Examining the Effect of Medication Adherence on Risk of Subsequent Fracture Among Women with a Fragility Fracture in the U.S. Medicare Population

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ABSTRACT

BACKGROUND: In the United States, osteoporosis affects approximately 10 million people, of whom 80% are women, and it contributes a significant clinical burden to the community. Poor adherence to osteoporosis medications adds to the overall burden of illness.

OBJECTIVE: To examine the association of osteoporosis medication adherence and the risk of a subsequent fracture among Medicare-enrolled women with a previous fragility fracture.

METHODS: This study was a retrospective observational analysis of U.S. administrative claims data among female Medicare beneficiaries who had a nontrauma closed fragility fracture between January 1, 2011, and December 31, 2011. Patients were required to have continuous medical and pharmacy enrollment 12 months pre- and postfracture date. In addition, patients were required to have an osteoporosis medication prescription for a bisphosphonate (alendronate, risedronate, pamidronate, etidronate, zoledronate, and tiludronate), calcitonin, denosumab, raloxifene, or teriparatide during the follow-up period. Adherence was calculated using cumulative medication possession ratio (MPR) from the treatment initiation date in 30-day increments. MPR was stratified into high adherence ($\text{MPR} \geq 80\%$), moderate adherence ($50\% \leq \text{MPR} < 80\%$), and low adherence ($\text{MPR} < 50\%$). Outcomes included first subsequent fracture after treatment initiation; patients were censored at treatment discontinuation, or end of the 12-month period posttreatment initiation. Covariates included demographics, comorbidities, osteoporosis medications, medications associated with falls, and health care utilization. Cox regression was used to model subsequent fractures with time-dependent cumulative MPR.

RESULTS: Of the 1,292,248 Medicare enrollees who had a fracture in 2011, a total of 103,852 (8.0%) women aged ≥ 65 years with a fragility fracture were identified. Overall, 27,736 (26.7%) patients were treated with osteoporosis medication within 12 months of the fragility fracture (mean time to treatment initiation was 85.0 ± 84.6 days). Over half of the patients were highly adherent ($\text{MPR} \geq 80\%$) to osteoporosis medications during the follow-up ($n = 14,112$; 50.9%). Almost a third of the patients had low adherence ($\text{MPR} < 50\%$; $n = 9,022$, 32.5%), followed by patients with moderate adherence ($50\% \leq \text{MPR} < 80\%$; $n = 4,602$, 16.6%). After adjusting for demographics and clinical characteristics, patients with low and moderate adherence to osteoporosis medications were 33% (hazard ratio [HR] = 1.33; 95% CI = 1.17-1.50, $P < 0.001$) and 19% (HR = 1.19; 95% CI = 1.02-1.38, $P = 0.026$) more likely to have a subsequent fracture, respectively, compared with patients with high adherence. Low adherence patients had a 32% and 34% increased risk for a hip/pelvis/femur fracture (HR = 1.32; 95% CI = 1.09-1.59, $P = 0.005$) and a clinical vertebral fracture (HR = 1.34; 95% CI = 1.09-1.63, $P = 0.005$), respectively, compared with high adherence patients.

CONCLUSIONS: Medicare-enrolled women with low and moderate adherence to osteoporosis medications had a higher risk of a subsequent fracture compared with high adherence patients. These results highlight

the importance of improving osteoporosis medication adherence among women enrolled in Medicare.

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What is already known about this subject

- Approximately 33% of women aged ≥ 50 years experience osteoporotic fractures.
- Results from previous studies have shown overall adherence to osteoporosis medications to be 26%-71% and that there is a systematic relationship between increased osteoporosis medication adherence and lower risk of fractures.
- A previous Medicare claims analysis has shown positive correlation between low adherence to osteoporosis medication use and increased risk of nonvertebral fractures.

What this study adds

- This analysis examined the possible causation between a subsequent fracture (vertebral, hip/pelvis, femur, other nonvertebral) and adherence to all osteoporosis medications among elderly women enrolled in Medicare who previously had a fracture.
- Compared with patients with high adherence to osteoporosis medications, patients with low adherence were 33% more likely to have a subsequent fracture and had a 34% increased risk for a clinical vertebral fracture, compared with high adherence patients.
- This analysis suggests that Medicare patients' lower adherence to osteoporosis medications is associated with increased risk for a subsequent vertebral or nonvertebral fracture within 12 months and aligns with previous research in different populations using longer follow-up periods.

With osteoporosis proven to be associated with mortality due to fragility fractures,¹⁻³ several medications have been made available to treat osteoporosis and improve the physical health of patients by significantly reducing the risk of fracture.⁴ However, the efficacy of osteoporosis medications informed via clinical trials may not reflect real-world practice. Real-world treatment patterns and/or

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FIGURE 1 Patient Selection Flow Diagram

^aThe following ICD-9-CM codes were used: hip: 733.14, 820.0, 820.2, 820.8; pelvis: 808.0, 808.2, 808.4, 808.8; femur: 733.15, 821.0, 821.2; clavicle: 810; humerus: 733.11, 812.0, 812.2, 812.4; forearm and wrist: 733.12, 813.0, 813.2, 813.4, 813.8, 814.0; tibia/fibula: 733.16, 823.0, 823.2, 823.4, 823.8; spine: 733.13, 805.2, 805.4, 805.8; E codes for trauma: E800-E848; E916-E919; E928.8-E928.9; E929.0-E929.1; E953; E957-E959; E960-E979; E988-E989; E999.

^b35,549 patients were excluded because they died; 1,454 patients were excluded due to disenrollment.

^cPaget's disease treatments: risendronate (30 mg), alendronate (40 mg), etidronate (200 or 400 mg), pamidronate (30 mg), and tiludronate (400 mg).

