1. ABSTRACT

- **Title**

Comparative effectiveness of osteoporosis medications among female Medicare Fee-For-Service (FFS) beneficiaries in the United States

- **Keywords**

Objectives	Endpoints
Primary	
To evaluate the comparative effectiveness of osteoporosis treatments on the incidence of hip, major osteoporotic, clinical vertebral, non-vertebral, and non-hip, non-vertebral fractures among PM women.	Hip fracture Major osteoporotic fracture is defined as non-vertebral fractures or clinical vertebral fractures. Clinical vertebral fracture Non-vertebral fracture sites include: pelvis, humerus, radius/ulna, hip, other femur) Non-hip, non-vertebral fracture sites (excludes hip and clinical vertebral fractures)
Secondary	
N/A	

- **Rationale and Background**

Oral bisphosphonates (BP), zoledronic acid (ZA) and denosumab are common therapies to treat osteoporosis among postmenopausal (PM) women. Clinical trials suggest that denosumab is more effective in increasing bone mass than bisphosphonates, but randomized controlled trials (RCT) designed to compare the fracture efficacy of Prolia with BP are lacking[1]. There are limited data on comparative effectiveness using real-world data. There have been 2 comparisons of the effectiveness of osteoporosis medications using real-world data in the United States, however, these studies were either underpowered, utilized indirect comparisons, used data from the early period after Prolia's® approval (which is likely biased due to preferential prescribing of Prolia® to high risk patient populations), or did not implement methods to mitigate the potential for unmeasured confounding.[2, 3]. We aimed to estimate the comparative effectiveness of

commonly used anti-resorptive osteoporosis medications (bisphosphonates and denosumab) on fracture risk among female Medicare Fee-for-service (FFS) beneficiaries in the United States.

- **Research Question and Objectives**

- **Study Design**

  A retrospective cohort study.

- **Setting**

  The database was extracted from the US Centers for Medicare and Medicaid Services' Chronic Condition Warehouse database from January 1, 2012 through December 31, 2019.

- **Subjects and Study Size, Including Dropouts**

  Data source

  The study populations were identified in a data sample from the US Centers for Medicare and Medicaid Services' Chronic Condition Warehouse database that includes 100% of Medicare beneficiaries in FFS plans who have a diagnosis of osteoporosis, evidence of osteoporotic fracture or documented use of a pharmacologic osteoporosis medication. Administrative claims from January 1, 2006 through December 31, 2019 were used for the study.

  Data from January 1, 2012 through December 31, 2018 was used for patient identification, and follow-up will be assessed through December 31, 2019 (Figure 1).

  Inclusion/ Exclusion criteria

  We included female patients in this study if they met all of the following criteria:

  - Use of denosumab, an oral BP (alendronate, ibandronate, risedronate) or ZA with at least one outpatient pharmacy claim for one of these medications
    - Date of prescription between January 1, 2012 through December 31, 2018
  - 66 years + 90 days (3 mo.) of age or older on the date of treatment initiation
  - At least 15 months (455 days) of continuous health plan enrollment preceding the date of treatment initiation

  We excluded patients from the study if they had a history of the following criteria during the 455-day baseline period:
  - Paget's disease of bone,
  - Cancer (excluding non-melanoma skin cancer),
  - Treatment with chemotherapy,
  - Treatment with hormonal therapy for cancer,
  - Treatment with radiation therapy for cancer,

- Exposed to > 1 OP drug (including any combination of study medications, teriparatide, abaloparatide, raloxifene, calcitonin, pamidronate, and etidronate) at treatment initiation (index date)

Study cohorts for analysis

Analyses to address each of the study objectives were be conducted separately within the following treatment cohorts:

- Treatment-naïve (new) users: patients who initiated one of the above listed study medications, without evidence of prior use of any study medication (no previous claim within available historical claims), and no prior use of teriparatide, abaloparatide, raloxifene, calcitonin, pamidronate, and etidronate using all available historical claims.
- Treatment-experienced (new) users: patients who newly initiated (no prior use using all available historical claims) one of the above listed study medications, with prior exposure to oral BP either during and/or before the baseline period (using all available historical claims) and no use of teriparatide, abaloparatide, raloxifene, calcitonin, pamidronate, and etidronate (using all available historical claims).
- Pairwise treatment comparisons for the three treatment cohorts listed above will include: denosumab vs. alendronate, denosumab vs. oral BP (alendronate, ibandronate, risedronate), denosumab vs. IV ZA

- **Variables and Data Sources**

  - *Outcome Variable(s)*
    Fracture outcomes for this study included: hip fracture, major osteoporotic (OP) fracture, which consisted of both non-vertebral (see fracture sites below) and clinical vertebral fractures, clinical vertebral fracture, non-vertebral fracture (pelvis, humerus, radius / ulna, hip, other femur), and non-hip, non-vertebral (NHNV) fracture (excludes hip and clinical vertebral fractures). These outcomes were evaluated separately and identified using a combination of ICD-9-CM, ICD-10-CM, HCPCS, CPT or ICD 9/10 procedure codes according to a previously validated algorithm[4].

