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ORIGINAL ARTICLE

Examining the treatment gap and risk of subsequent fractures among females with a fragility fracture in the US Medicare population

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Abstract
Summary Our aim was to evaluate the gap in osteoporosis treatment and the impact of osteoporosis treatment on subsequent fragility fractures. We found osteoporosis medication use lowered risk of subsequent fractures by 21% and that black race, higher CCI scores, dementia, and kidney diseases reduced the likelihood of osteoporosis medication use.
Introduction The goal of this study was to evaluate the predictors of osteoporosis medication use and compare the risk of fragility fractures within 1 year of a fragility fracture between osteoporosis treated and untreated women.
Methods We conducted a retrospective, observational cohort study using the national Medicare database. Elderly women (≥65 years) who were hospitalized or had an outpatient/ER service for fragility fracture between January 1, 2011 and December 31, 2011 were included. The outcomes of interest were the correlates of and time-to-osteoporosis medication use and risk of a subsequent fracture within 12 months for treated and untreated women. Cox regression was used to evaluate the predictors of treatment use and the risk of fracture based on treatment status.
Results Women (28,722) (27.7%) were treated with osteoporosis medication within 12 months of index fracture, and 74,979 (72.2%) were untreated. A number of patient characteristics were associated with a reduced likelihood of osteoporosis medication use, including black race, higher Charlson comorbidity index scores, presence of dementia, and kidney diseases in the baseline. The predictor most strongly and positively associated with osteoporosis medication use after fracture was osteoporosis medication use before fragility fracture (HR = 7.87; 95% CI 7.67–8.07). After adjusting for baseline characteristics, osteoporosis medication use lowered the risk of subsequent fractures by 21% (HR = 0.79, 95% CI 0.75–0.83) over 12 months compared to women without treatment.
Conclusions Demographics and clinical characteristics were strong predictors of osteoporosis medication use. In the US Medicare population, osteoporosis treatment significantly reduced the risk of fragility fractures.

Keywords Fracture risk assessment · Osteoporosis · Therapeutics

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Introduction

Osteoporosis affects an estimated 200 million women worldwide and leads to almost 9 million fractures per year, of which 16.9% occur among persons aged 80–89 years while 4.3% occur among women aged 90+ years [1, 2]. In addition, it has been reported that hip fractures constituted a major proportion (23%) of the 1.7 million hospitalizations for fragility fractures [3].

Over the years, antiresorptive and anabolic medication treatments have improved the physical health of patients by reducing

the risk of fracture [4]. Overall, randomized control trial (RCT) data have demonstrated that osteoporosis medications have reduced vertebral fractures by 40–70%, non-vertebral fractures by 20–36%, and hip fractures by up to 40% [5–8]. Recent real world evidence (RWE) studies have confirmed treatment efficacy reported from RCTs and prior head-to-head trials and have shown that osteoporosis treatments reduced the risk of fractures by 20–60% [9, 10]. Despite the availability of these efficacious treatments, a gap in osteoporosis treatment still exists due to several factors, including the underdiagnosis of osteoporosis in women, differences in the interpretation of bone mineral density (BMD) testing measurements (using dual-energy x-ray absorptiometry [DEXA]) across physicians [11], lower Medicare DEXA reimbursement, apparent concerns of adverse events, and lack of fracture liaison services in the US [12]. Therefore, a large proportion of women at risk for fractures remain undertreated [13–15].

To better understand this treatment gap, and the characteristics of women affected by this gap, several studies have examined predictors of osteoporosis medication use. Key patient characteristics associated with low rates of osteoporosis medication use include younger age, lower education level, high BMD T-score, high BMI, lack of glucocorticoid use, and absence of osteoporosis treatment prior to fragility fracture [11, 16, 17].

Due to the increased risk of osteoporosis diagnoses among women compared to men, post-menopausal women were the population of interest in our study [18, 19]. In light of these previous studies and the growing aging population in the US, there remains a dearth of RWE among osteoporotic women in the Medicare system. To better understand the wide extent of these treatment gaps among women, we used the 100% Medicare database, which is a primary strength in this analysis. To garner additional real-world evidence among Medicare enrolled osteoporotic women with a fragility fracture, this study aims to examine correlates of time to osteoporosis medication prescription within 12 months of index fragility fracture and the relative impact of treatment on risk for subsequent fractures over 12 months of follow-up.

Material and methods

Data source and study population

This was a retrospective observational cohort study based on US administrative claims data from fee-for-service Medicare beneficiaries (Study period: January 1, 2010 - December 31, 2012). 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 since there was no collection or use of personally-identifiable information in the conduct of this study [20]. Women who had an index fragility fracture between January 1, 2011 and December 31, 2011 were followed for 12 months to identify whether they had been prescribed osteoporosis medication and examined for their risk of subsequent fractures within 12 months from index date.

