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Clinical Research Article

Trends in Management of Osteoporosis Following Primary Vertebral Compression Fracture

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Abstract

Purpose: Osteoporosis affects more than 200 million individuals worldwide and predisposes to vertebral compression fractures (VCFs). Given undertreatment of fragility fractures, including VCFs, we investigate current anti-osteoporotic medication prescribing trends.

Methods: Patients 50 and older with a diagnosis of primary closed thoracolumbar VCF between 2004 and 2019 were identified from the Clinformatics® Data Mart database. Multivariate analysis was performed for demographic and clinical treatment and outcome variables.

Results: Of 143 081 patients with primary VCFs, 16 780 (11.7%) were started on anti-osteoporotic medication within a year; 126 301 (88.3%) patients were not started on medication. The medication cohort was older (75.4 ± 9.3 vs 74.0 ± 12.3 years, $P < .001$), had higher Elixhauser Comorbidity Index scores (4.7 ± 6.2 vs 4.3 ± 6.7, $P < .001$), was more likely to be female (81.1% vs 64.4%, $P < .001$), and was more likely to have a formal osteoporosis diagnosis (47.8% vs 32.9%) than the group that did not receive medication. Alendronate (63.4%) and calcitonin (27.8%) were the most commonly initiated medications. The proportion of individuals receiving anti-osteoporotic medication within the year following VCF peaked in 2008 (15.2%), then declined until 2012 with a modest increase afterward.

Conclusions: Osteoporosis remains undertreated after low-energy VCFs. New anti-osteoporotic medication classes have been approved in recent years. Bisphosphonates remain the most prescribed class. Increasing recognition and treatment of osteoporosis is paramount to decreasing the risk of subsequent fractures.

Key Words: vertebral compression fracture, osteoporosis, medication, trends

Osteoporosis predisposes to characteristic fragility fractures, which add to the growing economic burden of disease. The lifetime risk of fragility fracture in osteoporosis is estimated between 40-50% in women and 13-22% in men [1]. Vertebral compression fractures (VCFs) affect the anterior column of the spine, resulting in vertebral body height loss visible on radiograph, CT, and MRI [2]. Despite their high prevalence, a randomized clinical trial of over 6000 women with osteoporosis found that only one-fourth of radiographically identified VCFs had been clinically diagnosed [3]. Often, patients are asymptomatic or have back pain due to other causes, distracting from the diagnosis [4]. This is troublesome, as reduction in quality of life following VCF is nearly as severe as for hip fractures [1]. Patients with first-time VCF are 4 times more likely to have another VCF and 2 times more likely to have any other osteoporotic fragility fracture, underscoring the importance of diagnosis and treatment of the initial VCF [1]. Despite the magnitude of this problem, prevention and treatment of VCF remains suboptimal and challenging. Medication nonadherence is also a likely contributing factor to undertreatment of VCFs [5]. Bisphosphonates remain the most commonly prescribed anti-osteoporotic medication, but a study of national claims database information revealed a more than 50% decrease in prescribing rates from 2008 to 2012, citing questions about safety and optimal duration as the cause [6]. Within this current context of national undertreatment of fragility fractures in general and VCFs specifically, the goal of this study is to investigate national anti-osteoporosis medication prescribing trends from 2004 to 2019.

To the best of our knowledge, this represents the most recent and comprehensive study of anti-osteoporotic prescription patterns, incorporating 4 more years of data (2015-2019) that have not been published before and during which several anabolic agents including abaloparatide (2017) and romosozumab (2020) were Food and Drug Administration (FDA) approved. This is also the first analysis of osteoporosis prescription patterns using the Optum

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database, which includes patients with both commercial and Medicare advantage insurance plans.

Materials and Methods

Data included in this study were sourced from Optum's de-identified Clinformatics® Data Mart (CDM) Database [7]. This deidentified administrative health database is derived from a large, adjudicated claims data warehouse composed of claims data from recipients of commercial and Medicare advantage health plans affiliated with Optum. The database comprises more t 75 million individuals spanning all 50 states. The CDM includes approximately 3.2 million Medicare Advantage with Part D members (starting in 2006) obtained from an affiliate company. The claims for these patients include both primary and more advanced secondary/tertiary care and include both inpatient and outpatient files. The Stanford Institutional Review Board approved this retrospective study, which was exempt from consent requirements due to classification as no more than minimal risk.

