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Benefit of Adherence With Bisphosphonates Depends on Age and Fracture Type: Results From an Analysis of 101,038 New Bisphosphonate Users

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ABSTRACT: The relationship between high adherence to oral bisphosphonates and the risk of different types of fractures has not been well studied among adults of different ages. Using claims data from a large U.S. health care organization, we quantified adherence after initiating bisphosphonate therapy using the medication possession ratio (MPR) and identified fractures. Cox proportional hazards models were used to evaluate the rate of fracture among nonadherent persons (MPR < 50%) compared with highly adherent persons (MPR ≥ 80%) across several age strata and a variety of types of clinical fractures. In conjunction with fracture incidence rates among the nonadherent, these estimates were used to compute the number needed to treat with high adherence to prevent one fracture, by age and fracture type. Among 101,038 new bisphosphonate users, the proportion of persons with high adherence at 1, 2, and 3 yr was 44%, 39%, and 35%, respectively. Among 65- to 78-yr-old persons with a physician diagnosis of osteoporosis, the crude and adjusted rate of hip fracture among the nonadherent was 1.96 (95% CI, 1.48–2.60) and 1.74 (95% CI, 1.30–2.31), respectively, resulting in a number needed to treat with high adherence to prevent one hip fracture of 107. The impact of high adherence was substantially less for other types of fractures and for younger persons. Analysis of adherence in a non–time-dependent fashion artifactually magnified differences in fracture rates between adherent and nonadherent persons. The antifracture effectiveness associated with high adherence to oral bisphosphonates varied substantially by age and fracture type. These results provide estimates of absolute fracture effectiveness across age subgroups and fracture types that have been minimally evaluated in clinical trials and may be useful for future cost-effectiveness studies.
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Key words: bisphosphonate, adherence, compliance, fracture, osteoporosis

INTRODUCTION

Long-term adherence with bisphosphonates has been shown to be poor in osteoporosis.[1–4] Approximately one half of persons discontinue bisphosphonate therapy within 1–2 yr. Recent studies of bisphosphonates adherence and fracture risk have not examined the risk of nonadherence on nonhip, nonvertebral fractures and the impact of age on bisphosphonate effectiveness. Moreover, adherence has sometimes been evaluated only at the end of study and not in a more precise, time-varying manner, before fractures occur.[5–7] This problem may result in substantial inaccuracies in determining the effect of adherence on fracture risk.

In light of these limitations of past studies, we evaluated the relationship between bisphosphonate adherence and several types of fracture and explored how these relationships were affected by age. We also assessed the effect of fracture on adherence to determine the impact of adherence misclassification caused by failure to measure it in a time-varying manner.

MATERIALS AND METHODS

Data source and eligible population

After institutional review board approval, we used the administrative claims databases of a U.S. health care organization covering ~17 million persons living in eight U.S.

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census regions. We identified persons with medical and pharmacy benefits filling prescriptions for alendronate, risedronate, or ibandronate from January 1998 to July 2005. We identified new bisphosphonate users as those initiating therapy after at least a 6-mo period without any bisphosphonate prescription. The date of the first filled bisphosphonate prescription after this 6-mo period was defined as the index date. Baseline demographic characteristics, comorbidities, and health services utilization were examined in the 6 mo before the index date except for current glucocorticoid exposure and current estrogen exposure, which were evaluated as time-varying.

Adherence with bisphosphonates and drug exposure time

Adherence with bisphosphonates was quantified using the medication possession ratio (MPR), calculated by summing the total amount of bisphosphonate filled after the index date and dividing it by the calendar time since the index date.[8] MPR was computed for every observation day and evaluated at the time of each fracture event for every person in the cohort. Observation time was censored at the fill date of a nonbisphosphonate medication known to impact bone turnover (i.e., teriparatide, raloxifene, and calcitonin), disenrollment from the health plan, or the end of the study period. Switching to a different bisphosphonate dosing interval (e.g., daily to weekly) or formulation (e.g., alendronate to risedronate) was permitted and did not censor observation time.

