

No Increased Risk of Nonunion with Bisphosphonate Use in a Medicare Claims Cohort Following Operatively Treated Long-Bone Fractures

Tyler J. Thorne, BA, Lillia Steffenson, MD, Dillon C. O'Neill, MD, Lucas S. Marchand, MD, Brook I. Martin, PhD, and Justin M. Haller, MD

Investigation performed at the University of Utah, Salt Lake City, Utah

Background: The diagnosis of a fragility fracture represents an important intervention event for the initiation of medical osteoporosis treatments. However, it is unclear if osteoporosis medications increase the risk of nonunion if administered in the setting of acute fracture. The purpose of the present study was to investigate whether bisphosphonates or selective estrogen receptor modulators/hormone replacement therapy (SERM/HRT) are associated with nonunion following fracture in a Medicare population.

Methods: A retrospective analysis of Medicare claims from 2016 to 2019 was performed to identify patients ≥ 65 years of age who had a surgically treated long-bone fracture as identified with Current Procedural Terminology (CPT) codes and International Classification of Diseases, 10th Revision (ICD-10) codes. Successive claims were linked for each beneficiary through 1 year following the fracture to determine fracture union status. Multivariable logistic regression models were specified to identify the association between medications and fracture union status while controlling for age, sex, race, Charlson Comorbidity Index (CCI), and fracture type.

Results: Of the 111,343 included fractures, 10,452 (9.4%) were associated with a diagnosis of nonunion within 1 year. The nonunion group was younger (79.8 ± 8.3 versus 80.6 ± 8.4 years; $p < 0.001$), more likely to be White (92.4% versus 90.9%; $p < 0.001$), and more likely to have a CCI of ≥ 2 (50.9% versus 49.4%; $p < 0.001$). Bisphosphonate use was more common in the nonunion group (12.2% versus 11.4%; $p = 0.017$). When controlling for race, age, sex, and CCI, neither bisphosphonates (OR, 1.06 [95% CI, 0.99 to 1.12]; $p = 0.101$) nor SERM/HRT (OR, 1.13 [0.93 to 1.36]; $p = 0.218$) were associated with nonunion. Bisphosphonate use within 90 days post-fracture was not significantly associated with nonunion (OR, 0.94 [95% CI, 0.86 to 1.03]; $p = 0.175$), and the timing of medication administration did not influence fracture union status.

Conclusions: The rate of nonunion after operatively treated long-bone fractures was 9.4%. In this cohort, use of a bisphosphonate or SERM/HRT was not associated with fracture union status at 1 year. Orthopaedic surgeons should not withhold or delay initiating medical therapies for osteoporosis in the setting of acute fracture out of concern for nonunion.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Osteoporosis-related fragility fractures are an important cause of morbidity and mortality in the elderly¹⁻³. Orthopaedic surgeons are in a unique position to identify and help treat osteoporosis. The diagnosis of a fragility fracture provides an important opportunity to initiate the medical management of osteoporosis, as patients with a prior fragility fracture have twice as high a risk of another fracture as the general population⁴.

Currently, treatment with bisphosphonates is the standard of care for the medical management of osteoporosis. However, the existing literature provides mixed conclusions regarding whether bisphosphonate use is safe in the acute fracture setting.

Theoretical concern regarding bisphosphonate-associated nonunion arises from the drugs' mechanism of action, inhibition of osteoclast-mediated bone-remodeling⁵. Prior animal

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (<http://links.lww.com/JBJS/H423>).

research has been inconclusive regarding the impact of bisphosphonates on fracture-healing. Some investigators have found that bisphosphonates have been associated with increased microdamage with decreased callus remodeling, whereas others have found that they have been associated with increased callus size and strength⁶⁻⁹. Human studies also have been divided, with some reports showing delayed time to union and increased nonunion rates following fracture in elderly patients taking bisphosphonates^{10,11}. However, other studies have demonstrated earlier union among those taking bisphosphonates, without increased nonunion rates, across a variety of fracture types¹²⁻¹⁶. Overall, prior research investigating the relationship between nonunion and bisphosphonate use is limited because nonunions are relatively rare events and the majority of existing studies have had small patient populations and inadequate durations of follow-up. Database cohorts offer a solution to this methodological issue. A prior database study showed that bisphosphonate use was associated with nonunion; however, the study population comprised individuals <65 years of age and was not reflective of the typical patient with a fragility fracture¹⁷. Additionally, few clinical studies have evaluated nonunion rates in patients taking selective estrogen receptor modulators (SERM) or hormone replacement therapy (HRT), despite their biological activity in bone and fracture-healing process¹⁸.

