Journal of Bone and Mineral Research, 2024, 1–9
https://doi.org/10.1093/jbmr/zjae079
Advance access publication: May 16, 2024
Research Article

Comparative effectiveness of denosumab vs alendronate among postmenopausal women with osteoporosis

Jeffrey R. Curtis[1,2], Tarun Arora[2], Ye Liu[1], Tzu-Chieh Lin[3], Leslie Spangler[3], Vanessa C. Brunetti[4], Robert Kees Stad[5], Michele McDermott[5], Brian D. Bradbury[3], Min Kim[3,*]

[1]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL, 35233, United States
[2]Foundation for Advancing Science, Technology, Education and Research, Birmingham, AL, 35244, United States
[3]Amgen Inc., Center for Observational Research, Thousand Oaks, CA, 91320, United States
[4]Amgen Ltd., Center for Observational Research, Uxbridge, UB8 1DH, United Kingdom
[5]Amgen Inc., Global Medical, Thousand Oaks, CA, 91320, United States
* Corresponding author: Min Kim, Amgen Inc., Center for Observational Research, 1 Amgen Center Dr, Thousand Oaks, CA 91320, United States (mkim08@amgen.com).

Abstract

Although clinical trials have shown that denosumab significantly increases bone mineral density at key skeletal sites more than oral bisphosphonates, evidence is lacking from head-to-head randomized trials evaluating fracture outcomes. This retrospective cohort study uses administrative claims data from Medicare fee-for service beneficiaries to evaluate the comparative effectiveness of denosumab vs alendronate in reducing fracture risk among women with PMO in the US. Women with PMO ≥ 66 yr of age with no prior history of osteoporosis treatment, who initiated denosumab ($n = 89\,115$) or alendronate ($n = 389\,536$) from 2012 to 2018, were followed from treatment initiation until the first of a specific fracture outcome, treatment discontinuation or switch, end of study (December 31, 2019), or other censoring criteria. A doubly robust inverse-probability of treatment and censoring weighted function was used to estimate the risk ratio associated with the use of denosumab compared with alendronate for hip, nonvertebral (NV; includes hip, humerus, pelvis, radius/ulna, other femur), non-hip nonvertebral (NHNV), hospitalized vertebral (HV), and major osteoporotic (MOP; consisting of NV and HV) fractures. Overall, denosumab reduced the risk of MOP by 39%, hip by 36%, NV by 43%, NHNV by 50%, and HV fractures by 30% compared with alendronate. Denosumab reduced the risk of MOP fractures by 9% at year 1, 12% at year 2, 18% at year 3, and 31% at year 5. An increase in the magnitude of fracture risk reduction with increasing duration of exposure was also observed for other NV fracture outcomes. In this cohort of almost half-a-million treatment-naive women with PMO, we observed clinically significant reductions in the risk of MOP, hip, NV, NHNV, and HV fractures for patients on denosumab compared with alendronate. Patients who remained on denosumab for longer periods of time experienced greater reductions in fracture risk.

Keywords: osteoporosis, fracture prevention, antiresorptives, general population studies, statistical methods

Lay Summary

Osteoporosis-related fractures can have a significant impact on the health and quality of life of women with postmenopausal osteoporosis, as well as pose a significant burden to society. Although clinical trials have shown that denosumab is more effective at increasing bone mineral density compared with alendronate, there is a lack of evidence evaluating the fracture risk between these 2 commonly used osteoporosis therapies. In this study using Medicare claims data for almost 500 000 women with postmenopausal osteoporosis with no prior history of osteoporosis medication use, we compared the risk of fracture—an important outcome to patients and health care providers—between denosumab and alendronate. Advanced analytic methods were implemented to ensure the study results were valid and were not unduly influenced by biases common in observational studies.

We observed clinically meaningful reductions (from 30% up to 50%) in the risk of hip, nonvertebral, non-hip nonvertebral, hospitalized vertebral, and major osteoporotic fractures for patients treated with denosumab compared with alendronate. Patients who remained on denosumab for longer periods of time experienced greater reductions in fracture risk than those who remained on alendronate.

Introduction

Postmenopausal osteoporosis (PMO) affects millions of women worldwide. The prevalence of PMO in women aged ≥50 yr has been estimated at 15.4% in the US and 22.1% in the EU.[1,2] Osteoporosis can greatly affect quality of life due to increased risk of fractures and subsequent effect on mobility, ambulation, and self-care.[3-5] A recent systematic review, including data from 36 countries, reported a 22.8% median 1-yr mortality rate after hip fracture.[6] Osteoporosis represents a significant economic burden due to complications following fractures,[7] with one study reporting an annual facility-related hospital cost of $5.1 billion USD for fracture care in women aged ≥55 yr in the US, which is a greater annual cost than myocardial infarction, stroke, or breast cancer.[8]

Management of osteoporosis includes non-pharmacological (eg, diet, exercise, calcium, and vitamin D supplementation)