International Classification of Diseases, Clinical Modification, 9th Edition (ICD-9-CM) and 10th (ICD-10-CM) Edition codes were used to identify patients 50 and older who were diagnosed with a primary (first occurrence) of closed thoracolumbar vertebral compression fracture (VCF) without neurologic injury from January 1, 2004, to December 31, 2019 [8]. Only patients who were enrolled in the insurance database at least 1 year before VCF were included. Patients with a diagnosis of neoplasms, intraspinal abscesses, inflammatory spondylosis, osteomyelitis, or transportation/spinal cord injuries in the year prior to the VCF were excluded. We also excluded patients who were already on anti-osteoporotic medications within the year before the VCF to prevent an overlap with anti-osteoporotic medication rates post-VCF. Baseline demographics and comorbidities, including age and sex, were collected. To account for the general health status of each patient prior to injury, the composite Elixhauser Comorbidity Index (ECI) was calculated using ICD-9-CM and ICD-10-CM codes, as previously described [9, 10]. The ECI is a method of categorizing comorbidities of patients based on the ICD diagnosis codes found in administrative data. The index contains 30 categories (including cardiac comorbidities, hypertension, neurological disorders, diabetes, cancer, anemia, obesity, renal failure, liver disease, drug abuse, vascular disorders, pulmonary disease, and HIV/AIDs), and a weighting algorithm is used, based on the association between comorbidity and death, in order to produce an overall score for the ECI. The number of patients with osteoporosis diagnosis codes and average follow-up time after the VCF were also queried.

National Drug Category and Generic Drug codes were used to identify prescription claims filed for the following medications: abaloparatide (Tymlos), alendronate (Fosamax), calcitonin (Miacalcin), denosumab (Prolia), ibandronate (Boniva), raloxifene (Evista), risedronate (Actonel), romosozumab (Evenity), teriparatide (Forteo), and zoledronate (Reclast). Types of anti-osteoporotic medications prescribed were collected. A complete list of drug codes can be found in Supplementary Table S1 [8]. Patients were stratified into 2 groups: those who received anti-osteoporotic medication ("medication") and those did not ("no medication") within a year following the VCF diagnosis. Information was also collected on patients who were placed on anti-osteoporotic medication within 2 years, as well as anytime following the VCF. Descriptive analysis was used to report differences in patient demographics between the 2 groups. Separate trends analysis for age-stratified, sex-stratified, and overall rates of anti-osteoporotic medication prescription over time were carried out and reported. CPT-4 codes were used to identify dual-energy X-ray absorptiometry (DEXA) scans/screens that were performed in the year following the VCF. A trends analysis was performed to report rates of DEXA screening for the study sample over time.

ICD-9-CM and ICD-10-CM codes were used to identify patients with a secondary fragility fracture of the vertebrae, hip, distal radius, and proximal humerus within a 1-, 2-, 3-, 4-, and 5-year period after the initial VCF. Only patients with the full follow-up were included in each analysis. A complete list of codes used to identify secondary fragility fractures can be found in Supplementary Table S1 [8]. Multivariate regression analyses, adjusting for age, sex, race, region, and ECI were used to assess for significant differences in secondary fragility fracture rates between patients who received anti-osteoporotic medication after the primary VCF vs those who did not. Multivariate regression analysis was also used to identify independent factors associated with prescription of anti-osteoporotic medication within 1 year following the primary VCF. Results from the regression analyses have been reported as adjusted odds ratio (OR) and 95% confidence intervals (CI), along with their *P*-values. Cohorts were propensity score matched for secondary fragility fracture comparisons to adjust for differences in characteristics between the groups, using the nearest neighbor method [11]. The variables included for matching were age, sex, ECI, race, region, and osteoporosis diagnosis code.

Comparisons of categorical and continuous variables were conducted using chi-squared tests and Student's t-test, respectively. Propensity score matching and multivariate regression analysis was performed using version 4.2.0 of the R programming language (R Foundation for Statistical Computing). Graphs were produced using version 9 of GraphPad Prism. Statistical significance was defined as $P < .05$, and all tests used were two-sided. All statistical and graphical analyses were conducted in R.

Results

A total of 448 328 patients with VCFs from 2004 to 2019 were identified. After applying exclusion criteria, 143 081 patients were included in our analysis [8]; 16 780 (11.7%) patients were started on anti-osteoporotic medication within a year after VCF, and 126 301 (88.3%) were not started on medication.

Across the medication and no medication groups, 66.3% of our patients were female and 76.0% White, with slightly more patients from the southeastern United States (28.3%; Table 1). The medication cohort was older (75.4 ± 9.3 vs 74.0 ± 12.3 years, $P < .001$), more likely to be female (81.1% vs 64.4%, $P < .001$), more likely to have an osteoporosis diagnosis code (47.8% vs 32.9%), and had a higher ECI (4.7 ± 6.2 vs 4.3 ± 6.4, $P < .001$; Table 1), than the no medication group. Patients in the medication group were more likely to have had a DEXA scan within a year after the VCF (44.5% vs 14.9%, $P < .001$) and had longer follow-up time (1366 ± 1094 vs 1188 ± 1064 days, $P < .001$; Table 1).