Given the high morbidity and mortality associated with fragility fractures in the elderly, along with the increased risk of subsequent fragility fractures, it is important to further investigate the relationship between osteoporosis treatments and fracture nonunion. The primary purpose of the present study was to investigate the association of bisphosphonate and SERM/HRT therapies on fracture union status with use of Medicare claims data. The secondary aim was to evaluate the impact of the timing of bisphosphonate and SERM/HRT use (pre-fracture as compared with post-fracture) on nonunion development.

Materials and Methods

Study Cohort

A retrospective analysis of a convenience cohort drawn from Medicare beneficiaries with a Part B (provider service) claim for back pain and/or osteoporosis from 2016 to 2019 was performed. Patients were included if they were ≥65 years of age and had a surgically managed fracture involving the humerus, radius/ulna, femur, or tibia as identified with Current Procedural Terminology (CPT) and International Classification of Diseases, 10th Revision (ICD-10) codes (see Appendix). Patients were then excluded if they were <65 years old at the time of the fracture, had Medicare through either the end-stage renal disease or Social Security Disability Insurance entitlement programs, had follow-up of <1 year (e.g., a fracture that had occurred in 2019), died within a year after the fracture, were not on Medicare Part D (pharmacy claims), or had insufficient 90-day claims history to calculate comorbidity. Demographic characteristics, including age, sex, race, and Charlson Comorbidity Index (CCI), were collected.

Outcomes

The primary outcome of this study was fracture status at 90 days and at 1 year, dichotomized as union or nonunion. Patients were considered to have a nonunion if they underwent primary surgical fixation and had a subsequent relevant CPT or ICD-10 code for nonunion within 1 year after the fracture (see Appendix). Patients were considered to have a union if they underwent primary surgical fixation and had no subsequent CPT or ICD-10 codes that pertained to nonunion.

Independent Variables of Interest

Bisphosphonate and SERM/HRT medication use in our cohort was identified from Medicare Part D (pharmacy) claims, under the assumption that fulfilling a claim meant that the patient was likely taking the medication (Table I). We classified patients with respect to use of each medication on the basis of their pharmacy claims history of 90 days prior to the fracture through 1 year following the fracture. We assessed the number of medication refills and the impact of refills on nonunion development.

A secondary analysis was based on the timing of medication in relation to the fracture. Medication use was classified on the basis of prescription claims and was categorized as use pre-fracture only (pharmacy claims within 90 days prior to the fracture), post-fracture only (within 90 days and 1 year after the fracture), or both pre- and post-fracture.

Statistical Analysis

Descriptive statistics were used for demographic characteristics, fracture types, rates of union and nonunion, and medication use. Separate multivariable logistic regression models with robust standard errors were then used to describe the association between each medication class and fracture status at 1 year, both overall and within each fracture type, while controlling for age, sex, and CCI. Variables included in the regression models were either dichotomous (sex, presence of the drug of interest, presence of each fracture type, coverage by a Medicare health maintenance organization [HMO]) or categorical (age grouped by 5-year increments, race, CCI). Age and comorbidity were included because the risk of nonunion is known to increase with both age and comorbidity¹⁷. A similar model was used in the secondary analysis

TABLE I Categorization of Drugs

Class	Drugs Included in Class
Bisphosphonate	Risedronate (Actonel), alendronate (Fosamax), ibandronate (Boniva), zoledronic acid (Reclast), pamidronate (Aredia), etidronate (Didronel)
HRT/SERM	Estrogen (Permarin), raloxifene (Evista), bazedoxifene (Conbriza, Viviant, Duavee, Duavive), tibolone (Livial, Tibofem, Ladybon)

examining the timing of medication use and nonunion development. Among those taking each class of medication, a conditional logistic regression model was used to examine the relationship between medication timing and nonunion while controlling for age, sex, race, CCI, and fracture type. Analysis was conducted with use of Stata/MP 17.0, accessed through Medicare's Virtual Research Data Center, and the results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Hypotheses testing was based on an alpha level of 0.001, given the large sample size inherent with database studies¹⁹. The number needed to harm (NNH) was calculated with the formula:

$$\frac{1}{\text{Incidence for Treatment} - \text{Incidence for Control}}$$

Source of Funding

Funding support was provided by internal funding through the LS Peery MD Discovery Program of the University of Utah Department of Orthopaedic Surgery.