Outcome assessment

The first occurrence of a fracture was the primary endpoint of the study. Fracture types were classified as hip; wrist/forearm; clinical vertebral; any nonvertebral (hip, wrist/forearm, humerus, clavicle, pelvis, and leg); and non-hip, nonvertebral (wrist/forearm, humerus, clavicle, pelvis, and leg). Fractures were identified using International Classification of Diseases (ICD-9) codes and were required to appear on an evaluation and management (E/M) claim from a physician. Fracture diagnoses associated with non-physician visit claims (e.g., an X-ray claim) were not considered to represent fracture events. Individuals who had a fracture in the 180 days before first bisphosphonate use were excluded from being at-risk for a fracture of that same type after the index date to not misclassify a follow-up visit for a recent fracture as an incident fracture.

Evaluation of the relationship between MPR and fracture rate

To evaluate the short-term impact of fractures on MPR, we identified all persons with a hip or nonvertebral fracture and evaluated the mean MPR for these individuals in the 3 and 6 mo before the fracture compared with immediately after the fracture. To evaluate the impact of MPR on fracture rate, we plotted MPR, calculated at the beginning of every 90-day interval after initiating bisphosphonates, and the incidence of hip fracture during that 90-day interval. To address the impact of considering MPR as a non–time-dependent variable, we also evaluated MPR at the end of 2.5 yr and compared it with the cumulative fracture rate during the preceding period. Data from both analyses were plotted and reflect the same fracture data from the exact same persons to illustrate the impact of considering MPR as a time-dependent versus a non–time-dependent variable. For all subsequent analyses, there was no limit on the amount of observation time, which extended up to 7 yr.

Statistical analysis

We used Cox proportional hazards models to estimate hazards ratios for relationship between adherence (MPR categories of >80%, 50–80%, <50%) and time to fracture. Time-varying adherence was examined using a MPR cut-point of 80%, following the convention of prior studies.[6] Models compared the rate of fracture among persons with MPR <50% to ≥80%. Estimates for MPR 50–80% were generally intermediate between these two groups and are not shown. Additional factors known or hypothesized to impact fracture rates included in models based on their clinical relevance.

Because of strong interactions between age, adherence, and fractures, we developed stratified models based on age groupings and varied the age strata cut-points in 5-yr intervals to identify age strata with the most homogeneous effect estimates. Age strata–specific model results for each fracture type were reported separately to describe this interaction. We also evaluated hazard ratios among the subgroup of persons with a physician E/M claim for osteoporosis, hypothesizing that these persons might have a greater risk for fracture and be more likely to benefit from high adherence to bisphosphonates.

Fracture incidence was examined within various age and sex strata to quantify the rate of fractures per 1000 person-years. Only individuals with MPR <50% throughout the study period were included to approximate an untreated population. For this analysis, we evaluated MPR beginning at 6 mo after the index date, because MPR shortly after beginning therapy is subject to a ceiling effect (e.g., MPR within the first month for all persons filling even a single bisphosphonate prescription is 100%). Using the absolute fracture rates coupled with the relative rate differences from above, we calculated the number needed to adhere (with MPR ≥ 80%) to oral bisphosphonates to prevent one fracture of a specific type. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Of the 101,038 persons initiating bisphosphonates, 48% were 55–64 yr of age, 30% were ≥65 yr of age, 58% had received a BMD test in the 6 mo before starting bisphosphonates, and 83%initiated a weekly bisphosphonate (Table 1). The mean ± SD length of postindex observation time was 26.7 ± 17 mo.