Of the patients, 11.7% were started on medication within a year, 13.7% were started on medication within 2 years, and 16.5% were started on medication at any point after the primary

Table 1. Baseline demographics and characteristics of patients started on medication within a year after VCF vs those who were not started on medication

Clinical characteristics	Patients started on medication within a year after VCF	Patients not started on medication within a year after VCF	Totals	*P*-value
Number, n (%)	16 780 (11.7)	126 301 (88.3)	143 081	
Age (years)				
Mean ± SD	75.4 ± 9.3	74.0 ± 12.3	74.1 ± 12.0	<.001
50-59	1256 (7.5)	17 800 (14.4)	19 056 (13.3)	
60-69	2946 (17.7)	23 860 (19.3)	26 806 (18.7)	
70-79	5885 (35.3)	36 234 (29.3)	42 119 (29.4)	
80-89	6561 (39.4)	45 618 (36.9)	52 179 (36.5)	
Sex, n (%)				<.001
Female	13 612 (81.1)	81 286 (64.4)	94 898 (66.3)	
Male	3167 (18.9)	45 005 (35.6)	48 172 (33.7)	
Race, n (%)				
White	12 526 (74.6)	96 223 (76.2)	108 749 (76.0)	<.001
Asian	621 (3.7)	3299 (2.6)	3920 (2.7)	
Black	977 (5.8)	9034 (7.2)	10 011 (7.0)	
Hispanic	1700 (10.1)	10 480 (8.3)	12 180 (8.5)	
Other/Unknown	956 (5.7)	7265 (5.8)	8221 (5.7)	
Region, n (%)				<.001
Northeast	1326 (7.9)	12 288 (9.7)	13 614 (9.5)	
Southeast	4165 (24.8)	36 359 (28.8)	40 524 (28.3)	
Midwest	3207 (19.1)	26 594 (21.1)	29 801 (20.8)	
Southwest	2898 (17.3)	21 514 (17.0)	24 412 (17.1)	
West	5174 (30.8)	29 467 (23.3)	34 641 (24.2)	
Unknown				
Elixhauser Comorbidity Index, Mean ± SD	4.7 ± 6.2	4.3 ± 6.7	4.4 ± 6.6	<.001
Osteoporosis Diagnosis code, n (%)	8016 (47.8)	41 566 (32.9)	49 582 (34.7)	<.001
Average follow-up time ± SD (days)	1366 ± 1094	1164 ± 1057	1188 ± 1064	<.001
DEXA within a year after VCF, n (%)	7461 (44.5)	18 863 (14.9)	26 324 (18.4)	<.001

Abbreviations: DEXA, dual-energy X-ray absorptiometry; VCF, vertebral compression fracture.

VCF. Among patients who were started on medication within a year after the VCF, alendronate was the most common (63.4%), followed by calcitonin (27.8%). Bisphosphonates were the most commonly prescribed medication class (72.0%), and no patients were started on PTH analogues (ie, abaloparatide, teriparatide) or romosozumab. The average number of days on medication for patients started on medication within a year after VCF was 541 ± 732 days (Table 2).

The number of individuals diagnosed with a VCF rose from 2096 in 2004 to 21 574 in 2019 [8] and the number of anti-osteoporotic medications prescribed within a year after the primary VCF rose from 247 in 2014 to 2241 in 2019 [8]. However, the proportion of individuals receiving anti-osteoporotic medication within the year following VCF was variable over time, with a peak at 2008 (15.2%), followed by a decline until 2012 and a modest increase thereafter (Fig. 1A). Prescribing trends for females and males followed a similar pattern, and females had higher rates of anti-osteoporotic medication prescription compared to males at all time points (Fig. 1B). The proportion of patients prescribed medication within a year after the primary VCF increased as age increased for the 50- to 59- and 60- to 69-year-old cohorts. However, rates of medication prescription were similar for patients in the 70- to 79- and 80- to 89-year-old groups (Fig. 1C). Rates of utilization of DEXA scans within a year following the VCF increased over time from 5.0% in 2006 to 20.0% in 2019 (Fig. 1D).

Secondary fragility fracture rates at 1, 2, 3, 4, and 5 years after diagnosis were higher in the medication than the no medication group [2126 (14.7%) vs 8126 (8.4%); 1894 (17.1%) vs 7204 (10.2%); 1455 (18.2%) vs 5764 (11.5%); 1116 (19.2%) vs 4472 (12.5%); and 865 (20.0%) vs 3574 (13.5%), at each time point, respectively; $P < .001$; Table 3].