Results

A cohort of 342,301 patients were identified on the basis of the initial inclusion criteria for surgically treated fractures. Following exclusions, 111,343 patients (137,959 fractures) remained for analysis (Fig. 1). Among the included patients, intertrochanteric fractures were the most common (72,549), followed by distal tibial fractures (28,704) (Fig. 1). Of the included patients, 100,891 (90.6%) achieved union at 1 year and 10,452 (9.4%) had a nonunion. Compared with the union group, the nonunion group was younger (mean and standard deviation, 79.8 ± 8.3 years compared with 80.6 ± 8.4 years; $p < 0.001$), more likely to be White (92.4% compared with 90.9%; $p < 0.001$), and more likely to have a CCI of ≥2 (50.9% compared with 49.4%; $p < 0.001$) (Table II). The nonunion group had a higher percentage of bisphosphonate use (12.2% compared with 11.4%; $p = 0.017$). As with our primary model, bisphosphonate use within 90 days post-fracture was not significantly associated with nonunion (OR, 0.94 [95% CI, 0.86 to 1.03]; $p = 0.175$). In the bisphosphonate group,

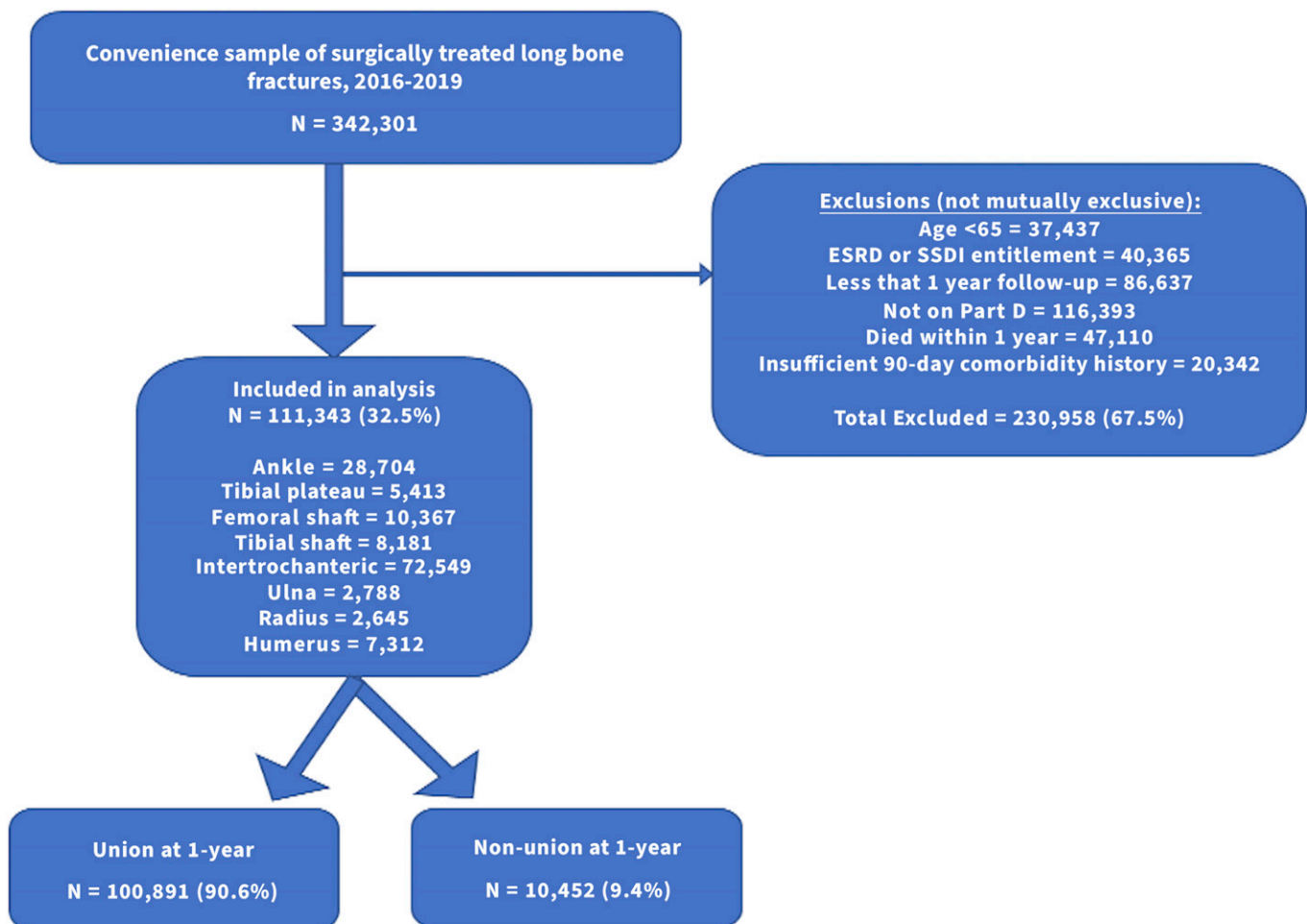


Fig. 1

Flow diagram of cohort selection for the study of the effect of select medications on the union status of surgically treated long-bone fractures at 1 year among Medicare beneficiaries. ESRD = end-stage renal disease, SSDI = Social Security Disability Insurance.