Only 44% of persons had a MPR ≥ 80% at 1 yr (data not shown). This proportion declined to 39% and 35% at years 2 and 3, respectively. Those initially prescribed weekly bisphosphonates had higher 1-yr MPR than those initially prescribed daily bisphosphonates (mean = 45% versus 38%, $p < 0.001$). Adherence at year 1 was a strong predictor

TABLE 1. DEMOGRAPHIC CHARACTERISTICS, COMORBIDITIES, AND HEALTH SERVICES UTILIZATION* OF PERSONS INITIATING BISPHOSPHONATE THERAPY (N = 101,038)

	N or mean	*Percent or SD*
Demographics		
Age (yr)		
45–54	21,633	21
55–64	48,426	48
65–74	17,535	17
≥75	13,444	13
Women	95,741	95
Prior fracture		
Hip	856	0.9
Wrist/forearm	1,026	1.0
Clinical vertebral	1,498	1.5
Nonhip, nonvertebral	2,377	2.4
Any nonvertebral	2,856	2.8
Other selected comorbidities		
Osteoporosis	42,605	42.2
Diabetes	6,799	6.7
Rheumatoid arthritis	2,847	2.8
Hyperlipidemia	29,024	28.7
Smoking	1,256	1.2
Hyperthyroidism	1,412	1.4
Charlson comorbidity index	0.4	1.0
Prior use of selected medications		
Systemic estrogen	21,811	21.6
Teriparatide	58	0.0
Raloxifene	5,749	5.7
Nasal calcitonin	3,179	3.2
Systemic glucocorticoids	9,396	9.3
Health services utilization		
Outpatient visits	3.2	3.1
Any hospitalization	5,214	5.2
BMD test	58,577	58.0
Other Screening tests		
Mammography	34,348	34.0
Colonoscopy	5,836	5.8
Fecal occult blood test	21,867	21.6
Flexible sigmoidscopy	730	0.7
PSA screening	979	1.0
Bisphosphonate use on the index date		
Alendronate weekly	58,814	58.2
Alendronate daily	13,377	13.2
Risedronate weekly	25,076	24.8
Risedronate daily	3,550	3.5
Ibandronate monthly	221	0.2

* All factors assessed in the 6 mo before first bisphosphonate use.

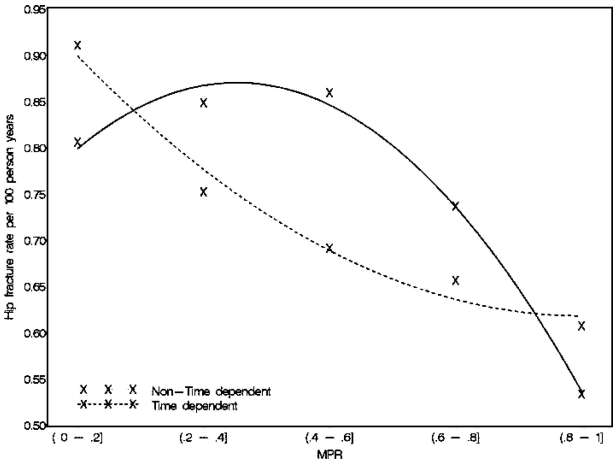

FIG. 1. Relation between adherence (MPR) and rate of hip fracture among persons 65–78 yr of age considering MPR as a time-dependent variable (dotted curve) or a non–time-dependent variable (solid curve). For each 90-day interval after bisphosphonate initiation, we evaluated the relation between the MPR at the beginning of the interval and the rate of fracture for the next 90 days (dotted curve) and summed over all 90-day intervals through the end of 2.5 yr. In a non–time-dependent analysis (solid curve), we also evaluated the relation between the MPR at the end of 2.5 yr and the rate of fracture.

of adherence at year 2; 80% of bisphosphonate users with MPR ≥ 80% at year 1 remained adherent with MPR ≥ 80% at year 2. Among persons who experienced a hip fracture, the mean adherence in the 3 and 6 mo after the fracture was 9% and 7% lower than the mean adherence in the 3 and 6 mo preceding the fracture ($p < 0.0001$ for both). Differences in mean MPR before and after nonvertebral fractures were of smaller magnitude (~4%).

In the analysis with a time-dependent MPR (Fig. 1, dotted curve), there was a strong linear relation between increasing adherence and decreasing fracture rate, with no threshold effect. When MPR was measured only once at the end of the study, the relation also was strong (solid curve). However, the shape of the curve was different and magnified the differences in fracture rates between the adherent and nonadherent, particularly for persons with intermediate adherence (MPR 20–80%).