Data of patients were obtained from the 100% fee-for-service Centers for Medicare & Medicaid Services (CMS) database. The Medicare database captured a comprehensive collection of 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 Codes, as appropriate.

Patient selection criteria

Women were included in the study if they had (1) an inpatient hospital stay with a primary discharge diagnosis of fragility fracture, defined as a fragility fracture (closed fractures without trauma codes) of the hip, pelvis, femur, clavicle, humerus, forearm and wrist, tibia/fibula, or spine (Supplemental Table 1) or (2) at least 2 medical claims for clavicle, humerus, forearm, wrist, tibia/fibula, or spine fractures in an outpatient setting not more than 90 days from the same fracture site between January 1, 2011 and December 31, 2011. Fractures with a trauma code identified within 7 days before or after any fracture claim date were excluded. The index date was defined as the date of the first observed fragility fracture claim in an outpatient setting or the date of discharge in an inpatient setting. Further, women were included if they were aged at least 65 years as of the index date and had continuous Medicare enrollment in Parts A, B, and D for at least 12 months before and after the index date. Women were excluded from the study if they had claim-based evidence of cancer, Paget's disease, or treatments for Paget's disease (Supplemental Table 1) during the study period.

Baseline patient characteristics

Demographics and clinical characteristics were measured for the 12 months prior to the index fragility fracture to determine potential predictors of treatment. Baseline characteristics included demographics, comorbidities (identified via ICD-9-CM diagnosis codes), Charlson Comorbidity Index (CCI) score [21], medication use (osteoporosis medications, glucocorticoids, and anticonvulsant drugs), and healthcare utilization.

Outcome variables

The primary outcome was time to osteoporosis medication within 12 months after the index fragility fracture. Osteoporosis medication use was defined as the occurrence of a claim for a

bisphosphonate (alendronate, risedronate, pamidronate, etidronate, zoledronate, or tiludronate), calcitonin, denosumab, raloxifene, or teriparatide, as evidenced from Part B and/or Part D Medicare files. Time to osteoporosis medication, defined as the period from the index fragility fracture to the first osteoporosis medication claim date, was calculated in days. Women were evaluated overall and stratified into three subgroups by their index fragility fracture site: fractures in the hip or pelvis or femur regions denoted as "hip/pelvis/femur fractures," fractures in the vertebral regions denoted as "clinical vertebral fractures," fractures in the non-vertebral regions of clavicle, humerus, forearm, wrist, or tibia/fibula denoted as "other non-vertebral fractures."

Subsequent fracture events were captured during the 12-month follow-up period, identified using the same criteria as the index fragility fracture, and reported by overall as well as clinical vertebral, hip/pelvis/femur, and other non-vertebral fractures for treated and untreated women. If the subsequent fracture during the follow-up period was the same fracture site as the index fragility fracture, a gap of ≥180 days was required for it to be considered a subsequent fracture. However, if the subsequent fracture was at a different site than the index fracture, it was considered an incident fracture and no gap was required. Women treated for osteoporosis were defined as those prescribed an osteoporosis treatment during the 12-month follow-up period after index fragility fracture. Untreated women diagnosed with osteoporosis were defined as those who had no treatment within 12 months after the initial fragility fracture. For treated women, subsequent fractures were identified after treatment initiation during the follow-up period and censored at treatment discontinuation or 12 months after the index fragility fracture. Treatment discontinuation was defined as no evidence of an osteoporosis prescription at any time after the run-out date of the previous prescription fill.

Statistical analysis

Counts, percentages, means, and standard deviations were provided for appropriate variables. T-tests and chi-square tests were used to detect statistical differences among continuous and categorical variables, respectively. Baseline variables including age, US geographical region, race, clinical risk scores, comorbidities, osteoporosis-related medications and procedures, physician specialty, and healthcare resource utilization were measured during the 12-month baseline period. Cumulative incidence of treatment use and subsequent fractures were evaluated descriptively using a cumulative density plot. In order to evaluate predictors of treatments, certain variables were also measured post-index as time-dependent variables. Time-dependent variables included subsequent fracture, BMD test (yes/no), and rheumatology and endocrinology visits. First, a Cox proportional hazards model was used to evaluate the association between time to osteoporosis medication prescription and predictors of prescription use. The dependent variable was time to treatment and the independent variables (i.e., predictors) were baseline characteristics and time-dependent variables, including subsequent fractures, BMD tests, and rheumatology and endocrinology visits. A variance inflation factor of ≥ 10 was used to assess multicollinearity of the dependent variables.

To evaluate the risk of fracture between treated and untreated women, a Cox proportional hazards model was used to evaluate time to subsequent fracture within 12 months of the index fragility fracture. Women in the untreated cohort were followed until the subsequent fracture or 12 months after the index date. Women in the treated cohort were followed until the discontinuation of osteoporosis treatment, subsequent fracture, or 12 months after index date.