TABLE II Demographic Characteristics

Characteristic	Union (N = 100,891)	Nonunion (N = 10,452)	P Value
Age* (yr)	80.6 ± 8.4	79.8 ± 8.3	<0.001
Age group (% of patients)			<0.001
65-69 yr	10.8	12.3	
70-74 yr	17.7	19.4	
75-79 yr	17.8	18.6	
80-84 yr	18.1	17.5	
≥85 yr	35.6	32.2	
Sex (% of patients)			0.372
Male	21.3	20.9	
Female	78.7	79.1	
Race (% of patients)			<0.001
White	90.9	92.4	
Black	3.4	2.7	
Other/multiple	5.7	4.9	
Charlson Comorbidity Index (% of patients)			<0.001
None	26.8	24.8	
1	23.8	24.3	
≥2	49.4	50.9	
Pharmacy prescription filling (% of patients)			
Bisphosphonates	11.4	12.2	0.017
HRT/SERM	1.1	1.2	0.211

*The values are given as the mean and the standard deviation.

48% of patients received a single prescription and 52% received ≥2 prescriptions. In the HRT/SERM group, 34% of patients received a single prescription and 66% received ≥2

prescriptions. For both medications, the rates of prescriptions filled were not significantly different between patients who did or did not experience a nonunion following the fracture.

Nonunion by Fracture Type

Ulnar fractures (18.0%) and humeral fractures (17.7%) were associated with the highest rates of nonunion, followed by femoral shaft fractures (17.1%), radial fractures (17.0%), and tibial plateau fractures (16.5%) (Table III). Distal tibial and intertrochanteric fractures were associated with the lowest rates of nonunion (9.5% and 9.1%, respectively).

Nonunion by Fracture Type and Medication Use

When controlling for race, age, sex, Medicare HMO coverage, and CCI, neither bisphosphonates (OR, 1.06 [95% CI, 0.99 to 1.12]; $p = 0.101$) nor SERM/HRT (OR, 1.13 [95% CI, 0.93 to 1.36]; $p = 0.218$) were associated with nonunion (Table IV). Among patients with distal tibial fractures, bisphosphonate use was associated with nonunion (OR, 1.23 [95% CI, 1.08 to 1.39]; $p = 0.001$) but SERM/HRT had no impact on union rate (OR, 1.24 [95% CI, 0.88 to 1.76]; $p = 0.214$). Neither bisphosphonates nor SERM/HRT were associated with nonunion of tibial plateau fractures (OR, 0.96 [95% CI, 0.76 to 1.21] [$p = 0.716$] and 0.96 [95% CI, 0.50 to 1.87] [$p = 0.915$], respectively), femoral fractures (OR, 0.89 [95% CI, 0.77 to 1.02] [$p = 0.103$] and 1.63 [95% CI, 1.08 to 2.47] [$p = 0.021$], respectively), tibial shaft fractures (OR, 1.01 [95% CI, 0.82 to 1.24] [$p = 0.945$] and 1.17 [95% CI, 0.68 to 2.01] [$p = 0.578$], respectively), intertrochanteric fractures (OR, 1.07 [95% CI, 0.99 to 1.15] [$p = 0.110$] and 1.04 [95% CI, 0.81 to 1.33] [$p = 0.762$], respectively), ulnar fractures (OR, 1.27 [95% CI, 0.97 to 1.68] [$p = 0.085$] and 1.11 [95% CI, 0.53 to 2.31] [$p = 0.790$], respectively), radial fractures (OR, 1.21 [95% CI, 0.89 to 1.63] [$p = 0.228$] and 0.77 [95% CI, 0.34 to 1.73] [$p = 0.528$], respectively), or humeral fractures (OR, 0.96 [95% CI, 0.79 to

TABLE III Rates of Nonunion by Fracture Location

Location	Unadjusted		Adjusted*
	Union (no. of patients)	Nonunion (no. of patients)	Nonunion Rate (95% CI)
Overall (n = 111,343)	100,891 (90.6%)	10,452 (9.4%)	9.3% (9.2%-9.5%)
Distal tibia (n = 28,704)	25,929 (90.3%)	2,775 (9.7%)	9.5% (9.2%-9.9%)
Tibial plateau (n = 5,413)	4,506 (83.2%)	907 (16.8%)	16.5% (15.5%-17.5%)
Femoral shaft (n = 10,367)	8,582 (82.8%)	1,785 (17.2%)	17.1% (16.4%-17.8%)
Tibial shaft (n = 8,181)	6,948 (84.9%)	1,233 (15.1%)	14.9% (14.1%-15.6%)
Intertrochanteric (n = 72,549)	65,881 (90.8%)	6,668 (9.2%)	9.1% (8.9%-9.3%)
Ulna (n = 2,788)	2,278 (81.7%)	510 (18.3%)	18.0% (16.6%-19.5%)
Radius (n = 2,645)	2,190 (82.8%)	455 (17.2%)	17.0% (15.6%-18.4%)
Humerus (n = 7,312)	6,017 (82.3%)	1,295 (17.7%)	17.7% (16.8%-18.5%)

*The overall model is adjusted for age, sex, race, CCI, bisphosphonates, HRT/SERM, HMO Medicare, and fracture type. The overall estimates from this model are adjusted for the means of all covariates except fracture type.