Received: December 7, 2023. **Revised:** April 23, 2024. **Accepted:** May 15, 2024

and pharmacological therapies. According to current US treatment guidelines, oral bisphosphonates (BP; alendronate, ibandronate, and risedronate), IV BP (ibandronate and zoledronic acid), RANK-L inhibitors (denosumab), and anabolics (abaloparatide, romosozumab, and teriparatide) are all appropriate choices for initial therapy among women with PMO at high risk for fracture.[9-11]

Randomized clinical trials (RCTs) have demonstrated that denosumab is more effective in increasing bone mineral density (BMD) compared with oral and IV BP over 12 mo of follow-up.[12,13] However, the head-to-head efficacy of denosumab vs BP on fracture outcomes—the clinical endpoint of greatest interest to healthcare providers—has not been evaluated in large-scale RCTs.[14] A meta-analysis comprised of RCTs found that greater improvements in BMD translated to more fracture reduction within the treatment group, though these findings may not be applicable to individual patients and have not been studied in the clinical practice setting.[15] Moreover, results from RCTs may not be generalizable to patients receiving care in real-world clinical practice because patients included in RCTs are inherently different from patients seen in routine clinical care.[16]

Real-world data can be used to answer questions that are difficult to address through RCTs, though conducting a real-world comparative effectiveness study is challenging, as confounding by indication is a common concern. Women prescribed denosumab are more likely to be older, have more comorbidities, and are at greater risk for fracture compared with those taking oral BP.[17,18] The few cohort studies examining the comparative effectiveness of denosumab vs alendronate—the most widely used oral BP[19]—have reported inconsistent results, potentially due to insufficient sample size and the inability to account for imbalances in important fracture-related risk factors that were either unavailable or inadequately captured (ie, unmeasured confounding) between patients receiving both medicines.[20-22] To address this evidence gap, the objective of our study was to assess the comparative effectiveness of denosumab vs alendronate on the risk of osteoporotic fractures in a large, representative cohort of postmenopausal women in the US.

Materials and methods

Study design

We conducted an active comparator, new user, retrospective cohort study[23] using the US Centers for Medicare and Medicaid Services' Chronic Condition Warehouse database, which includes 100% of Medicare beneficiaries in Fee-for-Service plans.[24] This was the second part of a 2-phase study; in the first phase, we assessed the comparability of denosumab and alendronate users using negative control outcomes to evaluate the potential impact of unmeasured confounding. We found sufficient balance in measured and unmeasured confounders between both treatment groups.[25] The associated protocols for both studies received institutional approvals. This study was registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS49101).

Study population

Administrative claims were used to identify our study population of women with PMO who were newly treated with denosumab or alendronate between January 1, 2012 and December 31, 2018. Eligible patients had no prior history of osteoporosis treatment (including alendronate, risedronate, oral and IV ibandronate, zoledronic acid, denosumab, abaloparatide, teriparatide, calcitonin, and raloxifene) using all available prior data starting from January 1, 2006, and at least 455 d of continuous health plan enrollment preceding the date of treatment initiation, and were 66 yr or older (including the required 455-d baseline period) on the date of treatment initiation (Figure S1). Patients were excluded if they had a history of Paget's disease of bone, cancer (excluding non-melanoma skin cancer), chemotherapy, hormonal therapy for cancer, or radiation therapy during the baseline period.

Follow-up

Adopting an as-treated approach, patients were followed 1 d after treatment initiation until the earliest of either a specific fracture outcome (eg, when evaluating hip fracture as an outcome, patients were not censored for non-hip fractures), discontinuation (allowing for a 60-d grace period after the end of the last prescription supply for alendronate and the indicated 182-d dosing interval for denosumab), switch to a different osteoporosis treatment, diagnosis of Paget's disease or cancer (including any form of cancer treatment), end of Medicare enrollment, death, or end of available data (December 31, 2019).

Exposure assessment

Exposure to denosumab—60 mg administered via subcutaneous injection for the treatment of PMO—was assessed using specific National Drug Codes and Healthcare Common Procedure Coding System (HCPCS). Because HCPCS codes that identify denosumab (C9272, J0897) do not differentiate between indications for women with PMO (Prolia®) from patients with bone metastases (XGEVA®), our study population excluded any women with a prior cancer diagnosis or who received any form of cancer therapy during the baseline period. To further ensure that we were capturing women initiating denosumab for the treatment of PMO, we also employed algorithms that incorporate diagnosis codes, medication dosage, and the total cost or cost per unit of the drug (Methods S1). Exposure to alendronate (and oral BP) was captured solely using National Drug Codes through Part D prescription claims.