In order to determine whether the difference in secondary fragility fracture rate in the medication vs no medication group was due to differences in baseline characteristics and comorbidities between the groups, propensity score matching was performed. Characteristics of the propensity matched cohorts can be found in Supplementary Table S2 [8]. Secondary fragility fractures were again higher at 1, 2, 3, 4, and 5 years

Table 2. Patients on medication following first VCF

Medication	Patients started on medication within 1 year after VCF, n (%)	Patients started on medication within 2 years after VCF, n (%)	Patients started on medication any time after VCF, n (%)
Total	16 780 (11.7)	19 594 (13.7)	23 592 (16.5)
Abaloparatide	0 (0)	0 (0)	0 (0)
Alendronate	10 633 (63.4)	12 736 (65.0)	15 874 (67.3)
Calcitonin	4658 (27.8)	5064 (25.8)	5743 (24.3)
Denosumab	864 (5.1)	1179 (6.2)	1864 (7.9)
Ibandronate	1354 (8.1)	1700 (8.7)	2163 (9.2)
Raloxifene	309 (1.8)	428 (2.2)	595 (2.5)
Risedronate	0 (0)	0 (0)	0 (0)
Romosozumab	0 (0)	0 (0)	0 (0)
Teriparatide	0 (0)	0 (0)	0 (0)
Zoledronate	88 (0.52)	117 (0.60)	176 (0.75)
Medication class			
PTH analogues	0 (0)	0 (0)	0 (0)
Bisphosphonates	12 074 (72.0)	14 553 (74.3)	18 213 (77.2)
Calcitonin (agonist)	4658 (27.8)	5064 (25.8)	5743 (24.3)
Denosumab (RANK ligand inhibitor)	864 (5.1)	1179 (6.2)	1864 (7.9)
Raloxifene (SERM)	309 (1.8)	428 (2.2)	595 (2.5)
Romosozumab (sclerostin inhibitor)	0 (0)	0 (0)	0 (0)
Mean days on medication ± SD (days)	541 ± 732	537 ± 727	546 ± 741

Abbreviations: SERM, selective estrogen receptor modulator; VCF, vertebral compression fracture.

after diagnosis in the medication than the no medication group [2126 (14.7%) vs 1129 (8.5%); 1894 (17.1%) vs 1131 (10.8%); 1455 (18.2%) vs 1055 (13.1%); 1116 (19.2%) vs 929 (14.8%); and 865 (20.0%) vs 808 (16.5%), at each time point, respectively; P < .001; Table 4].

Table 5 presents the results of multivariate analyses to estimate the association of each variable (age, sex, treatment modality: medication within 1 year vs no medication, ECI, race, region, and osteoporosis diagnosis code) on the rate of secondary fragility fracture at 1, 2, 3, 4, and 5 years post-diagnosis. After adjusting for these variables in multivariate regression, being started on an anti-osteoporotic medication within a year after the VCF had a 72% greater risk of a secondary fracture within a year following diagnosis of VCF (adjusted OR = 1.72, 95% CI = 1.633-1.813, $P < .001$). Female patients were 35% more likely to be diagnosed with a secondary fragility fracture within a year following VCF (adjusted OR = 1.35, 95% CI = 1.277-1.417, $P < .001$). For each 1-year increase in age, secondary fracture risk was 2% higher (adjusted OR = 1.02, 95% CI = 1.020-1.024, $P < .001$). For each 1-point increase in ECI, secondary fracture risk was 1% higher (adjusted OR = 1.01, 95% CI = 1.008-1.014). White patients were 14%, 13%, and 12% more likely to experience a secondary fracture within a year after VCF compared to Asian (adjusted OR = .86, 95% CI = 0.749-0.978, $P < .05$), Black (adjusted OR = 0.87, 95% CI = 0.802, 0.952, $P < .01$), and Hispanic/Latino (adjusted OR = 0.88, 95% CI = 0.816-0.953, $P < .01$) patients, respectively. Compared to patients from the West, patients from the Southeast, Southwest, Northeast, and Midwest were 26% (adjusted OR = 1.26, 95% CI = 1.188,1.341, $P < .001$), 25% (adjusted OR = 1.25, 95% CI = 1.165-1.331, $P < .001$), 30% (adjusted OR = 1.30, 95% CI = 1.199 −1.407, $P < .001$), and 59% (adjusted OR = 1.59, 95% CI = 1.494-1.690, $P < .001$) more likely to experience a secondary fracture within a year after VCF, respectively. Patients with an osteoporosis diagnosis code were 72% (adjusted OR = 1.72, 95% CI = 1.633-1.813, $P < .001$) more likely to experience a secondary fragility fracture 1-year post-VCF diagnosis. Information about the results of multivariate regression for secondary fragility fractures after 2, 3, 4, and 5 years post-VCF diagnosis are included in Table 5.

Following adjustment for age, sex, race, region, ECI, and osteoporosis diagnosis, independent factors associated with prescription of anti-osteoporotic medication within 1 year of VCF were female sex (adjusted OR = 2.03, 95 CI = 1.950-2.123), older age (adjusted OR = 1.001, 95% CI = 1.000-1.003), identifying as Asian compared to White (adjusted OR = 1.31, 95% CI = 1.194-1.428), identifying as Hispanic/Latino compared to White (adjusted OR = 1.17, 95% CI = 1.106-1.238), and having an osteoporosis diagnosis code (adjusted OR = 1.53, 95% CI = 1.481-1.587).