TABLE IV Analysis of Nonunion at Each Fracture Location by Medication Class*

Location	Bisphosphonates		SERM/HRT	
	Nonunion OR (95% CI)	P Value	Nonunion OR (95% CI)	P Value
Overall	1.06 (0.99-1.12)	0.101	1.13 (0.93-1.36)	0.218
Distal tibia	1.23 (1.08-1.39)	0.001	1.24 (0.88-1.76)	0.214
Tibial plateau	0.96 (0.76-1.21)	0.716	0.96 (0.50-1.87)	0.915
Femoral shaft	0.89 (0.77-1.02)	0.103	1.63 (1.08-2.47)	0.021
Tibial shaft	1.01 (0.82-1.24)	0.945	1.17 (0.68-2.01)	0.578
Intertrochanteric	1.07 (0.99-1.15)	0.110	1.04 (0.81-1.33)	0.762
Ulna	1.27 (0.97-1.68)	0.085	1.11 (0.53-2.31)	0.790
Radius	1.21 (0.89-1.63)	0.228	0.77 (0.34-1.73)	0.528
Humerus	0.96 (0.79-1.17)	0.702	0.84 (0.44-1.61)	0.598

*All models are adjusted for age, sex, race, HMO Medicare, and CCI. OR = odds ratio, HRT = hormone replacement therapy, SERM = selective estrogen receptor modulators.

1.17] [$p = 0.702$] and 0.84 [95% CI, 0.44 to 1.61] [$p = 0.598$], respectively). Within this cohort, the nonunion rate was 9.3% among patients not taking bisphosphonates and 9.7% among those taking bisphosphonates. The calculated NNH was 250. With our observed cohort size and rate of nonunion, we had sufficient statistical power (>0.80) to detect a difference in the rate of

nonunion of as low as 0.8% for bisphosphonates and 1.7% for HRT/SERM.

Nonunion by Medication Timing

The majority of patients in the study never used a medication of interest during the study period; specifically, 88.5% never used bisphosphonates and 98.9% never used SERM/HRT. Among the patients who used bisphosphonates during the study period, the greatest percentage (5.8%) started the medication post-fracture (Table V). Additional logistics regression modeling demonstrated that the pre- or post-fracture timing of prescription filling was not significantly associated with fracture nonunion. Compared with those who took pre-fracture bisphosphonates only, those who took post-fracture bisphosphonates had a risk of nonunion that was higher, but not significantly so (OR 1.01 [95% CI, 0.82 to 1.23]; $p = 0.946$). Those who took both pre- and post-fracture bisphosphonates had a nonsignificantly lower likelihood of nonunion (OR, 0.90 [95% CI, 0.74 to 1.11]; $p = 0.322$). Compared with those with pre-fracture SERM/HRT use only, those with post-fracture SERM/HRT use only had a risk of nonunion that was lower, but not significantly so (OR, 0.79 [95% CI, 0.40 to 1.58]; $p = 0.508$). Those with both pre- and post-fracture SERM/HRT use had a likelihood of nonunion that was lower, but not significantly so (OR, 0.69 [95% CI, 0.36 to 1.31]; $p = 0.255$).

Discussion

Osteoporotic fragility fractures carry a high risk of morbidity and mortality, which has led to a multitude of anti-osteoporosis medications^{1,2}. Currently, the American Society for Bone and Mineral Research recommends the acute use of bisphosphonates following fracture to reduce the risk of future fractures²⁰. Despite these recommendations and the devastating impact of secondary osteoporotic fractures, there remains a treatment gap in this population^{4,20,21}. This is partly due to disagreement about the impact of these medications on fracture status in the elderly. The

TABLE V Analysis of Medication Timing and Adjusted Nonunion Rates by Timing*

	Bisphosphonates	SERM/HRT
Medication timing		
Total cohort (no. of patients)	111,343	111,343
None	88.5%	98.9%
Pre-fracture only	1.2%	0.1%
Post-fracture only	5.8%	0.3%
Pre- and post-fracture	4.5%	0.7%
Cohort taking respective drug (no. of patients)	12,817	1,218
Pre-fracture only	10.5%	9.3%
Post-fracture only	50.1%	30.5%
Pre- and post-fracture	39.4%	60.3%
Adjusted nonunion rate†		
Pre-fracture only	9.3% (7.7%-10.8%)	11.6% (5.6%-17.6%)
Post-fracture only	9.3% (8.6%-10.0%)	9.4% (6.3%-12.5%)
Pre- and post-fracture	8.4% (7.7%-9.2%)	8.3% (6.2%-10.3%)

*HRT = hormone replacement therapy, SERM = selective estrogen receptor modulators. †Conditional logistics regression model controlling for age, sex, race, HMO Medicare, CCI, and fracture type. The 95% CI is given in parentheses.

purpose of the present study was to investigate the impact of osteoporosis medications on the risk of nonunion of surgically treated fractures in a Medicare cohort.

