinical trials may be different from those observed in clinical practice settings. For example, Dowd et al. conducted a retrospective chart review of osteoporosis patients seen in an academic medical center. They found that a large proportion, perhaps the majority, of patients with osteoporosis who were candidates for treatment by their physicians were not eligible for entry into typical treatment trials.[26] Therefore, the results of this retrospective cohort study examining claims derived from a managed care population underscore the importance of supplementing controlled clinical trials with real-world observational studies to fully elucidate the potential risks and benefits of therapy and contribute to the collective evidence of effects on clinical and other outcomes.

Observational database studies have several advantages over controlled clinical trials: (a) real-world practice patterns can be observed over a variety of health plans and physician specialties, (b) a large number of patients can be followed over time, and (c) the patients may be more typical of those seen in actual practice because they are not excluded due to restrictive clinical trial exclusion criteria nor is their care driven by strict research protocols. Additionally, it is possible to generate comparative data for conditions with relatively low incidence (e.g., fragility fractures) since a sizeable patient population can be readily evaluated.

Disadvantages to observational database studies include (a) patient charts cannot be reviewed to confirm the accuracy of diagnosis codes in the database, (b) only clinically reported events that have been documented in medical claims can be evaluated, and (c) unidentified variables could influence the treatment and outcomes. Specifically, there may be underlying differences in the patient populations that are related to both the choice of treatment and the outcome measure, and without the ability to control for these variables, there may be some

inherent allocation bias.

Patients included in this analysis can be considered representative of a fully insured elderly population, eligible to receive prescriptions for osteoporosis therapy in a managed care setting. This study did not explore the rates or consequences of fracture among patients who lack health insurance (medical and prescription) benefits, or the differences in patterns of care among patients with differing copayment structures because the data were not available.

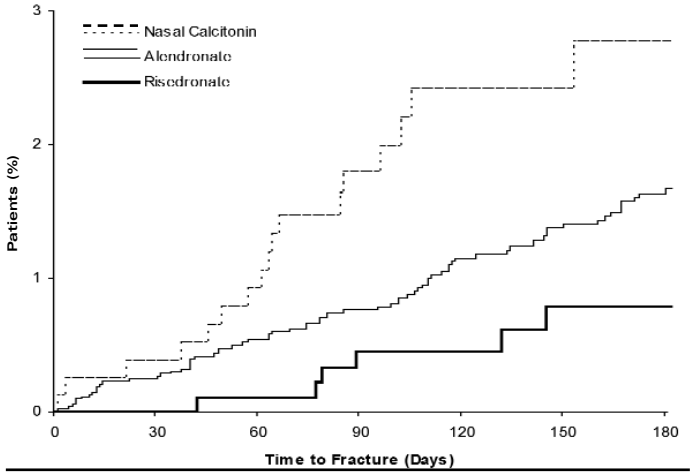
In these types of analyses, it is important to establish comparability between the patient populations prior to the initiation of treatment. For example, if one group of patients has a diminished health status that is correlated with an increased risk of fracture, then the study results could be biased. In the present study, the alendronate and risedronate patients were similar with respect to overall health status as assessed by age, sex, and resource utilization parameters such as prior hospitalization and physician visits as well as comorbid conditions and prescription drug use (prevalence of rheumatoid arthritis, prescription for oral glucocorticoids, and overall number of concomitant medications). Furthermore, similar rates of fractures in the 6-month pretreatment period were observed for alendronate and risedronate, suggesting that physicians did not show preference for a specific bisphosphonate in treating more-severe patients (as defined by those with previous fragility fractures).

Compared with risedronate or alendronate, nasal calcitonin did not have a higher proportion of patients with rheumatoid arthritis or a glucocorticoid prescription, but these patients did exhibit slightly more resource utilization in the form of physician visits, hospitalizations, and number of concomitant medications (all 3 resource utilization measures were statistically different) and a higher proportion of fragility fractures in the pretreatment period. However, these differences were either adjusted for in the final statistical model or did not significantly add to the final model and so are unlikely to account for the disparities in incidence of nonvertebral fractures in either the 6-month or 12-month analysis. Additionally, it should be noted that, while the total number of patients in the alendronate treatment group was substantially larger than that of the risedronate or nasal calcitonin treatment groups, these differences in sample size do not affect the study results since analyses were based on rates and proportions rather than absolute numbers of events.

When assessing the efficacy of specific drug therapies, it is desirable to have comparable persistence and compliance among the treatment cohorts. It is difficult to correlate adverse outcomes (i.e., fractures) with specific therapies if a disproportionate number of patients within one or more of the treatment cohorts is not actually using the drug or is not using the drug to the same extent (i.e., had varied levels of exposure).