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

patient behaviors are different when compared with those within a controlled clinical trial environment. Medication compliance and adherence have proved to be limiting factors in predicting overall real-world effectiveness of osteoporosis medications.⁵⁻⁸ As such, compliance among osteoporosis patients has been relatively poor and has therefore contributed to increased fracture risk—by as much as 50%—and associated hospitalizations.^{7,9}

Some major reasons for poor compliance include medication side effects, patients' perception of medication effectiveness, medication safety profile, and out-of-pocket medication cost.¹⁰ Other reported factors associated with low compliance include treatment administration frequency, patients' ability to follow

a treatment regimen over the long term, and the health consequences of osteoporosis.¹¹ Overall, poor medication compliance has contributed significantly to morbidity and medical costs.¹² Low adherence has been shown to decrease bone mineral density (BMD), leading to more severe types of osteoporotic fracture, and higher osteoporosis-associated health care spending.^{13,14}

To date, very few studies have explored the relationship of osteoporosis treatment adherence to subsequent fractures among Medicare enrollees. This study aims to examine the association of osteoporosis medication adherence and the risk of a subsequent fracture among Medicare-enrolled women with a previous fragility fracture.

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TABLE 1 Descriptive Baseline Characteristics of Treated Patients with a Fragility Fracture

Baseline Characteristics	All Patients		High Adherence (MPR ≥ 80%)		Moderate Adherence (50% ≤ MPR < 80%)			Low Adherence (MPR < 50%)		
Sample Size	27,736		14,112		4,602			9,022		
	n	%	n	%	n	%	P Value (vs. High) ^a	n	%	P Value (vs. High) ^a
Age (years, mean [SD])	81.3 (7.6)		81.0 (7.5)		81.8 (7.8)		<0.001	81.5 (7.7)		<0.001
Age group (years)										
65-74	6,071	21.9	3,148	22.3	973	21.1	0.098	1,950	21.6	0.215
75-84	11,398	41.1	5,995	42.5	1,772	38.5	<0.001	3,631	40.2	<0.001
≥85	10,267	37.0	4,969	35.2	1,857	40.4	<0.001	3,441	38.1	<0.001
Geographic location										
Northeast	4,613	16.6	2,374	16.8	741	16.1	0.254	1,498	16.6	0.664
North Central	7,953	28.7	4,320	30.6	1,251	27.2	<0.001	2,382	26.4	<0.001
South	10,354	37.3	5,044	35.7	1,758	38.2	0.003	3,552	39.4	<0.001
West	4,791	17.3	2,363	16.7	850	18.5	0.007	1,578	17.5	0.141
Unknown	25	0.1	11	0.1	2	0.0	0.441	12	0.1	0.195
Race										
White	24,965	90.0	12,771	90.5	4,062	88.3	<0.001	8,132	90.1	0.363
Black	615	2.2	251	1.8	128	2.8	<0.001	236	2.6	<0.001
Hispanic	763	2.8	321	2.3	155	3.4	<0.001	287	3.2	<0.001
Other/missing	1,393	5.0	769	5.4	257	5.6	0.726	367	4.1	<0.001
Medicaid dual-eligible or Part D low-income subsidy	8,386	30.2	3,992	28.3	1,619	35.2	<0.001	2,775	30.8	<0.001
Baseline comorbid indices										
Charlson Comorbidity Index score (mean [SD])	2.5 (2.1)		2.3 (1.9)		2.6 (2.2)		<0.001	2.6 (2.2)		<0.001
Chronic Disease Score (mean [SD])	6.4 (3.6)		6.3 (3.6)		6.6 (3.6)		<0.001	6.5 (3.6)		<0.001
Baseline comorbid conditions										
Congestive heart failure	4,131	14.9	1,892	13.4	737	16.0	<0.001	1,502	16.6	<0.001
Chronic obstructive pulmonary disease	7,119	25.7	3,299	23.4	1,263	27.0	<0.001	2,557	28.3	<0.001
Cerebrovascular disease	1,042	3.8	491	3.5	213	4.6	<0.001	338	3.7	0.286
Depression/bipolar disorders	6,317	22.8	2,967	21.0	1,193	25.9	<0.001	2,157	23.9	<0.001
Diabetes mellitus	6,268	22.6	3,032	21.5	1,105	24.0	<0.001	2,131	23.6	0.001
Kidney diseases	2,990	10.8	1,333	9.4	557	12.1	<0.001	1,100	12.2	<0.001
Liver diseases	307	1.1	144	1.0	51	1.1	0.610	112	1.2	0.117
Peripheral vascular diseases	1,828	6.6	822	5.8	320	7.0	0.006	686	7.6	<0.001
Rheumatoid arthritis	1,783	6.4	965	6.8	248	5.4	0.001	570	6.3	0.121
Dementia	4,094	14.8	1,907	13.5	843	18.3	<0.001	1,344	14.9	0.003
Thyroid-related disease	1,412	5.1	675	4.8	227	4.9	0.681	510	5.7	0.003
Previous fracture	19,877	71.7	9,624	68.2	3,265	70.9	<0.001	6,298	69.8	0.009
Physician specialty										
Rheumatology	2,910	10.5	1,726	12.2	374	8.1	<0.001	810	9.0	<0.001
Endocrinology	1,573	5.7	837	5.9	255	5.5	0.327	481	5.3	0.055
Baseline medication and procedures										
Any osteoporosis medication	18,286	65.9	10,003	70.9	3,327	72.3	0.066	4,956	54.9	<0.001
Bisphosphonate	15,265	55.0	8,423	59.7	2,745	59.6	0.963	4,097	45.4	<0.001
Denosumab	87	0.3	42	0.3	9	0.2	0.249	36	0.4	0.194
Calcitonin	1,749	6.3	624	4.4	447	9.7	<0.001	678	7.5	<0.001
Teriparatide	311	1.1	151	1.1	68	1.5	0.026	92	1.0	0.714
Raloxifene	1,841	6.6	1,356	9.6	216	4.7	<0.001	269	3.0	<0.001
Tamoxifen	20	0.1	12	0.1	1	0.0	0.157	7	0.1	0.847
Glucocorticoids	13,339	48.1	6,764	47.9	2,147	46.7	0.132	4,428	49.1	0.088
Anticonvulsants	3,111	11.2	1,542	10.9	540	11.7	0.131	1,029	11.4	0.259
Antipsychotics	1,640	5.9	771	5.5	331	7.2	<0.001	538	6.0	0.109