Sensitivity analysis

Two sensitivity analyses were conducted. First, baseline osteoporosis medication use was examined. Patients prescribed baseline osteoporosis medication were considered prevalent users, and patients without baseline osteoporosis medication use were considered new users. The results were stratified (predictors of treatment and fracture risk) to determine if there was a difference between prevalent and new osteoporosis medication users. Second, index fragility was stratified by fracture place of service (inpatient or outpatient) to determine if there was a difference in treatment utilization or subsequent fracture risk.

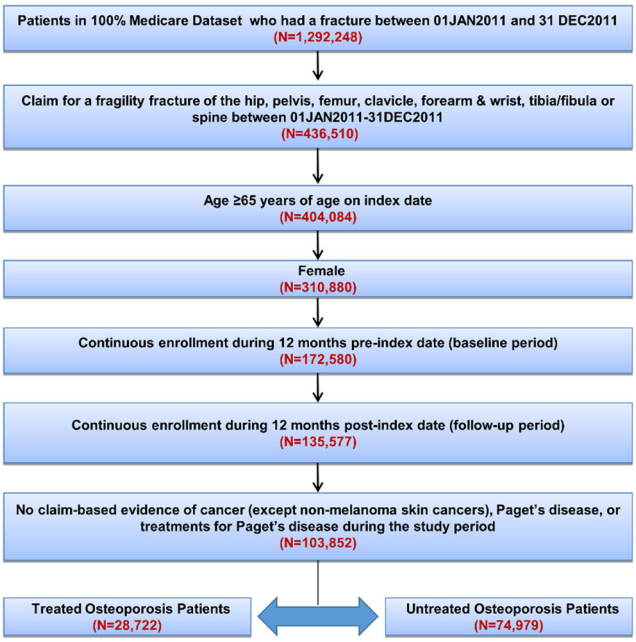
All analyses were carried out using SAS version 9.3 (SAS Institute, Inc., Cary, NC, US). Values of $p < 0.05$ were considered, a priori, to be statistically significant.

Results

Of the 1,292,248 total Medicare enrollees who had a fracture in 2011, a total of 103,852 (8%) women ≥65 years of age with a fragility fracture were identified based on the selection criteria, of which a majority had hip/pelvis/femur fractures (n = 55,158; 53%), followed by other non-vertebral fractures (n = 29,509; 28%) and clinical vertebral fractures (n = 19,252; 19%). Overall, 28,722 (27.7%) of women were treated with osteoporosis medication within 12 months of index fracture and 74,979 (72.2%) were untreated (Fig. 1).

Study Sample Characteristics and Unadjusted Outcome Patterns

Women had an average age of 82.0 ± 8.1 years. Women with a hip/pelvis/femur fracture were older and had higher mean CCI scores compared to those with clinical vertebral or other non-vertebral fractures. Overall, 12.3% of women had a BMD test



Note: 151 patients were not included in the treated versus untreated analysis because they had multiple osteoporosis medication claims on the treatment initiation date.

Fig. 1 Patient selection flow diagram

prior to the index fragility fracture, and those with clinical vertebral fracture had the highest proportion of glucocorticoid use (54.4%) and anticonvulsant therapy use (11.4%) during the baseline (Table 1). Additionally, 26% of women were prescribed osteoporosis medication in the baseline period.

Figure 2a shows the cumulative incidence of osteoporosis treatment during the 12-month follow-up period by index fragility fracture site. The highest proportion of female patients who were prescribed osteoporosis medication within 12 months of index fracture was found to be in clinical vertebral fracture patients (46.0%) followed by hip/pelvis/femur (23.9%) and other non-vertebral fracture patients (23.3%). The mean time to treatment use was 72.7 ± 82.5, 88.7 ± 90.7, and 98.4 ± 86.6 days for clinical vertebral, hip/pelvis/femur, and other non-vertebral fractures, respectively (Supplemental Table 2). Among female patients, 24.0% discontinued treatment, and the mean time to discontinuation was 118.9 days.

Cumulative incidence of subsequent fractures was measured over 12 months post-index date. Overall, 8.3% of women had a subsequent fracture, and the mean time-to-fracture was 175.8 ± 108.6 days (Supplemental Table 3). Hip/pelvis/femur fractures were the most common (57.5%) followed by other non-vertebral fractures (25.0%) and clinical vertebral fractures (18.1%). Women exposed to an osteoporosis treatment during the follow-up period had a significantly lower risk of fractures compared to those without treatment exposure (6.4 vs 9.0%, $p < 0.001$; Fig. 2b, Supplemental Table 3). There was a small proportion of women (3.3%) with a subsequent fracture prior to osteoporosis medication use during the follow-up period, and the mean time from subsequent fracture-to-medication prescription use was 54.4 ± 57.9 days (Supplemental Table 2).