Discussion

In this study, we found that 11.7% of adult patients were started on anti-osteoporotic medication within a year after a primary VCF. As defined by the World Health Organization, an osteoporosis diagnosis is made if a patient has a low bone mineral density (BMD) as measured by a DEXA scan, suffered a fragility fracture with a DEXA score in the osteopenia range, or suffered a hip or spine fracture from low-energy trauma, even in the

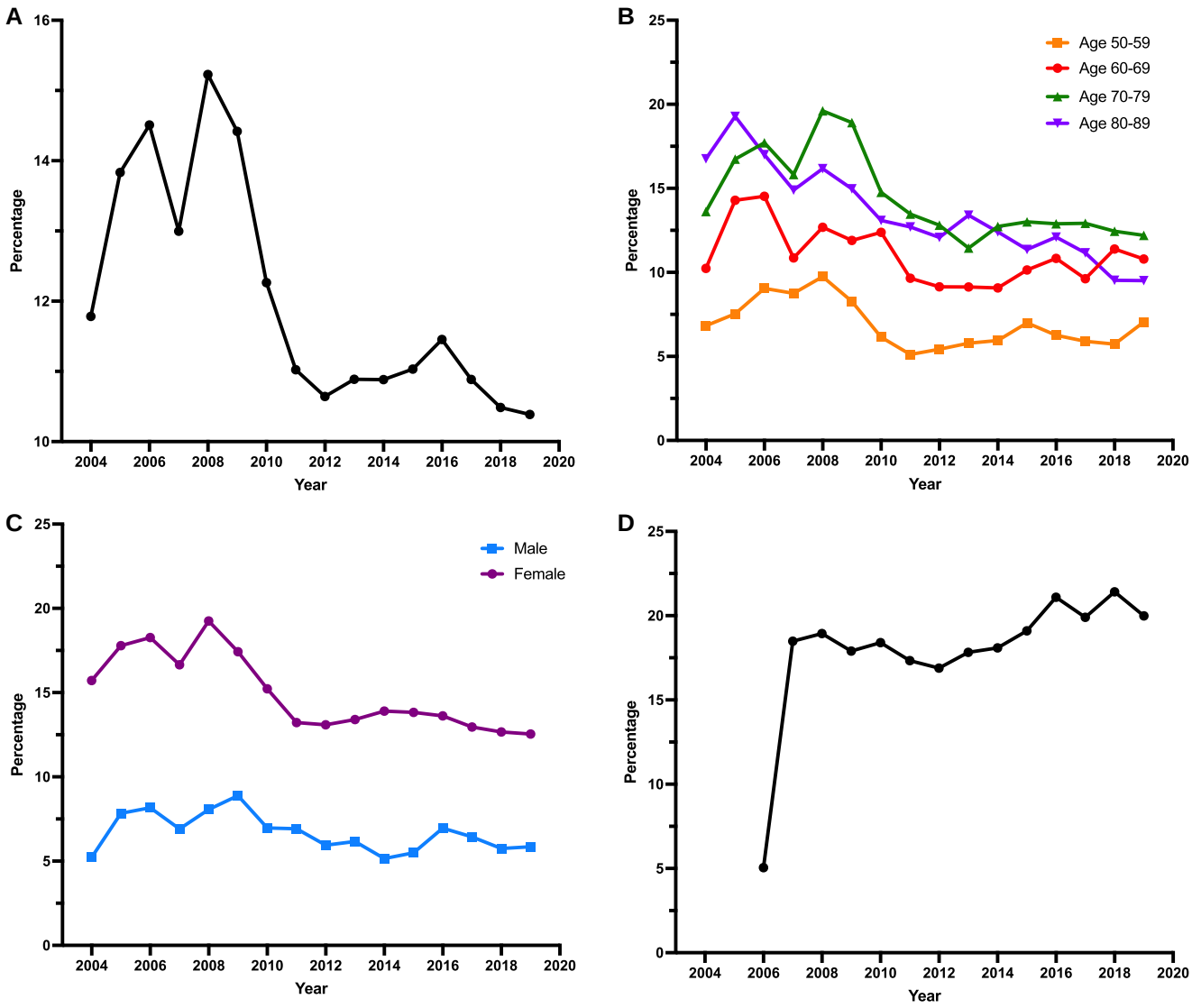

Figure 1. (a) Medication prescribing trends over time, all patients. Percentage of patients. (b) Medication prescribing trends over time, stratified by sex. Percentage of patients. (c) Medication prescribing trends over time, stratified by age. (d) DEXA scan trends within a year following VCF over time.

Abbreviations: DEXA, dual-energy X-ray absorptiometry; VCF, vertebral compression fracture.

context of a normal BMD [12]. Since we excluded all patients with diagnoses indicating traumatic or secondary causes of the VCF, our patient population is one that, by definition, met the criteria for osteoporosis. Interestingly, only 34.7% of the VCF patients had an osteoporosis diagnosis code in their claims, indicating undercoding of the osteoporosis diagnosis in these patients. This is in line with many studies demonstrating underdiagnosis and undertreatment of osteoporosis following low-energy VCF's, putting patients at risk of incurring additional fractures [13, 14].