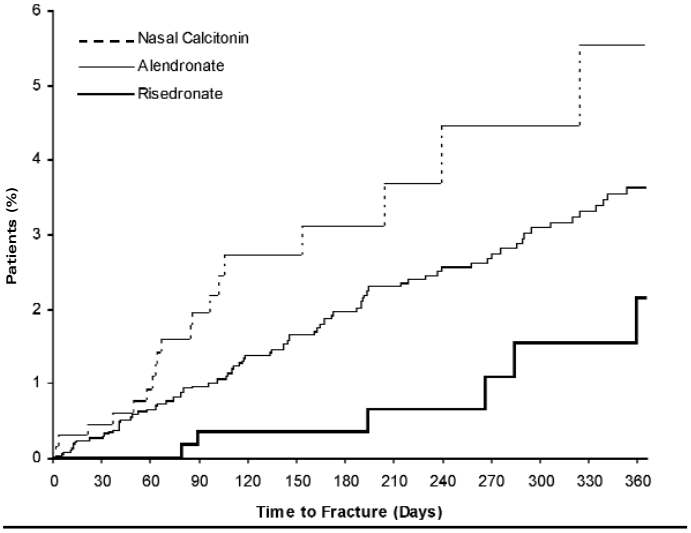
While observational database analyses cannot measure actual drug consumption, patterns of refills can be used as indica-

FIGURE 2A Kaplan-Meier Cumulative Distribution Functions for Time-to-Fracture After Initiation of Therapy: Overall 6-Month Population



** Results of the log-rank test (which reflects only crude differences in the survival curves) indicate that both alendronate and risedronate were significantly different from nasal calcitonin at P<0.05.*

FIGURE 2B Kaplan-Meier Cumulative Distribution Functions for Time-to-Fracture After Initiation of Therapy: 12-Month Subset



** Results of the log-rank test (which reflects only crude differences in the survival curves) indicate that both alendronate and risedronate were significantly different from nasal calcitonin and that risedronate was significantly different from alendronate at P<0.05.*

tors of persistence and continuation with therapy. The nasal calcitonin patients in the overall 6-month analysis of this study appeared to be somewhat less likely than risedronate or alendronate patients to continue on therapy. However, the nasal calcitonin patients in the 12-month subset demonstrated a similar rate of persistence relative to risedronate. While these descriptive results provide a general idea of persistence among the treatment groups, it actually is quite difficult to assess the relationship between persistence with therapy and fracture rates in the present study. This is because the study design inherently reduces the potential problem of nonpersistence by censoring patients who fail to refill the index therapy within 30 days of the previous prescription. Thus, any patient who fails to continue therapy is not followed any further to observe incident fractures. Consequently, all (100%) of the patients who fractured in this study were "persistent" with therapy since they had no gaps exceeding 30 days.

Calculating other measures of persistence, such as cumulative drug availability (CDA), would provide no additional benefit because all patients who fracture are censored on the fracture date, and only patients who do not fracture have the opportunity to be censored based on poor persistence. Due to the study design, CDA measures would indicate that the patients who fracture have better persistence than those who do not fracture. Thus, it is not necessary to "adjust" for persistence in the present study since the design of the study reduces the opportunity for such bias.

The present study showed that in the first 6 months of therapy, patients initiating treatment with risedronate had a significantly lower RR of nonvertebral fractures compared with patients initiating treatment with nasal calcitonin. Within the first 12 months of therapy, risedronate patients exhibited a significantly lower RR of nonvertebral fractures compared with both nasal calcitonin and alendronate. Alendronate patients exhibited fracture rates that were numerically lower than patients receiving nasal calcitonin, but the differences did not reach statistical significance following adjustment for age, sex, fracture history, estrogen use, and concomitant medication use, at either 6 or 12 months. These analyses substantiate that the early antifracture efficacy of risedronate seen in clinical trials also occurs in the actual clinical practice environment that we studied.

Within managed care, optimal control of osteoporotic patients begins by accurately identifying those patients who are at risk of osteoporosis and providing necessary treatment interventions. Appropriate therapy and persistence with therapy are crucial to the successful management of osteoporotic patients, as delayed treatment can result in further bone loss.[27,28] In selecting both the 6-month and 12-month cohorts for the present study, 48% of the potentially eligible patients did not fill a second prescription within 45 days (Figures 1A and 1B) and therefore did not meet the inclusion criteria. Overall, this reflects a rather low rate of persistence with osteoporosis therapies, in general, and presents an important opportunity for MCOs and managed care pharmacists to improve patient outcomes through initiatives that target persistence. In addition, adequate treatment should, in practice, reduce the occurrence of fractures, thus reducing morbidity and associated utilization of resources and costs. Future studies should explore differences in cost-effectiveness related to differences in clinical effectiveness across therapeutic agents. Managed care plans are challenged to develop effective medical management strategies to predict which patients are at highest risk for osteoporosis and subsequent nonvertebral fracture and to aggressively manage those patients for whom bisphosphonate therapy is indicated.

Conclusions

This observational study of primarily elderly women showed that those who received 6 or 12 months of therapy with either risedronate or alendronate had lower rates of nonvertebral fractures compared with health plan members who received prescriptions for nasal calcitonin, but only risedronate maintained a significantly lower risk of fracture after adjustment for age, sex, prior fragility fracture, number of concomitant prescriptions in the pretreatment period, and use of HT. At 12 months of drug use, risedronate was associated with a statistically significant 58% lower RR of nonvertebral fractures compared with alendronate (incidence of 0.9% for risedronate patients versus 2.4% for alendronate patients) and 59% lower RR after adjustment for potentially confounding factors. This study also identified a great opportunity to improve adherence with pharmacotherapy for osteoporosis since nearly one half of patients who received an initial prescription for one of these 3 drugs to treat osteoporosis did not obtain a refill of the original prescription.

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