Outcome assessment

Hip, nonvertebral (NV; including pelvis, humerus, radius/ulna, hip, and other femur fractures), hospitalized vertebral (HV), non-hip nonvertebral (NHNV), and major osteoporotic (MOP; consisting of NV and HV) fractures were identified using ICD-9/10 and HCPCS codes (Table S1). Hip, NV, and NHNV fractures were identified using one inpatient or one outpatient diagnosis code combined with an HCPCS or ICD-9/10 fracture repair procedure code. Hospitalized vertebral fractures were identified using one inpatient diagnosis code because of the concern regarding misclassifying pre-existing vertebral fractures as incident outcomes during follow-up (Methods S1). These algorithms were validated in a large National Institutes of Health-funded cohort linking Medicare claims data to adjudicated fracture medical records (eg, X-rays, magnetic resonance imaging, computed tomography scans) and were shown to have positive predictive values ranging from 90.9% to 98.4%.[26] Only the first fracture that

occurred (of the specific outcome of interest) during follow-up was analyzed. Patients were not censored for fracture outcomes that occurred at different sites.

Baseline patient characteristics

Based on subject-matter expertise, a total of 118 different patient characteristics were selected a priori that represent potential confounders (Tables S2 and S3). Covariates, including demographics, comorbidities, comedications, and healthcare service utilization, were captured during the baseline period; the history of fractures and prior treatment were assessed using all available data prior to treatment initiation.

In order to examine the potential imbalance of unmeasured confounders, such as BMD between the treatment groups in a similar patient population, we used a separate database linking Medicare claims to a large national electronic health record data system (PCORnet®) to calculate baseline Fracture Risk Assessment Tool (FRAX®) scores, which predict the 10-yr probability of hip and MOP fractures (Methods S1),[27,28] among women with PMO newly initiating (no prior history of) denosumab ($n = 1088$) and oral BP ($n = 1662$) from 2019 to 2020.

Statistical analyses

We used multivariate logistic regression with treatment as the outcome to calculate propensity scores, which estimate the conditional probability of receiving either denosumab or alendronate. Multivariate Cox proportional hazards models with censoring events as the outcome were used to estimate the conditional probability of being censored between treatment groups. Inverse probability of treatment weights (IPTWs) and inverse probability of censoring weights (IPCW) were used to adjust for confounding at treatment initiation and account for potential bias from informative censoring during follow-up in the fracture outcome models, respectively.[29,30] Both IPTW and propensity score matching perform similarly to minimize bias due to confounding.[31] As opposed to propensity score matching, IPTW avoids exclusion of unmatched patients from the cohort, allowing for greater retention of the original study population. To remove outliers, we trimmed 0.5% of patients at each end of the IPTW distribution. Balance before and after weighting was assessed using standardized mean differences (SMDs), where an SMD >0.1 indicated a clinically meaningful difference between the 2 treatment groups.[32]

The cumulative incidence of each outcome was estimated using augmented inverse probability of treatment and censoring-weighted estimation functions.[33] The estimator is doubly robust; if either the treatment/censoring model or the outcome model is properly specified, then the estimate is consistent. The risk ratios (RRs) and risk differences of each outcome, along with 95% CIs, were estimated at 1, 2, 3, 5, and >5 yr for the denosumab and alendronate cohorts to mirror time points reported by previously published RCTs and estimate the treatment effect over an extended follow-up. Prior to initiating comparative analyses, we had 80% statistical power to detect a RR <0.88 or RR >1.13 for the MOP fracture outcome.

The primary analyses were repeated among patients using any oral BP (alendronate, ibandronate, or risedronate) as the comparator; secondary analyses were conducted for all outcomes and treatment comparisons within the following subgroups: women (1) 80 yr and older, (2) with history of any fracture, and (3) with no history of fracture. Follow-up was limited to 5 yr for these subgroup analyses, given smaller sample size and patient attrition over time.

Sensitivity analyses to assess the robustness of our findings included: (1) an intention-to-treat (ITT) analysis, wherein patients were not censored for treatment switching/discontinuation, to evaluate the potential magnitude of selection bias; (2) a broader (ie, sensitive) definition of vertebral fracture including those identified using an inpatient diagnostic code or an outpatient diagnostic code combined with an associated fracture repair or spine imaging code; and (3) quantitative bias analysis to assess the extent of residual confounding that would be required to explain the observed treatment effects (Methods S1).

Results

Study population and baseline characteristics

A total of 90 805 and 392 682 treatment-naïve patients who received denosumab and alendronate, respectively, were included in this study (Figure S2). Mean age at baseline was 75.5 and 74.6 yr in the denosumab and alendronate groups, respectively (Table 1). Before weighting, the majority of baseline characteristics were well balanced (105 of 118; SMD ≤ 0.1) between the treatment groups. Covariates where there were modest imbalances included age, race/ethnicity, calendar year of index drug initiation, history of vertebral fracture, systemic corticosteroid use, proton pump inhibitor use, chronic kidney disease stages 3–5, vitamin D deficiency, and number of outpatient visits (Table 1, Table S2). These differences suggested that the denosumab cohort was at higher fracture risk compared with the alendronate cohort.

After weighting and trimming, all covariates were balanced between denosumab ($n = 89\,115$) and alendronate ($n = 389\,536$) users. Histograms for the propensity score distributions showed good overlap, indicating comparability between the IPTW-weighted groups (Figure S3). The distribution and balance of covariates were similar between denosumab and oral BP users (Table S3).