Untreated women had a subsequent fracture much sooner compared to treated women (165.2 ± 109.4 vs 216.2 ± 95.3 days, $p < 0.001$). Importantly, the difference in cumulative incidence of fractures among treated and untreated women was evident from the beginning of the follow-up period (Fig. 2b). Among women with a fracture, there was a higher proportion of women with hip/pelvis/femur fractures (59.1 vs 51.5%, $p < 0.001$) and other non-vertebral fractures (25.4 vs 23.2%, $p < 0.001$) among untreated compared to treated women. However, there was a lower proportion of women with clinical vertebral fractures among untreated compared to those who were treated (16.0 vs 25.8%).

Multivariable analysis

The multivariable Cox proportional hazards model for predictors of osteoporosis treatment are shown in Table 2. Women diagnosed with dementia (HR 0.92, 95% CI: 0.89-0.96), and those who were black (HR 0.92, 95% CI 0.85-1.00), were significantly less likely to be prescribed osteoporosis treatment. For all fractures, women who had a BMD test after their first fragility fracture were significantly more likely to be prescribed an osteoporosis medication (HR 4.66, 95% CI 4.49–4.84). In addition, having a subsequent fracture during the follow-up increased the likelihood of being prescribed osteoporosis treatment by 48.7%, compared to no subsequent fracture (HR 1.49, 95% CI 1.39–1.59). The strongest predictor of treatment after a fragility fracture was use of osteoporosis treatment in the baseline period (HR 7.87, 95% CI 7.67–8.07). For specific factors of treatment initiation for each facture site, refer to Supplemental Table 4. There was no evidence of multicollinearity among the covariates in the Cox proportional hazards model.

When predictors of treatment were stratified by prior medication use, the results were generally consistent (Supplemental Table 5). Older age, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, glucocorticoid use, and time-varying subsequent fractures, BMD test, rheumatology visits, and endocrinology visits were significant predictors of treatment initiation. When predictors of treatment were stratified by place of service, the results were consistent, except that dementia was only a significant predictor among patients who had their fragility fracture in the inpatient setting (Supplemental Table 6).

After adjusting for covariates, including age, geographic region, comorbidities, and medication, the treated group was associated with a 20.9% lower risk of a subsequent fracture while on osteoporosis therapy, compared to the untreated group during 12 months after the

Table 1 Descriptive baseline characteristics for fragility fracture patients among Medicare population in the US