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TABLE 1 Descriptive Baseline Characteristics of Treated Patients with a Fragility Fracture (continued)

Baseline Characteristics	All Patients		High Adherence (MPR ≥ 80%)		Moderate Adherence (50% ≤ MPR < 80%)			Low Adherence (MPR < 50%)		
Sample Size	27,736		14,112		4,602			9,022		
	n	%	n	%	n	%	P Value (vs. High) ^a	n	%	P Value (vs. High) ^a
Baseline medication and procedures										
Tricyclic antidepressants	1,600	5.8	785	5.6	270	5.9	0.437	545	6.0	0.128
SSRIs	8,138	29.3	3,915	27.7	1,514	32.9	<0.001	2,709	30.0	<0.001
Benzodiazepines	3,198	11.5	1,664	11.8	497	10.8	0.068	1,037	11.5	0.492
Nonbenzodiazepines hypnotics	2,937	10.6	1,426	10.1	513	11.2	0.044	998	11.1	0.020
BMD test	5,839	21.1	3,289	23.3	896	19.5	<0.001	1,654	18.3	<0.001
Baseline all-cause health care utilization										
Any inpatient stay	20,195	72.8	10,072	71.4	3,431	74.6	<0.001	6,692	74.2	<0.001
Any ER visit	12,074	43.5	5,886	41.7	2,031	44.1	0.004	4,157	46.1	<0.001
Any outpatient visit	24,191	87.2	12,302	87.2	4,079	88.6	0.009	7,810	86.6	0.181
Any Part D prescriptions pharmacy visit	27,541	99.3	14,011	99.3	4,578	99.5	0.160	8,952	99.2	0.602
Any DME visit	12,429	44.8	6,138	43.5	2,113	45.9	0.004	4,178	46.3	<0.001
Any SNF visit	3,673	13.2	1,683	11.9	739	16.1	<0.001	1,251	13.9	<0.001
Any HHA visit	6,667	24.0	3,106	22.0	1,203	26.1	<0.001	2,358	26.1	<0.001
Any hospice visit	125	0.5	44	0.3	25	0.5	0.024	56	0.6	<0.001

^aBold P values indicate significance at $P < 0.05$.

BMD = bone mineral density; DME = durable medical equipment; ER = emergency room; HHA = home health agency; SD = standard deviation; SNF = skilled nursing facility; SSRI = selective serotonin reuptake inhibitor.

Methods

Data Source

This study was a retrospective observational analysis of U.S. administrative claims data of female fee-for-service (FFS) Medicare beneficiaries from January 1, 2010, through December 31, 2012, with identification of patients with a fragility fracture between January 1, 2011, and December 31, 2011. The Medicare database captures comprehensive demographic and clinical information. Study variables were measured from the database using enrollment records, *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes, Healthcare Common Procedure Coding System codes, and National Drug Code numbers, as appropriate.

This observational study was conducted under the provisions of Privacy Rule 45 CFR 164.514(e) and was exempt from investigational review board review and approval, as there was no collection or use of personally identifiable information in the conduct of this study.¹⁵

Study Population

Patients were included in the study if they had (a) an inpatient hospital stay with a primary discharge diagnosis of fragility fracture (closed fracture without trauma codes), defined as a fragility fracture of the hip, pelvis, femur, clavicle, humerus, forearm and wrist, tibia/fibula, or spine, or (b) had at least 2 medical claims for clavicle, humerus, forearm and wrist, tibia/fibula,

or spine fractures in an outpatient setting ≥ 90 days apart for the same fracture site between January 1, 2011, and December 31, 2011 (cohort entry).^{16,17} Fractures with a trauma code identified within 7 days before or after the fracture claim date were excluded. Further, patients were included if they were women aged ≥ 65 years on the fragility fracture date and had continuous FFS Medicare enrollment in Part A (hospitalization), Part B (outpatient medical care), and Part D (prescription drugs) for 12 months before and after the fragility fracture date. Patients were excluded from the study if they had claim-based evidence of cancer, Paget's disease, or treatments for Paget's disease during the study period (Figure 1) or if they died during the 1-year follow-up period.

Patients were required to have an osteoporosis medication prescription, defined as a record of a claim for a bisphosphonate (alendronate, risedronate, pamidronate, etidronate, zoledronate, and tiludronate); calcitonin; denosumab; raloxifene; or teriparatide during the follow-up period. Patients were then evaluated for subsequent fractures after treatment initiation until either treatment discontinuation, first subsequent fracture during the treatment, or the end of the 12-month follow-up period (after the treatment initiation), whichever came first. Discontinuation of treatment was defined as no evidence of any osteoporosis-related prescription at any time after the last date of the previous fill during the study follow-up.

Study Variables

Baseline demographic and clinical characteristics during the 12 months before the initial fragility fracture were measured among all treated osteoporosis patients. Baseline characteristics included demographics (gender, age, race, U.S. geographic region, and Medicaid dual-eligible or low-income subsidy); comorbidities (congestive heart failure, chronic obstructive pulmonary disease [COPD], cerebrovascular disease, depression, diabetes, kidney disease, liver disease, peripheral vascular disease, rheumatoid arthritis, dementia, thyroid disease, and baseline fracture); Charlson Comorbidity Index (CCI) score¹⁸; Chronic Disease Score¹⁹; medication use (osteoporosis medications, glucocorticoids, tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], benzodiazepines, nonbenzodiazepine hypnotics, and anticonvulsant drugs)²⁰; previous fracture (previous fragility fracture in baseline); physician specialty (rheumatology and endocrinology visits); and health care utilization. Health care utilization included inpatient, office, and emergency room (ER) visits, pharmacy claims, use of durable medical equipment, and home health agency, hospice, and skilled nursing facility claims.