We found that the bisphosphonate class (alendronate in particular) was the most commonly prescribed class of anti-osteoporotic medications. Bisphosphonates are currently considered the first-line therapy for the prevention and treatment of osteoporosis in the United States [6]. Approved in 1995, alendronate was the first bisphosphonate to obtain FDA approval for the treatment and prevention of osteoporosis [15]. Many other classes of medications have been FDA approved since then, including the anabolic PTH analogue teriparatide in 2002 and most recently the anabolic monoclonal antibody romosozumab in 2019 [16]. As previous studies have focused on medication prescribing trends prior to the approval of the newest anabolic agents (ie, romosozumab and abaloparatide) [17], we wanted to investigate osteoporosis treatment with these medications on the market. However, we found that none of the patients with a VCF were prescribed any of the anabolic agents, including teriparatide, abaloparatide, or romosozumab. The primary limitation of anabolic medications is their higher cost when compared to antiresorptive drugs and therefore lower insurance coverage [18]. Optum contains both commercially insurance patients and those on Medicare Advantage (Part D) plans. Medicare Part D plans listed the anabolic agents (teriparatide, abaloparatide) at the specialty formulary tier, indicating that patients would be subject to higher out-of-pocket costs [19]. Various insurance plans often require that a patient fail an oral therapy before authorizing an injectable therapy (eg, teriparatide, abaloparatide, romosozumab) [19]. In addition, fears of adverse side effects, such as osteosarcoma from PTH analogues and increased risk of cardiovascular events from

Table 3. Follow-up and secondary fractures following first VCF

	Patients started on medication within a year after VCF, n (%)	Patients not started on medication within a year after VCF, n (%)	Totals, n (%)	*P*-value
At least 1 year follow-up	14 431 (13.0)	96 868 (87.0)	111 299 (77.8)	
Secondary Fracture 1 year after VCF	2126 (14.7)	8126 (8.4)	10 252 (9.2)	<.001
At least 2 years follow-up	11 056 (13.5)	70 967 (86.5)	82 023 (57.3)	
Secondary Fracture 2 years after VCF	1894 (17.1)	7204 (10.2)	9098 (11.1)	<.001
At least 3 years follow-up	7979 (13.7)	50 092 (86.3)	58 071 (40.6)	
Secondary Fracture 3 years after VCF	1455 (18.2)	5764 (11.5)	7219 (12.4)	<.001
At least 4 years follow-up	5824 (14.0)	35 843 (86.0)	41 667 (29.1)	
Secondary Fracture 4 years after VCF	1116 (19.2)	4472 (12.5)	5588 (13.4)	<.001
At least 5 years follow-up	4321 (14.0)	26 457 (86.0)	30 778 (21.5)	
Secondary Fracture 5 years after VCF	865 (20.0)	3574 (13.5)	4439 (14.4)	<.001

Abbreviations: VCF, vertebral compression fracture.

Table 4. Propensity matching for secondary fractures following first VCF, comparing patients started on medication to those who were not

	Patients started on medication within a year after VCF	Patients not started on medication within a year after VCF	Totals	*P*-value
At least 1 year follow-up	14 431 (52.1)	13 258 (47.9)	27 689 (82.5)	
Secondary Fracture 1 year after VCF	2126 (14.7)	1129 (8.5)	3255 (11.8)	<.001
At least 2 years follow-up	11 056 (51.4)	10 435 (48.6)	21 491 (64.0)	
Secondary Fracture 2 years after VCF	1894 (17.1)	1131 (10.8)	3025 (14.1)	<.001
At least 3 years follow-up	7979 (49.7)	8072 (50.3)	16 051 (47.8)	
Secondary Fracture 3 years after VCF	1455 (18.2)	1055 (13.1)	2510 (15.6)	<.001
At least 4 years follow-up	5824 (48.1)	6278 (51.9)	12 102 (36.1)	
Secondary Fracture 4 years after VCF	1116 (19.2)	929 (14.8)	2045 (16.9)	<.001
At least 5 years follow-up	4321 (46.9)	4893 (53.1)	9214 (27.5)	
Secondary Fracture 5 years after VCF	865 (20.0)	808 (16.5)	1673 (18.2)	<.001

Variables included for propensity score matching were age, sex, comorbidity score, race, region, and osteoporosis code using nearest neighbor method.
Abbreviations: VCF, vertebral compression fracture.

romosuzumab, may dissuade patients and physicians from the use of these medications [20, 21].