Baseline characteristics	All fractures		Hip/pelvis/femur		Clinical vertebral		Other non-vertebral	
Sample size (*N*)	103,852		55,158		19,252		29,509	
	N/Mean	%/SD	*N*/Mean	%/SD	*N*/Mean	%/SD	*N*/Mean	%/SD
Age (mean)	82.0	8.1	83.6	7.7	81.7	7.7	79.1	8.1
Age group								
65–74	21,968	21.2%	8117	14.7%	3870	20.1%	9992	33.9%
75–84	38,857	37.4%	19,797	35.9%	7827	40.7%	11,261	38.2%
≥85	43,027	41.4%	27,244	49.4%	7555	39.2%	8256	28.0%
Geographic location								
Northeast	18,827	18.1%	10,142	18.4%	3164	16.4%	5527	18.7%
North Central	28,196	27.2%	14,128	25.6%	5684	29.5%	8414	28.5%
South	41,049	39.5%	22,498	40.8%	7475	38.8%	11,098	37.6%
West	15,637	15.1%	8296	15.0%	2921	15.2%	4429	15.0%
Unknown	143	0.1%	94	0.2%	8	0.0%	41	0.1%
Race								
White	94,363	90.9%	49,972	90.6%	17,667	91.8%	26,785	90.8%
Black	3549	3.4%	2155	3.9%	358	1.9%	1036	3.5%
Hispanic	2440	2.3%	1263	2.3%	422	2.2%	757	2.6%
Other/missing	3500	3.4%	1768	3.2%	805	4.2%	931	3.2%
Baseline comorbid indices								
Charlson Comorbidity Index	2.7	2.2	2.9	2.2	2.6	2.2	2.3	2.2
Baseline comorbid conditions								
Congestive heart failure	18,679	18.0%	11,255	20.4%	3490	18.1%	3948	13.4%
COPD	25,975	25.0%	14,227	25.8%	5402	28.1%	6359	21.5%
Cerebrovascular disease	4801	4.6%	2907	5.3%	829	4.3%	1071	3.6%
Depression/bipolar disorders	24,939	24.0%	14,673	26.6%	4500	23.4%	5779	19.6%
Diabetes mellitus	27,479	26.5%	14,609	26.5%	4654	24.2%	8230	27.9%
Kidney diseases	13,892	13.4%	8727	15.8%	2178	11.3%	2991	10.1%
Liver diseases	1082	1.0%	486	0.9%	273	1.4%	324	1.1%
Peripheral vascular diseases	7494	7.2%	4461	8.1%	1399	7.3%	1640	5.6%
Rheumatoid arthritis	4868	4.7%	2653	4.8%	1087	5.6%	1130	3.8%
Dementia	19,375	18.7%	13,397	24.3%	2582	13.4%	3412	11.6%
Parkinson's	3296	3.2%	1957	3.6%	627	3.3%	715	2.4%
Thyroid-related disease	5092	4.9%	2645	4.8%	1032	5.4%	1418	4.8%
Physician specialty								
Rheumatology	6799	6.5%	3225	5.8%	1739	9.0%	1841	6.2%
Endocrinology	4840	4.7%	2342	4.2%	975	5.1%	1526	5.2%
Baseline medication and procedures								
Bisphosphonate	23,091	22.2%	11,422	20.7%	5738	29.8%	5948	20.2%
Denosumab	114	0.1%	47	0.1%	41	0.2%	26	0.1%
Calcitonin	2559	2.5%	1182	2.1%	947	4.9%	433	1.5%
Teriparatide	470	0.5%	222	0.4%	139	0.7%	110	0.4%
Raloxifene	2337	2.3%	1153	2.1%	519	2.7%	669	2.3%
Tamoxifen	29	0.0%	18	0.0%	4	0.0%	7	0.0%
Glucocorticoids	45,252	43.6%	22,290	40.4%	10,479	54.4%	12,517	42.4%
Bone mineral density (BMD) test	12,787	12.3%	5609	10.2%	3111	16.2%	4073	13.8%
Anticonvulsants	11,441	11.0%	6148	11.1%	2200	11.4%	3099	10.5%
Baseline all-cause healthcare utilization								
Inpatient stay	79,296	76.4%	51,922	94.1%	12,563	65.3%	14,835	50.3%
ER visit	45,297	43.6%	23,460	42.5%	9917	51.5%	11,954	40.5%
Outpatient visit	88,701	85.4%	45,964	83.3%	17,468	90.7%	25,335	85.9%
Pharmacy claim	101,781	98.0%	53,997	97.9%	19,059	99.0%	28,791	97.6%
DME claim	45,733	44.0%	23,233	42.1%	9368	48.7%	13,154	44.6%
SNF visit	15,522	14.9%	9311	16.9%	2945	15.3%	3281	11.1%
HHA visit	25,794	24.8%	14,398	26.1%	5692	29.6%	5722	19.4%
Hospice visit	1133	1.1%	883	1.6%	90	0.5%	160	0.5%

DME durable medical equipment, *ER* emergency room, *HHA* home health aide, *SNF* skilled nursing facility

index fragility fracture (HR 0.79, 95% CI 0.75–0.83; Table 3). Older age (≥85 years: HR 1.50, 95% CI 1.40–1.59; 75–84 years: HR 1.29, 95% CI 1.21–1.38), diagnosis for rheumatoid arthritis (HR 1.15, 95% CI 1.05–1.27) or depression (HR 1.20, 95% CI 1.14–1.26), and baseline glucocorticoid (HR 1.08, 95% CI