Mean follow-up (allowing for censoring at the time of treatment discontinuation or switch) was longer for denosumab (1.5 yr) compared with alendronate (1.1 yr) across all fracture outcome analyses (Table S4).

Comparative fracture outcomes analyses

Patients newly treated with denosumab vs alendronate experienced a 39% decrease in the risk of MOP fracture (RR, 0.61; 95% CI, 0.48–0.74), 36% decrease in the risk of hip fracture (RR, 0.64; 95% CI, 0.39–0.90), 43% decrease in the risk of NV fracture (RR, 0.57; 95% CI, 0.42–0.71), 50% decrease in the risk of NHNV fracture (RR, 0.50; 95% CI, 0.35–0.64), and 30% decrease in the risk of HV fracture (RR, 0.70; 95% CI, 0.40–1.01) over the entire follow-up period (Figure 1A–E). The magnitude of MOP fracture risk reduction increased over time: patients experienced 9% (RR, 0.91; 95% CI, 0.85–0.97), 12% (RR, 0.88; 95% CI, 0.83–0.93), 18% (RR, 0.82; 95% CI, 0.77–0.87), and 31% (RR, 0.69; 95% CI, 0.62–0.76) reductions in MOP fracture risk over 1, 2, 3, and 5 yr of follow-up, respectively (Figure 1A). Similar reductions in risk over time were observed for hip, NV, and NHNV fractures (Figure 1B–D).

Table 1. Selected baseline patient characteristics of new users of denosumab and alendronate before and after weighting with inverse probability of treatment weights (IPTW).

Characteristic	Before IPTW			After IPTW			
	Alendronate $n = 392\,682$ n (%) or mean (SD)	Denosumab $n = 90\,805$ n (%) or mean (SD)	SMD	Alendronate $n = 478\,651$ n (%) or mean (SD)	Denosumab $n = 478\,651$ n (%) or mean (SD)	SMD	
Age at index date, continuous, mean (SD)	74.64 (6.81)	75.47 (7.34)	−0.12	74.80 (6.87)	74.90 (7.20)	−0.01	
Age at index date, categorical							
65–69	113 097 (28.80)	24 738 (27.24)	0.09	134 365 (28.07)	143 310 (29.94)	0.05	
70–74	108 505 (27.63)	22 605 (24.89)		131 025 (27.37)	122 629 (25.62)		
75+	171 080 (43.57)	43 462 (47.86)		213 261 (44.55)	212 711 (44.44)		
Race/ethnicity							
Non-white	66 993 (17.06)	8958 (9.87)	0.21	73 796 (15.42)	73 135 (15.28)	<0.01	
White	325 689 (82.94)	81 847 (90.13)		404 855 (84.58)	405 516 (84.72)		
Geographic region							
Midwest	99 529 (25.35)	22 429 (24.70)	0.10	121 288 (25.34)	122 090 (25.51)	0.01	
Northeast	60 541 (15.42)	14 335 (15.79)		74 040 (15.47)	72 757 (15.20)		
South	149 860 (38.16)	37 943 (41.79)		185 937 (38.85)	185 494 (38.75)		
West	82 752 (21.07)	16 098 (17.73)		97 386 (20.35)	98 311 (20.54)		
Calendar year of drug index date							
2012	44 280 (11.28)	5762 (6.35)	0.22	48 403 (10.11)	47 763 (9.98)	0.01	
2013	46 969 (11.96)	7863 (8.66)		54 252 (11.33)	54 417 (11.37)		
2014	50 256 (12.80)	11 723 (12.91)		61 617 (12.87)	61 183 (12.78)		
2015	55 741 (14.19)	14 059 (15.48)		69 319 (14.48)	69 355 (14.49)		
2016	58 884 (15.00)	15 133 (16.67)		73 525 (15.36)	73 619 (15.38)		
2017	66 265 (16.87)	17 129 (18.86)		82 836 (17.31)	83 095 (17.36)		
2018	70 287 (17.90)	19 136 (21.07)		88 700 (18.53)	89 219 (18.64)		
History of fracture							
Closed hip fracture in baseline	8750 (2.23)	2700 (2.97)	0.05	11 392 (2.38)	12 573 (2.63)	0.02	
Vertebral fracture in baseline	21 795 (5.55)	8700 (9.58)	0.15	29 749 (6.22)	30 623 (6.40)	0.01	
Non-hip nonvertebral fracture in baseline	11 979 (3.05)	3775 (4.16)	0.06	15 664 (3.27)	16 586 (3.47)	0.01	
Closed hip fracture, remote	7228 (1.84)	2637 (2.90)	0.07	9662 (2.02)	10 094 (2.11)	0.01	
Vertebral fracture, remote	11 714 (2.98)	5053 (5.56)	0.13	16 204 (3.39)	16 765 (3.50)	0.01	
Number of physician office visits per patient during baseline period, mean (SD)	13.08 (10.27)		16.29 (11.67)	−0.29	13.61 (10.63)	13.84 (10.04)	−0.02
Comorbidities							
Vitamin D deficiency	71 709 (18.26)		22 971 (25.30)	0.17	93 190 (19.47)	93 186 (19.47)	<0.01
Severe renal impairment	40 645 (10.35)		13 507 (14.87)	0.14	52 996 (11.07)	54 719 (11.43)	0.01
Stage 3–5 chronic kidney disease in baseline	19 532 (4.97)		7581 (8.35)	0.14	26 270 (5.49)	26 849 (5.61)	0.01
Arrhythmia	44 341 (11.29)		13 146 (14.48)	0.10	56 750 (11.86)	58 840 (12.29)	0.01
Medication use							
Proton pump inhibitor	107 736 (27.44)		30 348 (33.42)	0.13	136 290 (28.47)	137 790 (28.79)	0.01
Corticosteroid (oral or injectable)	174 841 (44.52)		48 198 (53.08)	0.17	220 623 (46.09)	221 656 (46.31)	<0.01