Adherence to osteoporosis treatments was measured by a medication possession ratio (MPR) using osteoporosis medication pharmacy claims. Overall MPR was calculated by dividing the cumulative days supply of the osteoporosis medications by the number of days of follow-up. The cumulative days supply was defined as the number of days during the follow-up period when the patient was in possession of the osteoporosis medication. Cumulative MPR was calculated from the treatment prescription date in 30-day increments and plotted against time (in months) for descriptive analysis. For each month, the numerator consisted of days supply of an osteoporosis prescription fill for the current month, plus the previous month(s), divided by the length of follow-up for that patient.^{13,21} Continuous MPR values were converted into categorical variables: high adherence $\text{MPR} \geq 80\%$,²² moderate adherence $50\% \leq \text{MPR} < 80\%$, and low adherence $\text{MPR} < 50\%$.²³ Time-dependent cumulative MPR was included as a primary predictor of subsequent fracture in the multivariate analysis.

Subsequent fracture events, which occurred after treatment initiation and before treatment discontinuation, were defined using the same criteria as initial fragility fractures. Fractures due to trauma were excluded, since those are not likely due to osteoporosis. Patient data were evaluated overall and stratified into 3 subgroups per subsequent fracture site: hip, pelvis, femur regions denoted as “hip/pelvis/femur fractures”; fractures in the vertebral regions denoted as “clinical vertebral fractures”; and fractures in the nonvertebral regions of clavicle, humerus, forearm and wrist, or tibia/fibula denoted as “other nonvertebral fractures.”

Statistical Analysis

Baseline and outcome variables were analyzed descriptively. Counts, percentages, means, and standard deviations were provided for appropriate variables. T-tests and chi-square tests were used for continuous and categorical variables, respectively.

The cumulative incidence of subsequent fractures was analyzed descriptively and stratified by MPR categories. In addition, cumulative MPR was analyzed each month after the osteoporosis medication prescription to evaluate adherence levels across the follow-up period.

Cox proportional hazards models were used to evaluate the causal relationship between time-dependent cumulative adherence and the first subsequent fracture after the osteoporosis medication prescription.^{21,24} The dependent variable was time to subsequent fracture, and the independent variables included demographics, comorbidities, baseline fracture, baseline medications, baseline BMD test (yes/no), health care utilization, and time-dependent cumulative adherence. For each patient, adherence levels were calculated in 30-day intervals, and appropriate cumulative adherence (up to the last 30-day increment before the first subsequent fracture) was applied to the first subsequent fracture in the multivariate analysis. Cox models were also used to evaluate subsequent fractures stratified by hip/pelvis/femur, clinical vertebral, and other nonvertebral fractures.

A sensitivity analysis was completed among patients with a baseline osteoporosis medication to examine the risk of fracture by controlling for pre-index osteoporosis medication MPR in the baseline period.

The healthy adherer effect is a commonly identified bias in observational studies, in which high adherence patients may differ in many ways compared with low adherence patients; therefore, there may be residual confounding due to unmeasured factors. While examining the effect of 1 preventive service (e.g., osteoporosis treatment) on fracture risk, the inability to adjust for all other related preventive behaviors could overestimate their effect.

Claims databases, such as Medicare, are unable to measure and control for all possible healthy-status and healthy-lifestyle behaviors. Therefore, we conducted diagnostic tests, in which several control outcomes (unrelated to osteoporosis) were tested for their association with time-dependent osteoporosis medication adherence.^{25,26} Differences across these unrelated “falsification” outcomes between adherence cohorts would reflect unmeasured differences in healthy behaviors in the sample. These falsification outcomes included inpatient admissions of pneumonia, organism unspecified (ICD-9-CM code 486), unspecified septicemia (ICD-9-CM code 038.9), chronic obstructive bronchitis with acute exacerbation (ICD-9-CM code 491.21), urinary tract infection site not specified (ICD-9-CM code 599.0), atrial fibrillation (ICD-9-CM code 427.31), and coronary atherosclerosis of native coronary artery (ICD-

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TABLE 2 Descriptive Outcomes Stratified by Medication Adherence

	All Patients (N = 27,736)		High Adherence (MPR ≥ 80%) (n = 14,112)		Moderate Adherence (50% ≤ MPR < 80%) (n = 4,602)			Low Adherence (MPR < 50%) (n = 9,022)		
	n	%	n	%	n	%	P Value ^a	n	%	P Value ^a
All fractures	1,765	6.4	677	4.8	402	8.7	<0.001	686	7.6	<0.001
Hip/pelvis/femur fractures	909	51.5	311	45.9	214	53.2	<0.001	384	56.0	<0.001
Clinical vertebral fractures	455	25.8	195	28.8	98	24.4	<0.001	162	23.6	<0.013
Other nonvertebral fractures	410	23.2	174	25.7	93	23.1	<0.001	143	20.9	0.025
Time from index fracture to osteoporosis medication prescription (mean [SD])	85.0	[84.6]	87.1	[86.1]	73.0	[72.8]	<0.001	87.9	[87.4]	0.493
Time from index fracture to osteoporosis medication prescription (median days)	57.0		59.0		51.0			58.0		

^aBold P values indicate significance at $P < 0.05$. P values were calculated using the high MPR cohort (MPR ≥ 80%) as the reference.

MPR = medication possession ratio; SD = standard deviation.

9-CM code 414.01).²⁴ For the falsification analysis, the same statistical methods as the primary analysis were used.