The association between low adherence (MPR < 80%) and each fracture type was most homogeneous within the age groups of 45–64, 65–78, and >78 yr; therefore, results for these groups are presented in Table 2. For hip fracture, the hazard ratio for low adherence among 65–78 yr olds, adjusted for multiple confounders, was 1.41 (1.13–1.76) and was somewhat greater for those with a physician diagnosis of osteoporosis. The magnitude of the hip fracture hazard ratio associated with low adherence was smaller for younger persons, and there were no differences in the rate of hip fracture between adherent and nonadherent individuals older than 78. In contrast, the benefits of high adherence on the incidence rate of vertebral fractures were observed irrespective of age, although some estimates did not reach statistical significance. The risk for nonhip, nonvertebral fractures were increased among persons of all ages, although the hazard ratios were much lower than for hip and vertebral fractures, suggesting less of a protective benefit from high adherence to bisphosphonates for these fracture types.

The largest significant hazard ratio for any age group and fracture type was for hip fractures among 65–78 year olds with osteoporosis, where nonadherent persons were observed to have an adjusted 1.74-fold greater risk for fracture. Inverting this estimate, the corresponding relative fracture rate of high bisphosphonate adherence in this age group was 0.57 (95% CI 0.43–0.77), a 43% relative risk reduction (RRR). This was very similar to the hazard ratios for clinical vertebral fractures irrespective of age among all persons with osteoporosis, where adjusted hazard ratios

Table 2. Crude and Adjusted* Fracture Hazard Ratios† Among the Nonadherent (MPR < 50%) Compared With the Adherent (MPR ≥ 80%) Among All Persons and Those With Osteoporosis (OP), by Age and Fracture Type

	45–64			*65–78*			*>78*		
Fracture type‡	*Events*	*Crude*	*Adjusted*	*Events*	*Crude*	*Adjusted*	*Events*	*Crude*	*Adjusted*
Hip									
All	158	1.26 (0.87–1.82)	1.11 (0.76–1.62)	483	1.59 (1.28–1.98)	1.41 (1.13–1.76)	86	0.95 (0.58–1.55)	0.87 (0.53–1.43)
Persons w/OP	110	1.21 (0.78–1.90)	1.08 (0.68–1.71)	294	1.96 (1.48–2.60)	1.74 (1.30–2.31)	48	1.00 (0.53–1.91)	0.88 (0.46–1.69)
Wrist/forearm									
All	803	1.22 (1.03–1.43)	1.21 (1.03–1.43)	480	1.03 (0.83–1.26)	0.97 (0.79–1.20)	44	2.23 (0.98–5.06)	2.21 (0.97–5.0)
Persons w/OP	426	1.23 (0.98–1.55)	1.22 (0.97–1.53)	301	1.01 (0.77–1.31)	0.93 (0.68–1.29)	21	2.59 (0.81–8.28)	2.93 (0.91–10.91)
Clinical vertebral									
All	264	1.33 (1.00–1.77)	1.28 (0.96–1.71)	441	1.66 (1.31–2.10)	1.48 (1.16–1.89)	44	1.53 (0.66–3.54)	1.39 (0.60–3.23)
Persons w/OP	171	1.79 (1.26–2.53)	1.70 (1.19–2.42)	309	1.94 (1.46–2.57)	1.70 (1.27–2.27)	26	1.68 (0.58–4.89)	1.72 (0.58–5.09)
Nonhip, nonvertebral									
All	1360	1.17 (1.04–1.33)	1.14 (1.01–1.30)	981	1.18 (1.02–1.37)	1.10 (0.95–1.28)	99	1.38 (0.85–2.25)	1.31 (0.80–2.15)
Persons w/OP	736	1.20 (1.01–1.42)	1.16 (0.97–1.38)	604	1.15 (0.95–1.39)	1.05 (0.90–1.27)	52	1.38 (0.71–2.68)	1.36 (0.70–2.64)
Nonvertebral									
All	1452	1.16 (1.03–1.31)	1.13 (1.00–1.28)	1265	1.25 (1.10–1.43)	1.14 (1.00–1.31)	157	1.06 (0.74–1.53)	0.98 (0.68–1.42)
Persons w/OP	802	1.19 (1.01–1.40)	1.14 (0.96–1.35)	768	1.30 (1.10–1.54)	1.19 (1.00–1.41)	85	1.08 (0.67–1.77)	0.99 (0.61–1.62)