Unless otherwise specified, all patient characteristics were evaluated during the 455-d baseline period prior to the index date. Remote fractures were assessed prior to the baseline period using all available patient history. Values are n (%) except where mean (SD) is indicated in the variable label. SD, standard deviation; SMD, standardized mean difference.

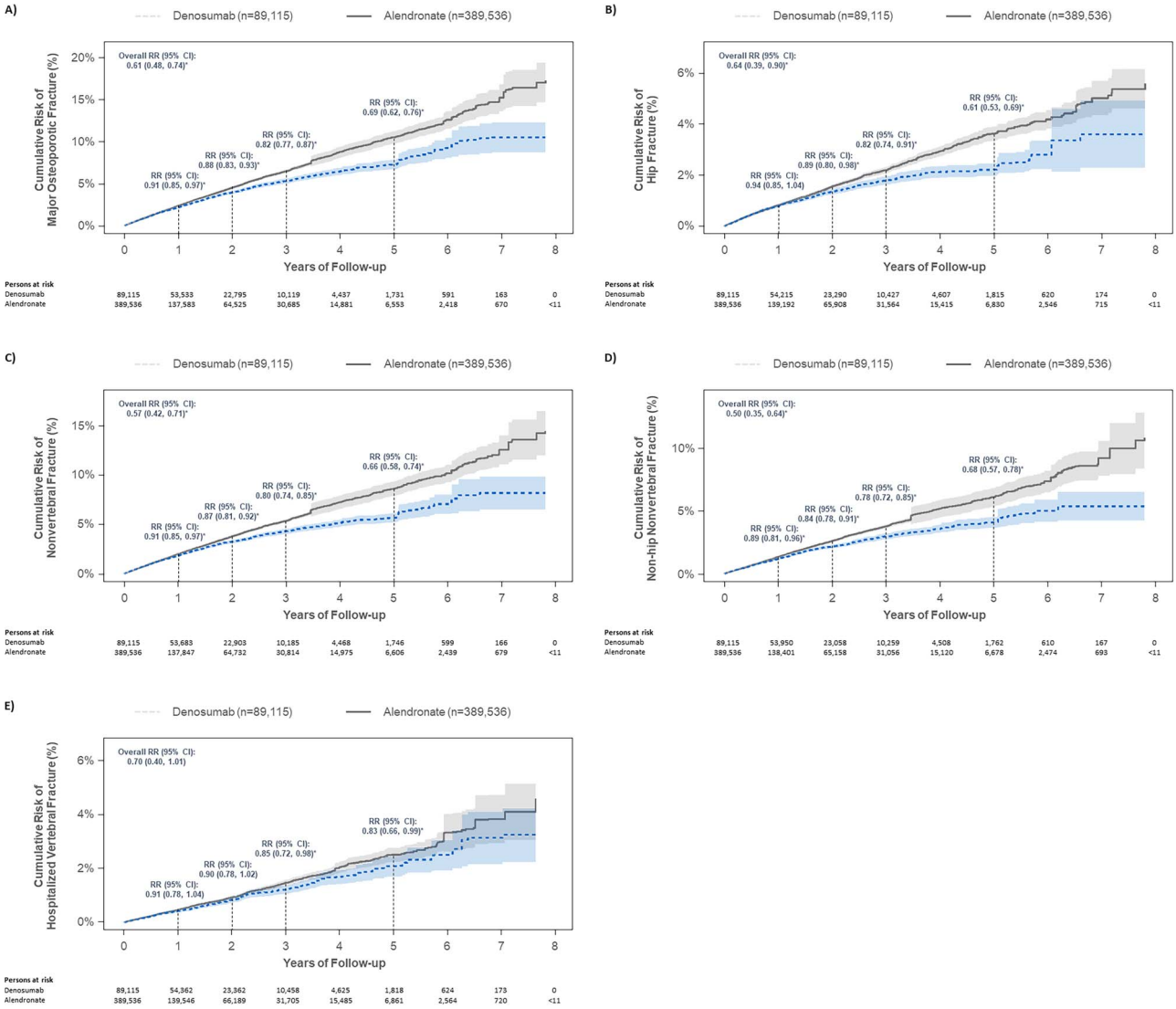

Figure 1. Cumulative incidence of fracture outcomes: (A) major osteoporotic (MOP) fracture; (B) hip fracture; (C) nonvertebral (NV) fracture; (D) non-hip NV (NHNV) fracture; (E) hospitalized vertebral (HV) fracture comparing patients initiating denosumab vs alendronate. *P <.05. CI, confidence interval; RR, risk ratio.