Guidelines from the National Osteoporosis Foundation indicate that after a vertebral fracture, patients should start osteoporosis treatment to prevent subsequent fractures, as many pharmacological agents have been shown to reduce vertebral fracture risk within the first year of treatment [22-24]. Of the patients who were started on medication, most were started on anti-osteoporotic medication within a year after the VCF, as compared to being started on medication at a later date. While the number of VCFs and anti-osteoporotic medications prescribed increased from 2004 to 2019, the proportion of patients receiving medication dropped from 2008 to 2012 and then slowly increased. This drop could potentially be explained by an uptick in the reporting of adverse effects linked to bisphosphonate use. A possible link between bisphosphonate use and esophageal cancer was first reported in 2009 [25], and in 2008 the FDA issued an alert reporting the possibility of severe and sometimes incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates [26]. In addition, risks of osteonecrosis of the jaw, atrial fibrillation, and atypical fractures of the femurs have been the subject of reports in peer-reviewed literature and lay press [27, 28].

The proportion of patients on medication increased as age increased (50-59, 50-69, 70-79) until age 80. Interestingly, rates of prescription were similar and oftentimes lower in the age 80 to 89, as compared to the 70 to 79 group. There are studies showing benefits in patients up to 89 years with pharmacological treatment of denosumab, risedronate, zoledronic acid, and teriparatide [29], and the Fracture Risk Assessment Tool, which estimates the 10-year risk for hip fracture and major osteoporotic fracture (spine, hip, humerus, and wrist) is validated for up to age 90 [30]. However, older patients may already be on several medications and less inclined to start an additional one (polypharmacy). There could also be multiple drug interactions making it more difficult to prescribe an anti-osteoporotic medication. Other explanations may include

Table 5. Multivariate logistic regression models

	Started on medication within a year after VCF	Secondary fracture after 1 year of VCF	Secondary fracture after 2 years of VCF	Secondary fracture after 3 years of VCF	Secondary fracture after 4 years of VCF	Secondary fracture after 5 years of VCF
	Logistic OR (95% CI)	Logistic OR (95% CI)	Logistic OR (95% CI)	Logistic OR (95% CI)	Logistic OR (95% CI)	Logistic OR (95% CI)
Age, years, mean (SD)	**1.001 (1.000, 1.003)***	**1.02 (1.020, 1.024)*****	**1.02 (1.022, 1.027)*****	**1.03 (1.025, 1.031)*****	**1.03 (1.028, 1.035)*****	**1.03 (1.024, 1.033)*****
Elixhauser Comobidity Score, mean (SD)	**0.99 (0.985, 0.995)*****	**1.01 (1.008, 1.014)*****	**1.01 (1.007, 1.014)*****	**1.01 (1.005, 1.014)*****	**1.01 (1.004, 1.014)*****	**1.01 (1.002, 1.014)****
Sex						
Male (ref)						
Female	**2.03 (1.950, 2.123)*****	**1.35 (1.277, 1.417)*****	**1.42 (1.346, 1.508)*****	**1.49 (1.398, 1.591)*****	**1.58 (1.471, 1.706)*****	**1.55 (1.432, 1.669)*****
Race						
White (ref)						
Asian	**1.31 (1.194, 1.428)*****	**0.86 (0.749, 0.978)***	**0.82 (0.705, 0.939)****	**0.79 (0.668, 0.921)****	**0.73 (0.604, 0.876)*****	**0.71 (0.544, 0.819)*****
Black	**0.90 (0.838, 0.964)****	**0.87 (0.802, 0.952)****	**0.85 (0.768, 0.928)*****	**0.88 (0.790, 0.978)***	**0.86 (0.756, 0.969)***	**0.89 (0.808,0.966)***
Hispanic/Latino	**1.17 (1.106, 1.238)*****	**0.88 (0.816, 0.953)****	**0.89 (0.823, 0.968)****	**0.92 (0.840, 1.007)**	0.90 (0.814, 1.000)	0.90 (0.808, 1.006)
Region						
West (ref)						
Southeast	**0.67 (0.641, 0.701)*****	**1.26 (1.188, 1.341)*****	1.20 (1.128, 1.283)*****	**1.13 (1.051, 1.214)*****	**1.09 (1.003, 1.184)***	**1.07 (0.944, 1.127)***
Southwest	**0.78 (0.740, 0.817)*****	**1.25 (1.165, 1.331)*****	**1.21 (1.125, 1291)*****	**1.15 (1.067, 1.241)*****	1.08 (0.989, 1.170)	1.06 (0.945, 1.128)
Northeast	**0.61 (0.575, 0.654)*****	**1.30 (1.199, 1.407)*****	**1.19 (1.093, 1.301)*****	1.11 (0.999, 1.224)	1.05 (0.931, 1.183)	0.97 (0.844, 1.105)
Midwest	**0.72 (0.684, 0.753)*****	**1.59 (1.494, 1.690)*****	**1.49 (1.392, 1.585)*****	**1.36 (1.261, 1.459)*****	**1.26 (1.162, 1.374)*****	**1.12 (1.017, 1.221)****
Osteoporosis Code diagnosis						
Unaffected (ref)						
Affected	**1.53 (1.481, 1.587)*****	**1.50 (1.434, 1.567)*****	**1.48 (1412, 1.553)*****	**1.43 (1.348, 1.501)*****	**1.39 (1.308, 1.479)*****	**1.26 (1.300, 1.492)*****
Started on medication within a year after VCF						
No (ref)						
Yes		**1.72 (1.633, 1.813)*****	**1.64 (1.549, 1733)*****	**1.50 (1404, 1.597)*****	**1.42 (1.315, 1.525)*****	**1.37 (1.211, 1.432)*****