In our cohort, no increased risk of nonunion was observed in association with bisphosphonate or SERM/HRT use. While bisphosphonate use was higher in the nonunion group (12.2% versus 11.4%), this difference was not significant when controlling for age, sex, race, comorbidities, and fracture type. While it can be argued that this result would have been significant if the present study had utilized an alpha of 0.05, it is a well-understood statistical principle that inferences based on a larger sample require a decreased alpha threshold¹⁹. The NNH of 250 seems to indicate the dangers of bisphosphonates; however, the number needed to treat (NNT) was 30 and 90 for the prevention of primary vertebral fractures and hip fractures, respectively. The NNT for vertebral fractures drops to 4 in patients with 2 prior fragility fractures and to 16 in patients with 1 prior fragility fracture²². This highlights the efficacy of bisphosphonate initiation following fragility fracture, and physicians should not be concerned about the risk of nonunion when there are 15-times greater odds of benefiting the patient than harming the patient.

Bisphosphonates had a nonsignificant OR of 1.06 for nonunion, compared with an OR of 1.17 in the large database study by Zura et al.¹⁷. However, the cohort in the study by Zura et al. was not representative of an elderly population, as the ages ranged from 18 to 63 years. This younger patient demographic has different indications and comorbidities than those of the geriatric fracture population. In a survey on bisphosphonate use in young adults, the most common indication was osteoporosis secondary to chronic glucocorticoid use²³, likely indicated for inflammatory diseases. Both chronic glucocorticoid use and inflammatory disease are factors that increase the risk of fractures and, potentially, nonunions²⁴. An additional explanation for the higher OR demonstrated by Zura et al. is that those investigators combined all osteoporotic medications into 1 category rather than separating them by class. In a randomized controlled trial of placebo versus zoledronic acid administration within 3 months after intertrochanteric femoral fracture, Lyles et al. reported no significant difference in delayed union between the groups²⁵.

Similarly, SERM/HRT was not associated with the risk of fracture nonunion, and, while the findings were not significant, they offered relatively lower ORs for nonunions of the radius, humerus, and tibial plateau. This is not surprising given the biological mechanism of SERM/HRT and data from previous animal models that have shown enhanced fracture-healing and earlier osseous bridging associated with SERM administration²⁶.

When examining nonunion rates across surgically treated fracture types, it is interesting to note that humeral fractures had one of the highest nonunion rates (17.7%). Similarly, Solomon et al. found a humeral nonunion rate of 16% in a database study of a population of geriatric patients who took bisphosphonates after a fracture¹¹. While the present study found a nonsignificant OR (0.96) for humeral fracture nonunion with bisphosphonate

use when controlling for confounders, Solomon et al. reported a significant risk overall (OR, 2.37) and among those who underwent operative treatment (OR, 1.91). However, the cohort in that study was small, with 81 nonunions overall and only 8 fractures that were treated operatively. In comparison, nearly 1,300 operatively treated humeral fractures went on to nonunion in the present study. Despite similar humeral nonunion rates in the 2 studies, the differences in reported bisphosphonate risks are likely due to the different sample sizes as well as the use of conservative treatment in the study by Solomon et al. as compared with operative treatment in the present study.

We found no differences in nonunion risk when the cohorts were stratified by the timing of medication initiation. Animal models focusing on medication timing have demonstrated that the time of bisphosphonate initiation impacts callus size and biomechanical strength⁶. However, these factors are unlikely to be clinically relevant, which helps to explain the lack of findings with respect to the timing of medication initiation in the present study and previous human studies¹³. Admittedly, the present study only separated bisphosphonate administration timing in relation to the fracture and lacked the precision to separate out exact timing differences in post-fracture administration as is done in animal models. These findings should encourage providers to start or continue patients on bisphosphonates after a fracture.