For each variable, the hazard ratio (HR), 95% confidence interval (CI), and P value were reported. All analyses were carried out using SAS software package 9.3 (SAS Institute, Cary, NC). P values < 0.050 were considered statistically significant.

Results

Of the 1,292,248 Medicare enrollees who had a fracture in 2011, a total of 103,852 (8.0%) women ≥ 65 years of age with a fragility fracture were identified. Overall, 27,736 (26.7%) patients were treated with osteoporosis medication within 12 months of the fragility fracture (Figure 1). During the baseline period, 66% of patients had an osteoporosis medication prescription.

The mean time to osteoporosis prescription from fragility fracture date was 85.0 ± 84.6 days. Over half of the patients were highly adherent (MPR ≥ 80%) to their osteoporosis medication (n = 14,112, 50.9%). Approximately one third of the patients had low adherence (MPR < 50%; n = 9,022, 32.5%), followed by patients with moderate adherence (50% ≤ MPR < 80%; n = 4,602, 16.6%). The median time to treatment initiation was 58, 51, and 59 days for the low, moderate, and high adherence patients, respectively.

Baseline characteristics for patients are shown in Table 1. Patients had an average age of 81.3 ± 7.6 years with a mean CCI score of 2.5 ± 2.1. The most common comorbid conditions included COPD (25.7%), diabetes mellitus (22.6%), depression/bipolar disorders (22.8%), and dementia (14.8%). Also, about half of the sample was prescribed glucocorticoids (48.1%) and bisphosphonates (55.0%) during the baseline period. Less than one quarter of patients had a BMD test during the baseline period (21.1%).

Patients with low and moderate adherence were older compared with patients with high adherence. In addition, during the baseline period, a greater proportion of moderate and low adherence patients were shown to have significantly greater clinical comorbidities, including congestive heart failure, COPD, depression/bipolar disorders, and dementia, compared with high adherence patients ($P < 0.001$). Moderate and low adherence patients had significantly lower rates of BMD tests compared with high adherence patients (19.5% and 18.3% vs. 23.3%, respectively, $P < 0.001$). A greater proportion of low adherence patients were prescribed glucocorticoids compared with high adherence patients (49.1% vs. 47.9%, $P = 0.088$), while fewer low adherence patients were prescribed bisphosphonates compared with high adherence patients (45.4% vs. 59.7%, $P < 0.001$). Low adherence patients were more likely to be prescribed SSRIs compared with high adherence patients (30.0% vs. 27.7%, $P < 0.001$).

The number of fractures by fracture type and stratified by MPR are shown in Table 2. Overall, 6.4% of treated patients had a subsequent fracture during the follow-up period while on therapy. Patients with high adherence had the lowest proportion of fractures (4.8%). Hip/pelvis/femur fractures were the most common type of fracture across all adherence levels, followed by clinical vertebral fractures and other nonvertebral fractures. Low (56.0%, $P < 0.001$) and moderate adherence (53.2%, $P < 0.001$) patients had a higher proportion of hip/pelvis/femur fractures compared with high adherence patients (45.9%).

Figure 2 shows the cumulative incidence of subsequent fracture by MPR. Overall, high adherence patients had a lower cumulative incidence of a subsequent fracture compared with moderate and low adherence patients.

The cumulative MPR after treatment initiation suggested that there was a gradual decline over the 12 months after treat-

FIGURE 2 Cumulative Incidence of Subsequent Fracture Stratified by Medication Possession Ratio

MPR = medication possession ratio.

ment initiation: the MPR at 3, 6, 9, and 12 months was 83%, 76%, 71%, and 68%, respectively.

Effect of Adherence on Risk of Subsequent Fracture

The multivariable Cox proportional hazards models for predictors of subsequent fracture are shown in Table 3.

Patients with low adherence were 33% more likely to have a subsequent fracture (HR=1.33; 95% CI=1.17-1.50, $P<0.001$) compared with patients with high adherence to osteoporosis medications. Moderate adherence patients had a 19% higher risk of a subsequent fracture (HR=1.19; 95% CI=1.02-1.38, $P=0.026$) compared with high adherence patients. When the subsequent fractures were stratified by fracture type, the results were generally consistent with overall findings on fractures. Low adherence patients had a 32% and 34% increased risk for a hip/pelvis/femur fracture (HR=1.32; 95% CI=1.09-1.59, $P=0.005$) and a clinical vertebral fracture (HR=1.34; 95% CI=1.09-1.63, $P=0.005$), respectively, compared with high adher-

ence patients. The effect of MPR level on other nonvertebral fractures was not statistically significant in our analysis.

Other baseline covariates that significantly increased the risk of a subsequent fracture included older age (≥ 85 years: HR=1.61; 95% CI=1.40-1.86, $P<0.001$; 75-84 years: HR=1.36; 95% CI=1.18-1.56, $P<0.001$); higher CCI score (HR=1.09; 95% CI=1.05-1.13, $P<0.001$); thyroid-related disease (HR=1.23; 95% CI=1.01-1.48, $P=0.039$); and baseline TCA use (HR=1.26; 95% CI=1.05-1.51, $P=0.013$). However, black race (HR=0.58; 95% CI=0.39-0.88, $P=0.009$); kidney diseases (HR=0.84; 95% CI=0.71-0.99, $P=0.037$); and BMD tests (HR=0.86; 95% CI=0.76-0.98, $P=0.019$) were associated with lower likelihood of a subsequent fracture.