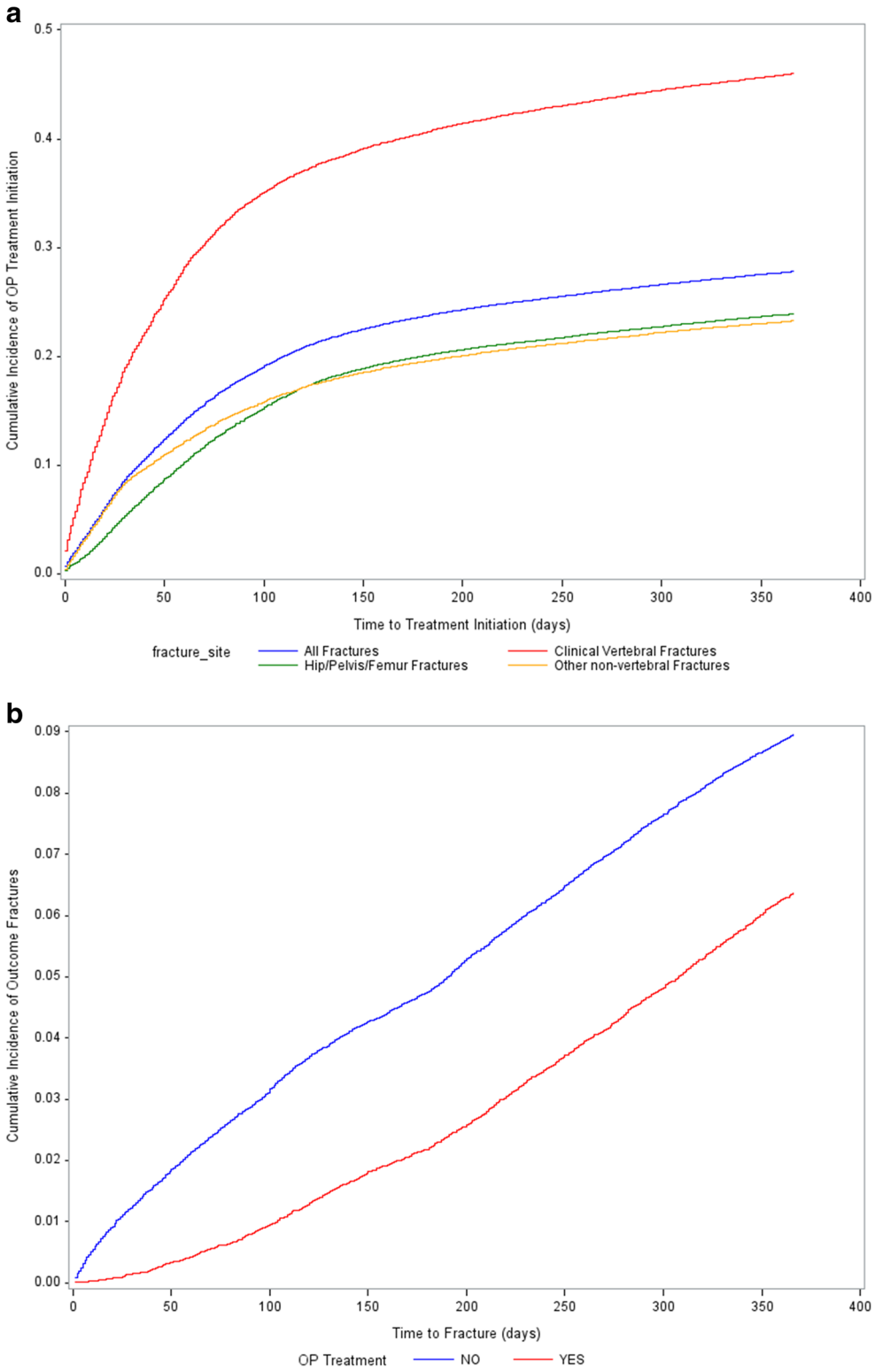


Fig. 2 **a** Unadjusted time-to-osteoporosis treatment initiation comparing different fracture sites. **b** Unadjusted time-to-fracture comparing treated and untreated osteoporosis patients

1.03–1.13) and anticonvulsant use (HR 1.19, 95% CI 1.11–1.26) were other factors associated with increased risk of subsequent fracture.

The results were consistent when stratified by prior medication prescription use and place of service (Supplemental Tables 7, 8). Prevalent osteoporosis medication users had a

Table 2 Cox proportional hazards model for time-to-initiation of osteoporosis medication within 12 months of the index fracture date

	Time-to-initiation		
	All fractures		
Covariates	Hazard Ratio	95% CI	*P* value
Age group			
65–74 (reference)			
75–84	1.05	1.02–1.09	0.001
≥85	0.99	0.96–1.02	0.484
Geographic location			
Northeast (reference)			
North Central	1.16	1.12–1.20	<0.001
South	1.02	0.99–1.06	0.210
West	1.14	1.10–1.19	<0.001
Unknown	0.78	0.53–1.16	0.216
Race			
White (reference)			
Black	0.92	0.85–1.00	0.046
Hispanic	1.19	1.10–1.27	<0.001
Other/missing	1.32	1.25–1.39	<0.001
Baseline comorbid conditions			
Charlson Comorbidity Index	0.98	0.97–0.98	<0.001
Congestive heart failure	0.97	0.94–1.01	0.150
Congestive obstructive pulmonary disease	1.09	1.06–1.13	<0.001
Kidney diseases	0.94	0.90–0.98	0.003
Liver diseases	1.08	0.97–1.21	0.160
Rheumatoid arthritis	1.03	0.97–1.08	0.340
Dementia	0.92	0.89–0.96	<0.001
Baseline medication and procedures			
Any osteoporosis medication	7.87	7.7–8.07	<0.001
BMD test	1.13	1.1–1.17	<0.001
Glucocorticoids	1.02	1.0–1.05	0.059
Time-varying covariates during follow-up			
Subsequent fracture	1.49	1.39–1.59	<0.001
BMD Test	4.66	4.49–4.84	<0.001
Rheumatology visit	1.43	1.36–1.51	<0.001
Endocrinology visit	1.28	1.20–1.37	<0.001

greater reduction in fracture risk (HR 0.51; 95% CI 0.47–0.55) compared to new osteoporosis medication users (HR 0.80; 95% CI 0.73–0.87).