Each cell represents a separate result from a unique Cox proportional hazards model.

"Persons with OP" indicates that the person had a physician diagnosis of osteoporosis (ICD-9 733.0X) during the study period.

Number of nonvertebral fracture events is not the sum of hip fractures + nonhip, nonvertebral fractures because an individual who previously experienced a hip fracture in the 180 days preceding bisphosphonate use was excluded from being at-risk for another hip fracture but could experience a nonhip, nonvertebral fracture.

* Adjusted for age (except in >78-yr-old strata), sex, prior fracture, recent BMD test, recent screening test, comorbidities listed in Table 1, Charlson comorbidity index, number of outpatient visits, prior hospitalization, and use of glucocorticoids, systemic estrogens, and nonbisphosphonate osteoporosis medications.

† Estimates compare the rate of fracture among persons with MPR < 50% referent to those with MPR > 80%. Hazard ratios for persons with MPR 50–80% were generally intermediate between 1.0 and those presented.

‡ As coded from a physician Evaluation and Management (E/M) claim.

TABLE 3. FRACTURE INCIDENCE AMONG THE NONADHERENT (MPR < 50%) PER 1000 PERSON-YEARS AND NUMBER NEEDED TO ADHERE (NNA) FOR 1 YR TO PREVENT ONE FRACTURE BY AGE, SEX, AND FRACTURE TYPE

		Age						
		Women					*Men**	
Fracture type†	*Events used to compute rate (n)*	*45–54*	*55–64*	*65–71*	*72–78*	*>78*	*45–64*	*65–78*
Hip								
All pts	219	0.8	1.1	3.9	15.3	32.4		
NNA, All pts		6058	4406	691	176	n/a		
Persons w/OP†	136	1.1	1.6	3.6	19.1	39.5		
NNA, persons w/OP†		5238	3601	567	107	n/a		
Wrist								
All pts	354	5.5	6.6	7.2	10.7	15.5		
NNA, All pts		1008	840	n/a	n/a	117		
Persons w/OP†	182	6.2	7.6	9.3	12.3	18.8		
NNA, persons w/OP†		863	704	n/a	n/a	87		
Clinical vertebral								
All pts	193	1.5	1.9	4.0	11.4	14.2		
NNA, All pts		2687	2121	629	221	203		
Persons w/OP†	134	2.5	3.5	4.6	13.3	18.2		
NNA, persons w/OP†		906	647	449	155	136		
Nonhip, nonvertebral								
All pts	657	8.9	10.8	11.3	25.3	36.9		
NNA, All pts		773	637	580	259	98		
Persons w/OP†	332	10.7	13.1	14.6	26.7	45.1		
NNA, persons w/OP†		561	458	525	287	81		
Any nonvertebral								
All pts	796	9.3	11.4	14.7	35.2	61.0	8.4	13.1
NNA, All pts		780	636	340	142	290	863	553
Persons w/OP†	410	11.4	14.0	17.5	38.8	74.9	9.5	26.7
NNA, persons w/OP†		549	447	248	112	180	659	162

* Rates not provided when the number of events for that cell was <10.

† As coded from a physician evaluation and management (E/M) claim.