P-values: < .05*, < .01**, < .001***; *P*-values <.05 are bolded.
Abbreviations: CI, confidence interval; OR, odds ratio; VCF, vertebral compression fracture.

patient misconceptions about osteoporosis and lack of perceived benefits of therapy [31] and the perception that anti-fracture efficacy requires long-term treatment [32].

While many studies have shown the beneficial effects of pharmacological treatment in improving BMD and decreasing the rate of subsequent fractures [17, 24], we found increased rates of secondary fractures in patients started on medication within a year after VCF 1, 2, 3, 4, and 5 years post-VCF diagnosis. One potential interpretation of our data is that patients started on anti-osteoporotic medication are older with more comorbidities and therefore at higher risk of secondary fractures. To investigate this explanation, we performed propensity score matching for age, sex, ECI, race, region, and osteoporosis diagnosis code. Even after propensity score matching, we found increased rates of secondary fragility fractures in the medication group. After adjusting for demographics and comorbidities in multivariate logistic regression analysis, we found that being started on an anti-osteoporotic medication within a year after the VCF had aa 72% greater risk of secondary fracture within a year following diagnosis. However, a major limitation of the database is that we are unable to collect information on how severe the fractures were and how poor the BMD was. More specifically, DEXA results and T and/or Z-scores, as well as radiology reports, are not

available in this national database. Although we used extensive exclusion criteria to include only patients who suffered a low-energy VCF, it is possible that some patients who suffered a VCF from a traumatic cause were included. These residual confounders are likely impacting our results. It is likely that patients with the poorest bone health (ie, most severe osteoporosis as measured on DEXA scans) and worst fractures (as shown on imaging) are the patients being placed on medication and so, at baseline, are already at a much higher risk of experiencing a secondary fragility fracture.

Interestingly, in our multivariate analysis, we found that the western United States was associated with higher prescription of anti-osteoporotic medication and lower risk of secondary fragility fractures. Higher prescription rates in the West may be due to better patient education or stricter adherence to fracture prevention protocols [17]. The lower risk of secondary fragility fractures may be due to a higher prevalence of physical activity compared to other regions [33] and we speculate potentially higher levels of Vitamin D exposure (particularly in the winter months, as compared to the northeastern or midwestern United States) [34], which, in combination with calcium supplementation, has been shown to result in a significant decrease in fracture incidence [35].

This study has multiple limitations. Retrospective analyses of administrative databases such as Optum's deidentified CDM are limited by data available; incorrect or inaccurate coding may significantly impact our findings and conclusions. In addition, imaging data are not available, so we cannot assess the severity of these fractures. This database also does not include data on patient frailty, functional status, fracture radiographic characteristics, patient medication, or other management preferences, which are all important in fracture management decision-making. We may be missing important confounders (such as fracture severity and characteristics, frailty, functional status) that explains why patients who received treatment, either with anti-osteoporosis medications, experienced more secondary fragility fractures. Finally, we appreciate that the CDM database may not be the most comprehensive data source for elderly patients, given that the majority of elderly patients in the United States have Medicare insurance. In addition, inclusion in this particular database has been shown to be associated with zip codes that have wealthier, older, and more educated residents [36]. If this is the case, then we would expect even lower rates of osteoporosis medication prescriptions after VCF in the general population, given other data from our group showing higher rates of anabolic osteoporosis prescriptions in older, wealthier, and more educated patients [37]. Further work with additional datasets, such as the Medicare database, is needed to definitively address this important issue.

Taken together, our findings suggest that osteoporosis remains undertreated after low-energy vertebral compression fractures, with only 11.7% of eligible patients receiving prescriptions for anti-osteoporosis medications within 1 year after their osteoporosis-defining fragility fractures. New classes of anti-osteoporotic medications have been approved in recent years; few patients in this database were prescribed these newer medications. Bisphosphonates remain the most commonly prescribed class of medication. Older Hispanic and Asian females with more comorbidities and an official osteoporosis diagnosis were the most likely to receive osteoporosis treatment. Improvement in the recognition and treatment of osteoporosis is crucial to improve the health of our patients and decrease the risk of subsequent fractures.

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Disclosures

K.M., I.B., G.T., T.R., J.L., and C.Z. declare that they have no financial or nonfinancial conflict of interests to report.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

IRB Approval

Data included in this study were sourced from Optum's deidentified Clinformatics® Data Mart Database. The Stanford Institutional Review Board approved this retrospective study, which was exempt from consent requirements due to classification as no more than minimal risk.

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