Discussion

The current study was the first real-world retrospective observational analysis to examine the correlates of osteoporosis treatment and the relative impact of treatment on fracture risk in a large Medicare patient population. In the past, many studies have suggested the significant clinical and economic burden this disease has on the patient as well as society [22–24]. To date, few studies have explored and addressed the real-world factors that impact the treatment gap between index fragility fracture and risk of subsequent fractures post-treatment among female Medicare enrollees [25, 26].

Our analysis showed that only 28% of patients initiated treatment after the index fracture and that the treatment gap was almost 3 months. Almost half of all clinical vertebral fracture patients were prescribed an osteoporosis medication within 12 months of the index fracture and initiated treatment earlier than hip/pelvis/femur and other non-vertebral fracture patients. Clinical vertebral fractures are often associated with chronic pain and subsequent fractures; therefore, this may explain the greater likelihood of osteoporosis treatment use among clinical vertebral fracture patients [27, 28]. Also, among treated patients, the time from treatment to subsequent fracture was much longer for clinical vertebral fractures. This may be attributed to the fact that clinical vertebral fracture patients were more likely to be on treatment and the positive impact of the treatment reflected on the longer time-to-subsequent fracture for clinical vertebral fracture patients.

We conducted multivariate analysis for time to treatment use to identify potential determinants for the treatment gap among osteoporotic women. Numerous other studies have also shown that black patients are less likely to be on osteoporosis medication, which is consistent with our study, where black patients were 8% less likely to use osteoporosis medication [29–31]. The presence of kidney diseases and dementia at baseline were found to be predictors of a lower likelihood of treatment. Moreover, several osteoporosis medications are not

Table 3 Cox proportional hazards model for time-to-fracture within 12 months following the initial fracture claim

Covariates	Hazard ratio	95% CI	*P* value
Cohort			
Untreated			
Treated	0.79	0.75–0.83	<0.001
Age group			
65–74 (reference)			
75–84	1.29	1.21–1.38	<0.001
≥85	1.50	1.40–1.59	<0.001
Geographic location			
Northeast (reference)			
North Central	1.08	1.01–1.15	0.018
South	0.96	0.90–1.02	0.161
West	0.94	0.87–1.01	0.086
Unknown	0.09	0.01–0.63	0.015
Race			
White (reference)			
Black	0.59	0.51–0.68	<0.001
Hispanic	0.81	0.69–0.95	0.009
Other/missing	1.02	0.90–1.15	0.778
Baseline comorbid conditions			
Charlson Comorbidity Index	1.06	1.04–1.07	<0.001
Chronic obstructive pulmonary disease	1.04	0.99–1.10	0.122
Depression/bipolar disorders	1.20	1.14–1.26	<0.001
Diabetes mellitus	0.91	0.86–0.96	0.001
Kidney diseases	0.90	0.83–0.96	0.003
Liver diseases	1.25	1.04–1.51	0.019
Rheumatoid arthritis	1.15	1.05–1.27	0.003
Dementia	1.09	1.03–1.15	0.002
Baseline medication and procedures			
Glucocorticoids	1.08	1.03–1.13	0.001
Anticonvulsants	1.19	1.11–1.26	<0.001

approved to be used in patients with severe renal disease. At age 80 and above, the presence of renal and mental health complications raises the challenges to improve physical health by any margin.

In an elderly population, dementia may have a differential effect on osteoporosis treatment use and fracture risk. Patients with osteoporosis have been shown to have a 46% greater risk for dementia compared to non-osteoporosis control patients (HR 1.46, 95% CI 1.37-1.56) [32], while another study showed that dementia was an independent risk factor for developing hip fractures compared to non-dementia patients (HR 1.92, 95% CI 1.48–2.49) [33]. In addition, another article suggested that dementia patients are found to be 66% less likely to use osteoporosis medications (OR 0.34, 95% CI 0.19–0.59) compared to those without dementia [34]. Similarly, our results showed a dementia diagnosis was associated with a 7.6% lower likelihood of initiating osteoporosis treatment ($p < 0.001$) and 8.8% increased risk of fracture ($p = 0.002$).

Conversely, baseline osteoporosis medication and BMD testing showed an increased likelihood for further osteoporosis treatments being prescribed. A prior study suggested that more than half of patients (58%) resumed osteoporosis treatment during the 1 year after a BMD test [35]. Therefore, BMD testing has a temporal relationship with increased osteoporosis medication use over follow-up. In our current study, BMD test as a time-varying covariate was significantly associated with higher likelihood of osteoporosis medication use over time (HR 4.66, 95% CI 4.49–4.84). Furthermore, a recent research study suggested that among high-risk osteoporosis patients, a rheumatologist is 21% more likely to prescribe osteoporosis medications compared to a non-rheumatologist [36], which is consistent with our study that showed a rheumatology visit was associated with a 43% increased likelihood of osteoporosis medication use.