NNA, number needed to adhere, defined as the number needed to treat (NNT) with a ≥80% adherence to medication to prevent a facture of the type specified; n/a, not applicable, indicating that relative risk estimates from Table 2 did not show a protective effect.

were 1.70–1.72 (RRR = 41–42%). In contrast, the benefit of wrist fracture rate reduction was lower; among 45–64 year olds, the rate of wrist fractures was 1.22 among the nonadherent, with a corresponding RRR of 18% (95% CI 0.70–0.97). For all nonhip, nonspine fractures, there was approximately a 10–30% elevation in fracture rates for the nonadherent compared with the adherent, depending on age group.

Among the least adherent persons (MPR < 50%), the rates of fractures of all types steadily increased with age, and rates were numerically higher for the subgroup of persons with an osteoporosis claim (Table 3). Combining these fractures rates with the reduction in the fracture rate among adherent persons from Table 2 allowed calculation of the number needed to adhere to prevent one fracture. For hip fractures among 72–78 yr olds, for example, the number of persons needed to have high adherence (MPR ≥ 80%) to bisphosphonates for 1 yr to prevent one hip fracture was 176. This number decreased to 107 for the subgroup of persons with a physician claim for osteoporosis. The number of older persons needed to have good adherence to prevent a clinical vertebral fracture was similar. In contrast, based on a smaller effect size of oral bisphosphonates to reduce fracture risk for other types of fractures such as nonhip, nonvertebral, the number of persons needed to have high adherence to prevent one nonhip, nonvertebral fracture was generally much larger. For example, as shown for the younger women in the next to last set of rows, many hundreds of women would need to be adherent with bisphosphonates to prevent one nonhip, nonvertebral fracture.

DISCUSSION

Among persons enrolled in a large U.S. health care organization, we observed that the benefit of high adherence to oral bisphosphonates varied by age and fracture type. The greatest benefit of high adherence was among 65- to 78-yr-old individuals for hip and clinical vertebral fractures. The benefits of high bisphosphonate adherence on the rate of nonhip, nonvertebral fractures were much less. Based on higher age-related fracture rates, the number needed to treat with high adherence to prevent one fracture were generally greatest for older persons. We observed that adherence was significantly lower immediately after a fracture than in the prefracture time period. Thus, a unique feature of our study is its demonstration that analysis of adherence in a non–time-dependent fashion artifactually magnifies differences in fracture rates between adherent and nonadherent persons, particularly for persons with intermediate adherence.

For hip, clinical vertebral, and all nonvertebral fractures, our results are quite similar to the relative risk reductions for fracture observed in randomized, placebo-controlled bisphosphonate clinical trials for women in their 60s or 70s. For example, alendronate reduced the risk of hip and clinical vertebral fracture by 47% and 55%, respectively,[9,10] which is similar to our corresponding estimates of ~42–43%. Nonadherent persons 45–64 and 65–78 yr of age in our cohort had adjusted nonvertebral fractures rates 13–19% higher than adherent persons (corresponding RRRs = 12–16%). These data are very similar to the 12–20% decreased risk of nonvertebral fractures found with alendronate and are similar to the effect sizes observed in risedronate trials.[11–13]

We did not observe a significant protective effect of high adherence to bisphosphonates on the rate of hip and wrist fractures among individuals older than 78 and 65 yr of age, respectively. Consistent with our findings, a prior risedronate study showed no protective benefit of risedronate on the risk of hip fracture among women age ≥80 yr selected on the basis of at least one nonskeletal risk factor.[11] Similarly, a past study that evaluated women without a prevalent vertebral fracture[10] found no protective effect of alendronate on wrist fractures. As a unique feature of our study, the benefits for bisphosphonates for other groups of fractures such as nonhip, nonvertebral, or for younger and older women have not been typically evaluated in clinical trials.