The results comparing denosumab with oral BP users were consistent with the primary analysis (Figure S4A–E); alendronate comprised a majority (72%) of the oral BP use. The results across subgroups of patients 80 yr and older, and those with and without a history of fracture were also consistent with the overall findings over a 5-yr follow-up (Figure 2, Figure S5).

Sensitivity analyses

Findings remained consistent, though effect estimates moved closer to the null, using an ITT approach (Figure 3) and with a sensitive definition of vertebral fracture (Figure 4). In a separate population of Medicare patients with available linkage to electronic health record data, the mean 10-yr probability for MOP and hip fracture was 25.0% and 12.5% among denosumab users and 20.5% and 9.1% among oral BP users, respectively (Table S5). Based on the distribution of FRAX scores between treatment groups, and the positive association between FRAX scores and fracture risk, quantitative bias analyses revealed that the bias-adjusted effects of denosumab vs alendronate on fracture were at least equal to or larger in magnitude compared with the primary results for MOP (RR ≤0.60) and hip (RR ≤0.64) fracture (Table S6).

Discussion

In this study of nearly 500 000 older women with PMO in the US, we found that women using denosumab as compared with alendronate experienced a 30% to 50% reduction in the risk of MOP, hip, NV, NHNV, and HV fractures over an 8-yr time horizon. Similar reductions in fracture risk were observed in subgroups of women 80 yr and older, and those with and without a history of fracture. The magnitude of the fracture risk reduction increased with longer duration of exposure in all primary, secondary, and subgroup analyses except for HV fractures. We found nearly identical results when comparing against oral BPs as a class.

Complementary to the original Phase 3 RCT (FREEDOM), which was used as the basis for regulatory approval across the globe and demonstrated that denosumab reduces the risk

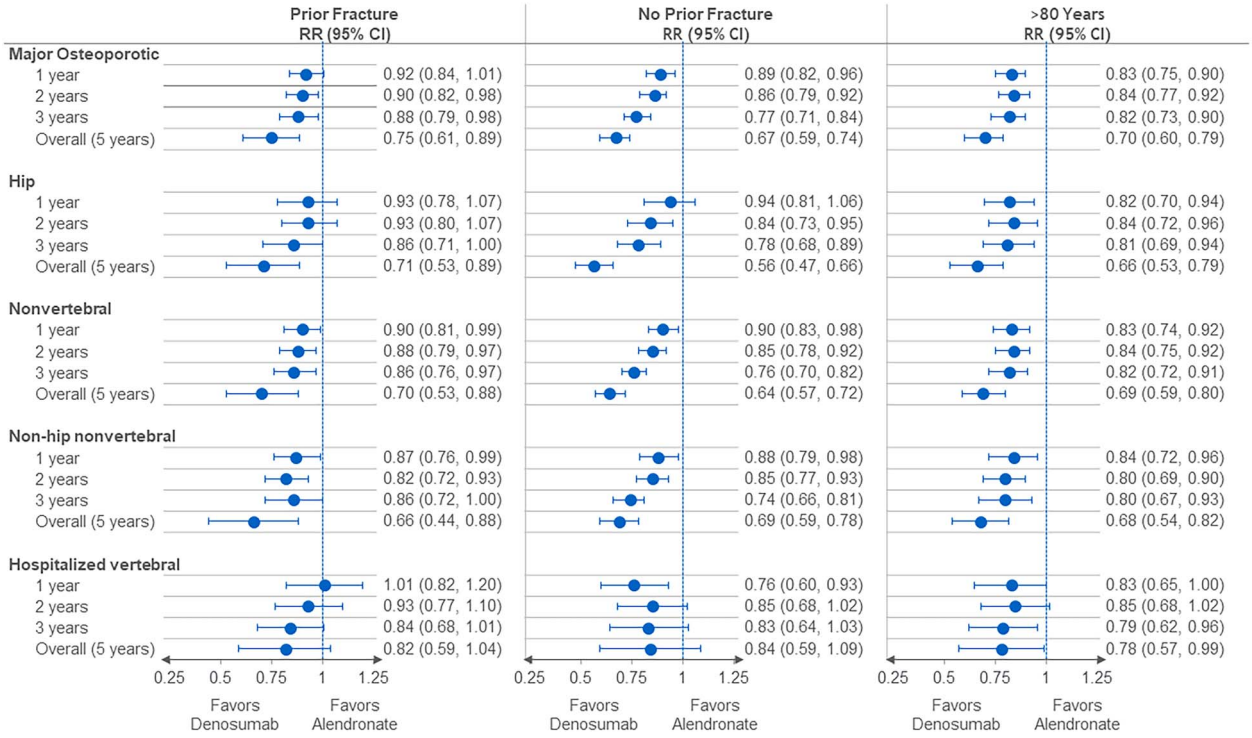

Figure 2. Effectiveness of denosumab compared with alendronate on the risk of major osteoporotic, hip, nonvertebral, non-hip nonvertebral, and hospitalized vertebral fractures among subgroups of patients with and without a history of fracture, and 80 yr and older. *P <.05. CI, confidence RR, risk ratio.