Results of the sensitivity analysis were generally consistent with those for the main analysis. When baseline osteoporosis medication MPR was controlled, low adherence patients had a 27% increased risk of fracture (HR=1.27; 95% CI=1.08-1.49,

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TABLE 3 Cox Proportional Hazards Models for Subsequent Fractures with Time-Dependent Adherence

	Any Fracture			Hip/Pelvis/Femur Fracture		
Covariates	Hazard Ratio	95% CI	P Value ^a	Hazard Ratio	95% CI	P Value ^a
Adherence						
High (MPR > 80%) (reference)						
Moderate (50% ≤ MPR < 80%)	1.19	1.02-1.38	0.026	1.11	0.88-1.39	0.372
Low (MPR < 50%)	1.33	1.17-1.50	<0.001	1.32	1.09-1.59	0.005
Age group (years)						
65-74 (reference)						
75-84	1.36	1.18-1.56	<0.001	1.19	0.95-1.49	0.126
≥85	1.61	1.40-1.86	<0.001	1.46	1.17-1.82	0.001
U.S. geographic region						
Northeast (reference)						
North Central	1.07	0.93-1.23	0.341	1.03	0.83-1.29	0.771
South	0.96	0.84-1.11	0.607	1.08	0.87-1.33	0.485
West	0.90	0.76-1.06	0.197	0.93	0.72-1.19	0.542
Race						
White (reference)						
Black	0.58	0.39-0.88	0.009	0.56	0.32-1.00	0.051
Hispanic	0.91	0.67-1.23	0.540	0.88	0.56-1.38	0.575
Other/missing	0.96	0.76-1.22	0.745	1.09	0.78-1.53	0.601
Baseline comorbid conditions						
Charlson Comorbidity Index score	1.09	1.05-1.13	<0.001	1.08	1.02-1.14	0.010
Chronic Disease Score	1.00	0.98-1.01	0.746	1.00	0.97-1.02	0.863
Congestive heart failure	0.87	0.75-1.01	0.062	0.90	0.73-1.11	0.305
Cerebrovascular disease	0.80	0.63-1.03	0.078	0.79	0.55-1.11	0.175
Depression/bipolar disorders	1.01	0.89-1.15	0.877	0.95	0.79-1.15	0.620
Diabetes mellitus	0.91	0.80-1.04	0.165	0.95	0.78-1.15	0.584
Kidney diseases	0.84	0.71-0.99	0.037	0.74	0.58-0.95	0.018
Liver diseases	1.42	0.98-2.06	0.062	1.55	0.88-2.72	0.130
Dementia	1.13	0.99-1.28	0.065	1.15	0.96-1.37	0.123
Thyroid-related disease	1.23	1.01-1.48	0.039	1.26	0.95-1.67	0.112
Previous fracture	1.04	0.93-1.17	0.512	0.75	0.59-0.96	0.020
Baseline medication and procedures						
Baseline osteoporosis medication	1.10	0.99-1.23	0.066	1.18	1.01-1.39	0.040
BMD test	0.86	0.76-0.98	0.019	0.86	0.71-1.04	0.115
Anticonvulsant therapies	1.06	0.91-1.23	0.437	1.00	0.80-1.26	0.988
Antipsychotics	1.11	0.92-1.34	0.263	1.01	0.78-1.32	0.935
Tricyclic antidepressants	1.26	1.05-1.51	0.013	1.51	1.16-1.96	0.002
SSRIs	1.08	0.97-1.21	0.171	1.15	0.96-1.36	0.123
Benzodiazepines	1.06	0.91-1.22	0.469	0.94	0.74-1.20	0.627
Nonbenzodiazepines hypnotics	1.11	0.95-1.28	0.182	1.24	1.00-1.53	0.054
Medicaid dual-eligible/Part D low-income subsidy	1.01	0.90-1.12	0.916	1.04	0.88-1.22	0.664
Health care utilization						
ER visit	1.04	1.01-1.07	0.005	1.05	1.01-1.10	0.024
Inpatient visit	1.05	1.00-1.10	0.036	1.12	1.05-1.21	0.001
	Clinical Vertebral Fracture			Other Nonvertebral Fracture		
Covariates	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Adherence						
High (MPR ≥ 80%) (reference)						
Moderate (50% ≤ MPR < 80%)	1.26	0.98-1.61	0.070	1.34	0.97-1.84	0.076
Low (MPR < 50%)	1.34	1.09-1.63	0.005	1.31	0.97-1.75	0.075
Age group (years)						
65-74 (reference)						
75-84	1.28	1.01-1.63	0.043	1.61	1.22-2.11	<0.001
≥85	1.43	1.12-1.84	0.004	2.12	1.58-2.84	<0.001

continued on next page

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TABLE 3 Cox Proportional Hazards Models for Subsequent Fractures with Time-Dependent Adherence (continued)