The present study had a number of limitations. First, it was a retrospective observational study, and we cannot make any claims regarding causation because of uncontrollable or unknown confounders. Our convenience cohort of available patients within the Medicare database may not be representative of the entire Medicare population. Additionally, the patient cohort only included patients who were enrolled in Medicare Part D for pharmacy claims, which could bias the findings, if that cohort is substantially different than the general Medicare population. However, the demographic characteristics of our cohort are likely representative of the elderly population at risk for fragility fractures. Of note, the present study demonstrated a much higher overall rate of nonunion (9.4%) as compared with the rates reported in the general literature (1.9% to 4.9%)^{17,27}. This finding was likely due to the narrow inclusion criteria of the present study and elderly study population. Mills et al. noted a 2.5-times increase in nonunions in patients ≥ 75 years of age compared with younger patients²⁷, and the mean age of the nonunion group in the present study was 77.7 years. However, the findings reported by Mills et al. contradict those of another Medicare claims study in which patients ≥ 65 years of age were found to be less likely to have a nonunion²⁸. This emphasizes the fact that multiple factors beyond age impact nonunions. The present study included only operatively managed fractures of the humerus, radius, ulna, femur, and tibia while leaving out common fragility fractures such as distal radial and proximal humeral fractures. Such fragility fractures are commonly managed with an initial trial of nonoperative treatment. If nonoperative management fails and surgery is required, these fragility fractures would likely be coded as being treated with standard open reduction and internal fixation despite receiving delayed operative fixation. In order to

limit any potential confounding, we chose not to include such injuries in the analysis. Other limitations include the use of claims-based data, the fact that patients were not prospectively followed, and the lack of imaging studies for review. Thus, a nonunion claim or code must have been submitted to be included, and it is possible that there were unobserved nonunions filed under other claims or codes. Furthermore, it was assumed that a claim for a medication prescription meant that the patient was using the medication.

Conclusions

Our analysis of Medicare claims data showed that the rate of nonunion after operatively treated long-bone fractures in individuals ≥ 65 years of age was 9.4%. In this cohort, the use of a bisphosphonate or SERM/HRT was not associated with fracture union status at 1 year.

Appendix

 Supporting material provided by the authors is posted with the online version of this article as a data supplement at [jbjs.org \(http://links.lww.com/JBJS/H424\)](http://links.lww.com/JBJS/H424). ■

Tyler J. Thorne, BA¹
Lillia Steffenson, MD¹
Dillon C. O'Neill, MD¹
Lucas S. Marchand, MD¹
Brook I. Martin, PhD¹
Justin M. Haller, MD¹