These findings may suggest that women value mobility, physical health, and the prevention of future fractures as important healthcare priorities, resulting in increased baseline screening and baseline osteoporosis medication as well as the consequent greater uptake in future osteoporosis medication. Additionally, prior osteoporosis medication may also suggest that the patient's physician was more likely to prescribe medications for osteoporosis in the future. Importantly, we found that a second fracture increased the likelihood of initiating osteoporosis treatment in the sample by 48.7%, suggesting that an additional fracture after the index fragility fracture can necessitate prescription of osteoporosis medication. With timely osteoporosis treatment during follow-up, risk of subsequent fractures can be managed and the effectiveness of osteoporosis treatment can be improved.

Our analysis resulted in treated-osteoporotic women being associated with a 21% lower likelihood of a subsequent fracture during the 12-month follow-up period. Among prevalent osteoporosis medication users, we found a 41% lower risk of fractures, and new users had a 20% lower risk of fractures during the study follow-up period. The results imply that continued exposure to osteoporosis treatment has a greater impact on fracture risk reduction compared to new exposure. Our study has a shorter follow-up period compared to RCT and other RWE studies; therefore, the impact may be greater with a longer follow-up. Additionally, a systematic review of RCTs demonstrated the impact of osteoporosis medication on time to fracture reduction, ranging from 6-36 months of treatment [37]. Our RWE study results among Medicare women can be tied to the fact that osteoporosis treatments show an increased effectiveness against subsequent fractures and support the efficacy demonstrated through RCTs in the past.

Limitations There are several important limitations to this study. CMS Medicare data does not include information for beneficiaries enrolled in a Medicare-managed care plan. The study sample was limited to Medicare fee-for-service enrollees; therefore, it is not generalizable to the entire elderly population in the US. While claims data are valuable for the efficient and effective examination of healthcare outcomes, treatment patterns, resource utilization, and costs, claims data are collected for the purpose of payment and not research. Therefore, certain limitations were associated with claims data use. First, the presence of a Part D claim for a filled prescription did not indicate whether the medication was actually consumed or taken as prescribed. Second, medications filled over-the-counter or provided as samples by the physician would not be observed in the claims data. Third, the presence of a diagnosis code on a medical claim was not a positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. For example, vertebral fractures are usually underdiagnosed in clinical practice and could potentially be misclassified, especially among vertebral compression fractures [38]. Finally, certain information was not readily available in claims data (or could be randomly missing) that may have influenced study outcomes, such as clinical and disease-specific parameters, including BMD T-scores, tobacco use, low calcium intake, and eating disorders. These unmeasured variables could lead to residual confounding. In addition, there is evidence of continued fracture reduction after 12 months and it has been shown that each additional month up to 24 months reduced non-vertebral fractures by another 7% [39]. Therefore, a 12-month follow-up may have underestimated the full benefit of longer treatment.

Our analysis was conducted from a large, comprehensive, administrative Medicare claims database that offers an adequate sample size to infer meaningful relationships between index fragility fracture, osteoporosis medication use, and subsequent fractures during the 12-month follow-up period for osteoporotic women. We examined a comprehensive list of osteoporosis medications among Medicare enrollees, which gave us a robust estimate of the predictors of osteoporosis medication use. In addition, we were able to adjust for all the observable confounders that could mediate and/or confound the relationship in our models. Furthermore, we conducted two sensitivity analyses, which confirmed our results.

In conclusion, clinical vertebral fracture patients were the most likely to be treated with osteoporosis medications compared to hip/pelvis/femur and other non-vertebral fracture patients in our Medicare sample. After adjusting for baseline demographic and clinical characteristics, treated osteoporotic women had a significantly lower risk for subsequent fractures compared to untreated osteoporotic women; this adds sufficient value to the need of timely and effective osteoporosis treatment among elderly osteoporotic women with fragility fractures. Considering that osteoporosis treatment use post-fracture is low (below 50% for all sites) and mean times to treatment ranged from 2 to 3 months, our findings reflect that osteoporosis treatment management can be improved. There is a need for coordination of care to close this treatment gap to improve treatment rates as well as timing of osteoporosis treatment post-fracture to reduce future fractures effectively. Collaborations across orthopedic providers and payers and implementing an integrated model of care [40] may improve access and use of osteoporosis treatments in the US Medicare population.

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Compliance with ethical standards

Conflict of interest L. Xie, A. Keshishian and O. Baser are employees of STATinMED Research, a paid consultant to Eli Lilly Inc. in connection with the study design, data analysis, and development of this manuscript.

N. Boytsov, R. Burge, K. Krohn, L. Lombard, and X. Zhang are employees and stock owners of Eli Lilly and Co.

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