Covariates	Clinical Vertebral Fracture			Other Nonvertebral Fracture		
	Hazard Ratio	95% CI	P Value ^a	Hazard Ratio	95% CI	P Value ^a
U.S. geographic region						
Northeast (reference)						
North Central	0.89	0.71-1.11	0.296	1.60	1.16-2.19	0.004
South	0.77	0.62-0.97	0.025	1.18	0.86-1.63	0.300
West	0.68	0.51-0.90	0.007	1.42	0.99-2.04	0.056
Race						
White (reference)						
Black	0.80	0.38-1.70	0.566	0.58	0.26-1.31	0.188
Hispanic	1.14	0.68-1.90	0.615	0.69	0.36-1.32	0.263
Other/missing	0.86	0.56-1.32	0.482	0.86	0.50-1.49	0.597
Baseline comorbid conditions						
Charlson Comorbidity Index score	1.10	1.03-1.17	0.005	1.08	1.00-1.18	0.051
Chronic Disease Score	0.98	0.96-1.01	0.173	1.02	0.99-1.06	0.235
Congestive heart failure	0.87	0.68-1.11	0.259	0.91	0.65-1.28	0.594
Cerebrovascular disease	0.77	0.50-1.19	0.237	0.84	0.47-1.49	0.545
Depression/bipolar disorders	0.93	0.74-1.17	0.534	1.35	1.02-1.79	0.038
Diabetes mellitus	0.91	0.72-1.15	0.418	0.90	0.68-1.20	0.479
Kidney diseases	1.04	0.78-1.39	0.778	0.84	0.56-1.25	0.391
Liver diseases	0.94	0.46-1.92	0.868	2.40	1.21-4.74	0.012
Dementia	1.26	1.00-1.59	0.048	0.93	0.68-1.27	0.627
Thyroid-related disease	1.21	0.88-1.67	0.245	1.14	0.74-1.76	0.565
Previous fracture	1.15	0.96-1.38	0.119	1.28	1.01-1.61	0.039
Baseline medication and procedures						
Baseline osteoporosis medication	1.05	0.89-1.24	0.593	1.13	0.87-1.45	0.363
BMD test	0.93	0.76-1.14	0.485	0.76	0.58-0.99	0.044
Anticonvulsant therapies	1.04	0.80-1.34	0.794	1.22	0.90-1.66	0.201
Antipsychotics	1.19	0.85-1.67	0.316	1.31	0.90-1.91	0.163
Tricyclic antidepressants	0.92	0.65-1.30	0.624	1.29	0.88-1.89	0.199
SSRIs	1.08	0.89-1.31	0.440	1.04	0.82-1.32	0.741
Benzodiazepines	1.14	0.90-1.44	0.272	1.09	0.80-1.48	0.600
Nonbenzodiazepine hypnotics	1.01	0.78-1.30	0.962	1.02	0.74-1.40	0.916
Medicaid dual-eligible/Part D low-income subsidy	0.94	0.77-1.14	0.525	1.01	0.80-1.28	0.927
Health care utilization						
ER visit	1.02	0.97-1.07	0.429	1.06	0.98-1.15	0.139
Inpatient visit	1.01	0.94-1.09	0.737	0.96	0.85-1.07	0.435

^aBold P values indicate significance at $P < 0.05$.

BMD = bone mineral density; CI = confidence interval; ER = emergency room; MPR = medication possession ratio; SSRI = selective serotonin reuptake inhibitor.

$P = 0.004$) compared with high adherence patients (Appendix A, available in online article).

The falsification outcomes analysis showed that none of the unrelated control outcomes were significantly associated with osteoporosis medication adherence. Therefore, this analysis suggests a lack of healthy adherer bias in our study population (Appendix B, available in online article).

Discussion

The current study was a real-world retrospective observational analysis to examine the correlates of subsequent fracture and the relative impact of medication adherence on risk of fracture in a large Medicare patient population. In this study, low

adherence was associated with a significantly higher fracture risk compared with high adherence.

This analysis was conducted in a large, comprehensive administrative Medicare claims database that offers a large sample of postmenopausal females for evaluating the association between osteoporosis medication adherence and subsequent fractures. We examined a comprehensive list of osteoporosis medications among Medicare enrollees. In addition, we adjusted for observable confounders that could potentially mediate and/or confound the relationship in our models. Additionally, we used time-dependent cumulative MPR that allowed us to evaluate how changing adherence affected the outcome.

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To date, few studies have explored and addressed the effect of adherence on subsequent fractures among Medicare enrollees. Research in the past has highlighted low persistence and adherence rates among osteoporotic women. A 2007 study (Adachi et al.) showed that only 43% of patients on bisphosphonates had MPR $\geq$ 80% over a 2-year period.²⁷ Another study (Downey et al., 2006) reported 12-month adherence at 60% among patients with alendronate and risedronate use.²⁸ These results are similar to the current study, in which 12-month adherence was 68%. The study found that half of the patients had high adherence, and the remaining patients had either low or moderate adherence to their osteoporosis therapy. Specifically, 32% of patients had low adherence, which is consistent with previous research that reported 28%-42% of patients with low adherence.^{13,29} Therefore, a significant proportion of the Medicare study sample had suboptimal adherence to their osteoporosis medications, leading to a reduction in treatment effectiveness and resulting in higher fracture risk.

In this study, low adherence among Medicare patients was associated with a 33% increased risk of fracture, whereas moderate adherence was associated with a 19% increased risk of fracture; therefore, as adherence increased, the risk of fracture decreased by as much as 14% within only 12 months. The study supports previous literature demonstrating that increased adherence has a protective effect on fracture risk. Additionally, the protective effect was observed across fracture types. Patients with low adherence had a 34% increased risk for clinical vertebral fractures and an approximately 32% increased risk for hip/pelvis/femur fractures, compared with high adherence. One study (Sampalis et al., 2012) showed that MPR $\geq$ 80% resulted in 9.1% significantly lower odds of fracture risk compared with MPR $<$ 80%.³⁰

Results from another study (Patrick et al., 2010) showed a similar effect, using cumulative proportion of days covered (PDC), a similar measure to MPR: PDC of $\geq$ 80% resulted in a 22% significantly lower risk of fracture, while a cumulative PDC of 20%-39% resulted in a 16% significantly lower risk of fracture compared with patients with an adherence of 0%-19%.³¹ Furthermore, other studies have also demonstrated that MPR has a significant effect on hip, radius, spine, and humerus fractures. Specifically, patients with MPR $<$ 50% had an 85% increased risk for a hip fracture and a 67% increased risk of any major osteoporotic fracture compared with the MPR $\geq$ 80%.²⁶

Similarly, another study (Burge et al., 2017) showed that a low MPR of teriparatide was associated with 64% higher likelihood of any fracture, 156% higher odds of clinical vertebral fracture, and 44% higher odds of another nonvertebral fracture, when compared with high MPR.²⁴ Therefore, our

results among Medicare patients are consistent with studies in other populations showing the effect of medication adherence is significant on any subsequent fracture as well as clinical vertebral and hip/pelvis/femur fracture types.