¹Department of Orthopaedic Surgery, University of Utah, Salt Lake City, Utah

Email for corresponding author: justin.haller@hsc.utah.edu

References

- Brown JP, Adachi JD, Schemitsch E, Tarride JE, Brown V, Bell A, Reiner M, Oliveira T, Motsepe-Ditshego P, Burke N, Slatkowska L. Mortality in older adults following a fragility fracture: real-world retrospective matched-cohort study in Ontario. *BMC Musculoskelet Disord*. 2021 Jan 23;22(1):105.
- Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ 3rd. Population-based study of survival after osteoporotic fractures. *American Journal of Epidemiology*. 1993 May 1;137(9):1001-5.
- Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA*. 2009 Feb 4;301(5):513-21.
- Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2010;15(4):721-39.
- Murakami H, Takahashi N, Sasaki T, Udagawa N, Tanaka S, Nakamura I, Zhang D, Barbier A, Suda T. A possible mechanism of the specific action of bisphosphonates on osteoclasts: tiludronate preferentially affects polarized osteoclasts having ruffled borders. *Bone*. 1995 Aug;17(2):137-44.
- Amanat N, McDonald M, Godfrey C, Bilston L, Little D. Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. *J Bone Miner Res*. 2007 Jun;22(6):867-76.
- Goodship AE, Walker PC, McNally D, Chambers T, Green JR. Use of a bisphosphonate (pamidronate) to modulate fracture repair in ovine bone. *Ann Oncol*. 1994; 5(Suppl 7):S53-5.
- Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res*. 2010;15(4): 613-20.
- Aydođan NH, Özel İ, İltar S, Kara T, Özmeriç A, Alemdarogđlu KB. The effect of vitamin D and bisphosphonate on fracture healing: An experimental study. *Journal of Clinical Orthopaedics and Trauma*. 2016 Apr-Jun;7(2):90-4.
- Rozental TD, Vazquez MA, Chacko AT, Ayogu N, Boussein ML. Comparison of radiographic fracture healing in the distal radius for patients on and off bisphosphonate therapy. *The Journal of Hand Surgery*. 2009 Apr;34(4): 595-602.
- Solomon DH, Hochberg MC, Mogun H, Schneeweiss S. The relation between bisphosphonate use and non-union of fractures of the humerus in older adults. *Osteoporos Int*. 2009 Jun;20(6):895-901.
- Li Y, Zhao WB, Wang DL, He Q, Li Q, Pei FX, Liu L. Treatment of osteoporotic intertrochanteric fractures by zoledronic acid injection combined with proximal femoral nail anti-rotation. *Chinese Journal of Traumatology*. 2016 Oct 1;19(5):259-63.
- Kim TY, Ha YC, Kang BJ, Lee YK, Koo KH. Does early administration of bisphosphonate affect fracture healing in patients with intertrochanteric fractures? *The Journal of Bone and Joint Surgery*. British volume. 2012 Jul;94-B(7):956-60.
- Hayer PS, Deane AKS, Agrawal A, Maheshwari R, Juyal A. Effect of zoledronic acid on fracture healing in osteoporotic patients with intertrochanteric fractures. *International Journal of Applied and Basic Medical Research*. 2017 Jan-Mar;7(1): 48-52.
- Seo JB, Yoo JS, Ryu JW, Yu KW. Influence of Early Bisphosphonate Administration for Fracture Healing in Patients with Osteoporotic Proximal Humerus Fractures. *Clin Orthop Surg*. 2016 Dec;8(4):437-43.
- Gulcu A, Sargin S, Konya MN, Aslan A. Effects of Zoledronic Acid Treatment on Fracture Healing, Morbidity and Mortality in Elderly Patients with Osteoporotic Hip Fractures. *Strategies in Trauma and Limb Reconstruction*. 2020;14(3): 126-31.
- Zura R, Xiong Z, Einhorn T, Watson JT, Ostrum RF, Prayson MJ, Della Rocca GJ, Mehta S, McKinley T, Wang Z, Steen RG. Epidemiology of Fracture Nonunion in 18 Human Bones. *JAMA Surg*. 2016 Nov 16;151(11):e162775.
- Gorter EA, Reinders CR, Krijnen P, Appelman-Dijkstra NM, Schipper IB. The effect of osteoporosis and its treatment on fracture healing a systematic review of animal and clinical studies. *Bone Reports*. 2021 Aug 16;15: 101117.
- Gómez-de-Mariscal E, Guerrero V, Sneider A, Jayatilaka H, Phillip JM, Wirtz D, Muñoz-Barrutia A. Use of the p-values as a size-dependent function to address practical differences when analyzing large datasets. *Sci Rep*. 2021 Oct 22;11(1): 20942.
- Conley RB, Adib G, Adler RA, Åkesson KE, Alexander IM, Amenta KC, Blank RD, Brox WT, Carmody EE, Chapman-Novakofski K, Clarke BL, Cody KM, Cooper C, Crandall CJ, Dirschl DR, Eagen TJ, Elderkin AL, Fujita M, Greenspan SL, Halbout P, Hochberg MC, Javaid M, Jeray KJ, Kearns AE, King T, Koinis TF, Koontz JS, Kuźma M, Lindsey C, Lorentzon M, Lyritis GP, Michaud LB, Miciano A, Morin SN, Mujahid N, Napoli N, Olinginski TP, Puzas JE, Rizou S, Rosen CJ, Saag K, Thompson E, Tosi LL, Tracer H, Khosla S, Kiel DP. Secondary Fracture Prevention: Consensus Clinical Recommendations from a Multistakeholder Coalition. *J Bone Miner Res*. 2020 Jan;35(1):36-52.
- Khosla S, Shane E. A Crisis in the Treatment of Osteoporosis. *J Bone Miner Res*. 2016 Aug;31(8):1485-7.
- Ensrud KE, Black DM, Palermo L, Bauer DC, Barrett-Connor E, Quandt SA, Thompson DE, Karpf DB. Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. *Archives of Internal Medicine*. 1997 Dec 8-22;157(22):2617-24.
- Xie J, Tong A, Kim SC. Patterns of bisphosphonates utilization in patients under age 45 in a large cohort of commercial insurance beneficiaries in the United States. *PLoS One*. 2015 Jan 22;10(1):e0115091.
- Zura R, Mehta S, Della Rocca GJ, Steen RG. Biological Risk Factors for Non-union of Bone Fracture. *JBJS Rev*. 2016 Jan 5;4(1):e5.
- Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S; Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture. *N Engl J Med*. 2007 Nov 1;357(18):1799-809.
- Spiro AS, Khadem S, Jeschke A, Marshall RP, Pogoda P, Ignatius A, Amling M, Beil FT. The SERM raloxifene improves diaphyseal fracture healing in mice. *J Bone Miner Metab*. 2013 Nov;31(6):629-36.
- Mills LA, Aitken SA, Simpson AHRW. The risk of non-union per fracture: current myths and revised figures from a population of over 4 million adults. *Acta Orthopaedica*. 2017 Aug;88(4):434-9.
- Zura R, Braid-Forbes MJ, Jeray K, Mehta S, Einhorn TA, Watson JT, Della Rocca GJ, Forbes K, Steen RG. Bone fracture nonunion rate decreases with increasing age: A prospective inception cohort study. *Bone*. 2017 Feb;95: 26-32.