Our results are consistent with data from Siris et al.[6] showing that high adherence to bisphosphonates resulted in a significantly decreased risk for fracture. Siris et al.'s effect estimates were described as nonproportional by age, but age strata–specific effect estimates were not provided, as we have done. Moreover, the majority of their analyses evaluated MPR at the end of 2 yr and evaluated the occurrence of any fracture during that observation period. In contrast to that approach, because the occurrence of a fracture impacts subsequent adherence, we showed that it is preferable to evaluate MPR before fracture occurrence. Additionally, in a non–time-dependent analysis and concordant with our results in Fig. 1 that used similar methods (solid curve), that study showed an inflection point in the risk for fracture at an MPR of ~50%. In other words, adherence <50% was not associated with an increased risk for fracture. In contrast, using a more comprehensive time-dependent approach, we did not observe an inflection point to suggest that bisphosphonate adherence below a certain threshold was irrelevant.

In contrast to data from randomized clinical trials that showed that the number needed to treat (NNT) with bisphosphonates to prevent one fracture ranged from several dozen up to 100 when considering a time frame of 3–4 yr,[9–12] we generally observed higher NNTs. In our population, the number of persons needed to have high adherence to prevent one fracture ranged from a minimum of 100 to much higher numbers (into the several thousands). A common inclusion criterion for many clinical trials is the presence of a prior vertebral fracture in addition to low bone mass; thus, many clinical trials intentionally select very high-risk patients. In contrast, our data reflect the wide spectrum of the severity of osteoporosis treated with bisphosphonates, and many of these individuals may be at relatively low absolute risk for fracture. Therefore, more individuals must be treated with bisphosphonates to prevent one fracture.

Our study has several strengths. It provides estimates of the age-specific benefits of high adherence to bisphosphonates on the risk of five different types/groups of fractures. In contrast to the carefully selected individuals that participate in clinical trials, most of whom have very low bone mass and/or prior fractures and reflect a restricted age range, we were able to evaluate the relative and absolute benefit of bisphosphonates in the more diverse population for whom physicians elect to start treatment. Although a pharmacy database might not always reflect actual medication-taking behavior, we have previously shown high concordance between pharmacy databases and self-reported current use of osteoporosis medications.[14] Moreover, we believe this study advances adherence research by showing different results that considered adherence in a non–time-dependent fashion compared to those from a time-dependent analysis. This important methodological point should guide future analyses in this area.

Our results should be interpreted in light of our observational study design. The reasons for nonadherence to bisphosphonate were diverse, and there is the possibility of residual confounding related to use of administrative claims data and unmeasured factors associated with adherence, such as use of calcium and vitamin D supplements. Nonadherent persons are likely to be different from adherent persons in several ways that are imperfectly captured in claims data, and this may affect the incidence of a variety of health-related events.[15] Reassuringly, our results for hip and vertebral fractures were generally similar to the effect sizes observed in randomized control trials (RCTs) of older persons with osteoporosis. Of interest, we did not observe protective effects of adherence in all age and fracture type strata, suggesting that our results do not simply reflect a selection bias favoring adherent persons (irrespective of medication use). Also, claims data may have less than perfect validity to identify fractures. For some fracture types, such as hip fractures, misclassification of fractures in claims data are uncommon.[16] For other types of fractures, misclassification may be greater. However, we would expect that misclassification of fractures is unlikely to be related to adherence and is thus nondifferential, which would reduce our observed benefits of adherence. Potential fracture misclassification may, however, have underestimated fracture event rates (Table 3) by up to 20–25%. This would decrease the number needed to adhere by that amount. Finally, our population was enrolled in a large U.S. health care organization where most individuals had commercial insurance. The generalizability of our results may or may not extend to other populations.

In conclusion, we showed that the benefit of high adherence to oral osteoporosis medications depends strongly on age and fracture type. The greatest benefit was observed among persons 65–78 yr of age on the rate of hip fracture, where a 1.5- to 2-fold greater increase in fracture rate among the nonadherent was observed and is similar to the magnitude of the antifracture benefit observed in random-

ized, placebo-controlled trials. Perhaps of greater interest, we showed a much more modest effectiveness of oral bisphosphonates dependent on age and for wrist and nonhip, nonvertebral fractures. These results suggest that there remain important unmet needs to reduce these types of fractures. Finally, we showed that the choice of analytic methods used may significantly impact the interpretation of the results of the relationship between adherence and fracture risk.

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