Limitations

There are several limitations to this study. First, the MPR informed via pharmacy claims assumes that a patient was in possession of the medication during the “days supply period”; however, there is no guaranteed compliance, that is, proof that the medication was actually consumed or taken as prescribed. Second, we did not require at least 2 medication prescription fills; therefore, our population may have included patients who discontinued their medication after the first fill. Third, medications provided as samples by the physician were not observed in the claims data. Also, medications prescribed during hospitalizations were not available in the data, which could have led to underestimating osteoporosis medication use during the study period.

Fourth, our analysis did not distinguish among osteoporosis medication types. The osteoporosis medications examined in this study represent drugs whose efficacy could have influenced the MPR. Fifth, the presence of a diagnosis code in a medical claim is not a confirmation of a disease, as the diagnosis code may be incorrectly coded or included as a rule-out diagnosis. Sixth, we excluded patients who died during the 1-year follow-up; therefore, we do not know if mortality had an effect on fracture risk. Finally, certain information was not readily available in claims data (or could have been randomly missing) that may have influenced study outcomes, such as BMD test results (T-score values), disease-specific parameters, and other laboratory results.

Conclusions

Medication adherence is a key factor in predicting a subsequent fracture in elderly women with a previous fragility fracture. After adjusting for several relevant covariates, our analyses of Medicare-enrolled women showed significantly higher risk for low and moderate adherent patients for any fracture, while those with low adherence had significantly higher risk of hip/pelvis/femur and clinical vertebral fractures within 12 months. An increasing trend toward subsequent fracture risk from suboptimal adherence for other nonvertebral fractures was also found. An integrated coordination of the care model system should incorporate medication adherence for osteoporosis patients so that orthopedists, pharmacists, and hospital administrators can collectively address near-term challenges and outcomes related to nonadherence and suggest tools to improve the adherence of osteoporosis patients.

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Study concept and design were contributed by Burge and Lombard, along with the other authors. Xie, Baser, and Keshishian took the lead in data collection, assisted by the other authors. Data interpretation was performed by Krohn and Zhang, with assistance from the other authors. The manuscript was written by Keshishian and Boytsov, along with the other authors, and revised by Boytsov, Keshishian, and Burge, along with the other authors.

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APPENDIX A Cox Proportional Hazards Model for Subsequent Fractures Among Those Who Had Previous Osteoporosis Treatment in Baseline

Covariates	Time from Osteoporosis Treatment Initiation to Any Fracture		
	Hazard Ratio	95% CI	P Value ^a
Adherence			
High (MPR ≥ 80%) (reference)			
Moderate (50% ≤ MPR < 80%)	1.09	0.91-1.30	0.355
Low (MPR < 50%)	1.27	1.08-1.49	0.004
Pre-index MPR	0.86	0.70-1.04	0.121
Age group (years)			
65-74 (reference)			
75-84	1.31	1.10-1.55	0.003
≥ 85	1.62	1.36-1.94	< 0.001
U.S. geographic region			
Northeast (reference)			
North Central	1.21	1.01-1.45	0.034
South	1.15	0.96-1.36	0.123
West	1.01	0.82-1.24	0.915
Race			
White (reference)			
Black	0.56	0.33-0.95	0.032
Hispanic	0.89	0.62-1.26	0.500
Other/missing	1.04	0.80-1.36	0.773
Baseline comorbid conditions			
Charlson Comorbidity Index score	1.09	1.04-1.14	< 0.001
Chronic Disease score	1.00	0.98-1.02	0.775
Congestive heart failure	0.96	0.81-1.14	0.636
Cerebrovascular disease	0.96	0.72-1.28	0.785
Depression/bipolar disorders	0.93	0.79-1.09	0.366
Diabetes mellitus	0.88	0.75-1.03	0.117
Kidney diseases	0.78	0.63-0.97	0.023
Liver diseases	1.70	1.08-2.66	0.021
Dementia	1.05	0.89-1.22	0.573
Thyroid-related disease	1.15	0.90-1.47	0.253
Any fracture	1.05	0.91-1.21	0.503
Baseline medication and procedures			
BMD test	0.85	0.74-0.98	0.027
Anticonvulsant therapies	1.07	0.89-1.29	0.452
Antipsychotics	1.19	0.95-1.48	0.126
Tricyclic antidepressants	1.25	1.00-1.57	0.051
SSRIs	1.15	1.00-1.32	0.048
Benzodiazepines	1.11	0.92-1.32	0.273
Nonbenzodiazepines hypnotics	1.09	0.91-1.30	0.364
Medicaid dual-eligible/ Part D low-income subsidy	1.00	0.88-1.15	0.960
Health care utilization			
ER visit	1.02	0.98-1.06	0.355
Inpatient visit	1.06	0.99-1.12	0.078

^aBold P values indicate significance at P < 0.05.

BMD = bone mineral density; CI = confidence interval; ER = emergency room;
MPR = medication possession ratio; SSRI = selective serotonin reuptake inhibitor.

APPENDIX B Cox Proportional Hazards Model for Risk of Falsification Outcomes and Medication Adherence of Osteoporosis Medications

Falsification Outcomes	Low vs. High Adherence		Moderate vs. High Adherence		P Value ^a
	HR	95% CI	HR	95% CI	
Pneumonia	1.25	0.97-1.60	1.23	0.92-1.64	0.062
Septicemia	1.29	0.95-1.75	1.38	0.98-1.95	0.064
Chronic obstructive bronchitis	1.42	1.05-1.92	1.42	0.99-2.02	0.017
Urinary tract infection	1.24	0.98-1.56	1.03	0.78-1.37	0.083
Atrial fibrillation	1.46	1.02-2.08	1.42	0.94-2.16	0.027
Coronary atherosclerosis	2.01	1.15-3.51	0.82	0.34-2.01	0.019

^aBonferroni adjustments were made for multiplicity control on the comparisons. The Bonferroni significance levels of 0.0084 (0.05/6) were used. Hypothesis test: whether at least 1 MPR group is significantly different in risk of falsification outcome.

CI = confidence interval; HR = hazard ratio.