of hip fracture by 40% at 3 yr compared with placebo,[34] we observed a plausible 18% reduction in hip fracture at 3 yr in the current study. The cumulative incidence of hip fracture in the denosumab arm of FREEDOM was 0.7% at 3 yr vs 1.8% in this analysis and baseline FRAX scores for MOP fractures among FREEDOM patients were lower compared with a Medicare patient population similar to the one used in this study (15.6% vs 25.0%), perhaps reflecting the higher risk patient population in this real-world cohort. The pattern of continuous, long-term increases in fracture reduction observed in our study is consistent with the higher rates of NV fractures observed among denosumab users during years 1 to 3 of FREEDOM as compared with years 4 to 10 of the open-label extension of the trial,[35] and the continuous BMD gains observed among denosumab users throughout the 10-yr FREEDOM and open-label extension trials.[36]

Previous non-interventional studies evaluating the potential fracture reduction benefit comparing denosumab and oral BP have produced conflicting results, which may be due in part to residual confounding. A Danish study using national registry data found no meaningful differences in the 3-yr risk of hip fracture and any fracture (hazard ratio [HR] ~1.05 and HR ~0.92, respectively)[20] and similar results were observed in a separate Danish study limited to patients with type 2 diabetes.[37] Because denosumab typically is used as second-line treatment in Denmark (following alendronate), patients treated with denosumab are likely to have more advanced disease (ie, more likely to fracture). There was no adjustment for BMD—an important determinant of fracture risk and prescribing choice—in either of these studies. In contrast, a smaller Swiss study that adjusted for BMD found meaningful reductions in the risk of any fracture (HR, ~0.54; 95% CI, 0.41–0.69), vertebral (HR, ~0.51, 95% CI; 0.39–0.68), and NV (HR, ~0.54; 95% CI, 0.44–0.65), but not hip fractures (HR, ~0.85; 95% CI, 0.43–1.67) with the use of denosumab vs alendronate.[22]

The present study should be evaluated while considering the following limitations. First, only clinical vertebral fractures were identified in this study, missing out on the vast majority of vertebral fractures that do not come to clinical attention.[38,39] Without access to successive patient radiographs, it is not possible to pinpoint the time when a new vertebral fracture occurred. As vertebral fractures are often asymptomatic or present as back pain, significant delays between the fracture episode and an eventual diagnosis can result in misclassification where prevalent fractures occurring prior to treatment initiation are captured as incident events, which is not as relevant for other fracture endpoints. Consequently, we identified vertebral fractures using validated algorithms with inpatient diagnoses only (positive predictive value = 98.4%), identifying clinically severe fractures types and intentionally favoring specificity over sensitivity.[40] Second, we cannot rule out the possibility of residual confounding due to missing information on BMD, a key confounder. We did, however, calculate FRAX scores and found a higher 10-yr probability of fracture in the denosumab cohort prior to treatment initiation. We then used quantitative bias analysis to re-estimate the RR of fracture for denosumab vs alendronate users and observed results that were consistent with, if not more pronounced than, our primary analysis (suggesting an even greater benefit), indicating that our findings are robust to unmeasured confounding.[28] In a separate study, we utilized negative control outcomes to assess whether first-line alendronate users were a suitable comparator to first-line denosumab users in a similar Medicare patient population and found that there would be minimal residual confounding

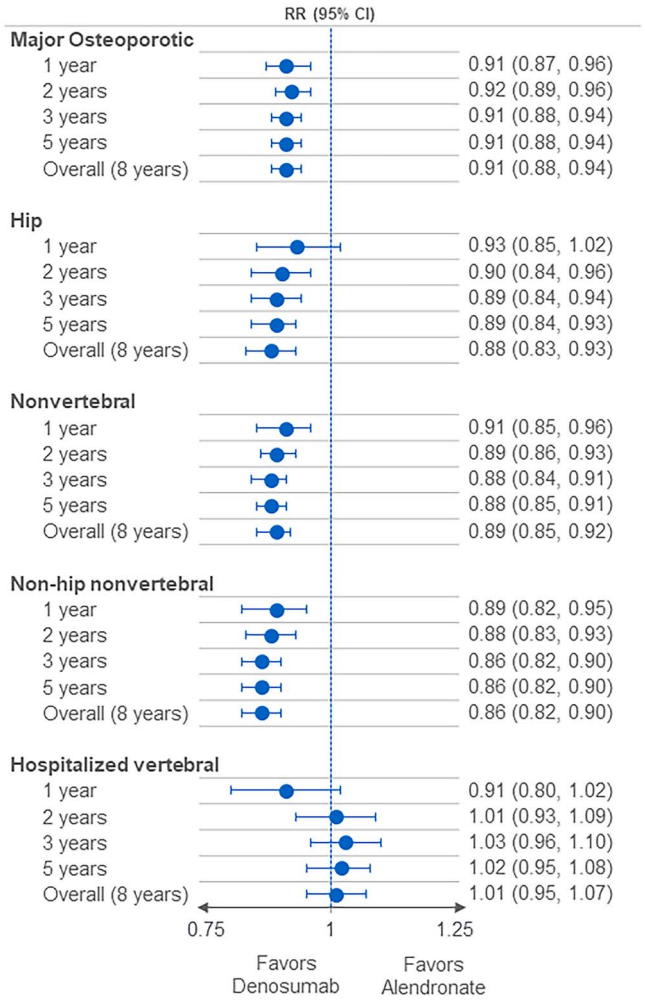

Figure 3. Effectiveness of denosumab compared with alendronate on the risk of fracture outcomes using anintention-to-treat analysis.

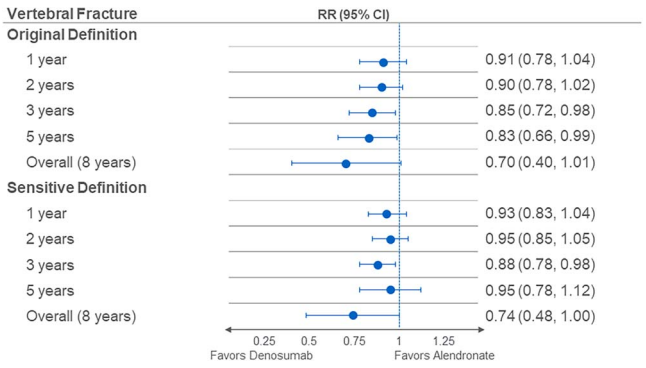

Figure 4. Effectiveness of denosumab compared with alendronate using a sensitive definition for vertebral fracture identified using inpatient diagnoses or outpatient diagnoses combined with procedure code (eg, vertebroplasty and kyphoplasty). CI, confidence RR, risk ratio.

between the 2 groups.[25] Lastly, we observed high treatment discontinuation rates in both groups over the 8-yr follow-up period, though patients remained on denosumab for 7 mo longer on average. We addressed the potential selection bias introduced by treatment discontinuation using IPCW, which reweights the contribution of patients remaining in the cohort over time during the follow-up period (based on their baseline clinical characteristics) to match the population at treatment initiation. This approach helps to address the bias that can be introduced when patients who discontinue treatment do so for reasons related to the fracture outcome. In the ITT analyses, we observed a consistent, though smaller, magnitude of fracture risk reduction likely caused by high levels of exposure misclassification, where patients were followed after they discontinued or switched therapy.

Conclusion

In the largest comparative effectiveness study conducted to date, we found clinically meaningful reductions in the risk of fracture for patients treated with denosumab vs alendronate in a representative cohort of almost half a million treatment-naïve women with PMO in the US. Over a nearly 8-yr follow-up period, we found greater reductions in the risk of fracture with longer duration of use, which provides complimentary evidence to the results from the original registrational clinical trial and its long-term extension. As fractures are associated with significant morbidity and mortality,[41-43] this study provides clinically meaningful evidence, comparing available osteoporosis medicines to help guide physicians, patients, and policymakers, and may translate into significant improvement in the quality of life of women with PMO.

Acknowledgments

Shravanthi Chidambaram, PhD, of BioScience Communications, New York, NY, provided medical writing support on behalf of Amgen Inc.

Author contributions

Jeffrey R. Curtis (conceptualization, investigation, methodology, writing—original draft, writing—review & editing), Tarun Arora (formal analysis, investigation, methodology, writing—review & editing), Ye Liu (formal analysis, investigation, methodology, writing—review & editing), Tzu-Chieh Lin (conceptualization, Methodology, writing—review & editing), Leslie Spangler (writing—review & editing), Vanessa C. Brunetti (writing—original draft, writing—review & editing), Robert Kees Stad (writing—review & editing), Michele McDermott (writing—review & editing), Brian D. Bradbury (conceptualization, methodology, writing—review & editing), and Min Kim (conceptualization, methodology, writing—original draft, writing—review & editing)

Supplementary material

Supplementary material is available at *Journal of Bone and Mineral Research* online.

Funding

This study was funded by Amgen Inc.

Conflicts of interest

J.R.C. has received consulting fees and research grants from Amgen.
T.A. has received research grants from Amgen.
Y.L. has received research grants from Amgen.
T.-C.L is an employee and owns equity in Amgen.
L.S. is an employee and owns equity in Amgen.
V.C.B. is an employee and owns equity in Amgen.
R.K.S. is a former employee and owns equity in Amgen.
M.McD. is an employee and owns equity in Amgen.

B.D.B. is an employee and owns equity in Amgen.
M.K. is an employee and owns equity in Amgen.

Data availability

Qualified researchers may request data from the deidentified and aggregated results of this study. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/

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