  - *Exposure Variable(s)*

    There were two sets of treatment groups used for this study as follows:
    1. Treatment-naïve users of osteoporosis (OP) medications
    2. Treatment-experienced users of OP medications

    Oral BPs include alendronate, ibandronate, and risedronate. IV ZA and denosumab will be identified by HCPCS and NDC codes. Oral BPs will be identified by NDC codes.

  - *Other Covariate(s)*

    All covariates will be identified using combinations of inpatient and outpatient ICD-9-CM or ICD-10-CM diagnosis or procedure codes, CPT-4 or HCPCS procedure codes, and/or National Drug Codes (NDC). The following variables will be considered in

development of propensity scores (to create inverse probability of treatment and censoring weights) for balancing denosumab patients to comparator patients in each pairwise treatment comparison:

- Demographics
- Year of index date
- Clinical history (e.g., time since most recent OP medication use)
- Use of healthcare facilities (e.g., office visits, ER visits, hospital visits)
- Charlson comorbidity index
- Chronic diseases/Medical conditions
- Medications that may influence risk of fracture

History and duration of osteoporosis medication use, and any prior fracture will be assessed using all available pre-index data for each patient; all other pre-index (baseline) characteristics including recent fracture history will be assessed during the 455-day baseline period.

- **Follow-up**

Patients were followed one day after treatment initiation until the earliest of: 1) a given fracture outcome, 2) treatment discontinuation (discontinuation date is defined as the prescription date + medication days' supply + 60 days grace period + 1) or switch to a different osteoporosis treatment (including any study medications, teriparatide, abaloparatide, raloxifene, calcitonin, pamidronate, and etidronate) , 3) end of Medicare enrollment, 4) evidence of any exclusion criteria during follow-up, 5) death or 6) or end of available data (December 31st 2019).

- **Statistical analyses**

Prior to conducting the comparative effectiveness analyses, a gated framework using negative control outcomes was implemented to ensure comparability between the two study groups and assess unmeasured confounding, after initial adjustment using propensity score matching[5].

Demographic and clinical characteristics were described separately for patients in each of the treatment cohorts, before and after propensity score weighting. After weighting, standardized mean differences (SMD) of $\leq$0.1 indicated covariate balance between treatment groups.

For the comparative effectiveness analysis, propensity score models to address confounding in initial treatment assignment were used to emulate randomization by balancing both treatment groups with respect to the probability of receiving treatment. Multivariate logistic models regressing treatment as the outcome and adjusting for were used to estimate the inverse probability of treatment weights (IPTW). To remove outliers, we trimmed 0.5% of subjects at each end of the IPTW distribution. Balance before and after weighting was assessed using standardized mean differences (SMD), where an SMD>0.1 indicated a clinically meaningful difference between the two treatment groups.

Because patients generally adhere to denosumab for longer periods of time compared to alendronate [6, 7], we used inverse probability of censoring weights (IPCW) to adjust for potential informative censoring by follow-up. Multivariate Cox Proportional Hazards models regressing censoring events (including treatment discontinuation/switch, exclusion criteria, end of Medicare enrollment, or death) as the outcome and adjusting for covariates were used to estimate the IPCW.

Cumulative incidence of each outcome was estimated using augmented inverse-probability of treatment and censoring weighted (IPCW=IPTW*IPCW) estimation functions, which produced risk ratios (RR) and risk differences (RD) of each outcome at 365, 730, 1,095, 1,825, and >1,825 days of follow-up [8]. The cumulative incidence was plotted with 95% confidence interval (CI) bands.

- **Results**

Patient characteristics

1. Treatment naïve

a. Denosumab vs Alendronate

Most baseline characteristics were similar between patients initiating denosumab and patients initiating alendronate with few exceptions. Approximately 75.9% of denosumab users and 83.8% of alendronate users had no prior history of osteoporotic fracture. Characteristics with standardized mean differences (SMD)s above 0.10 prior to weighting included mean age, white race, history of vertebral fractures, steroid use, chronic kidney disease (CKD) stages III – V, proton-pump inhibitor (PPI) use, vitamin D deficiency, osteoporosis diagnosis and mean number of outpatient visits. After adjustment with IPTW, all characteristics were balanced between both treatment groups (i.e. SMD $\leq$ 0.1).

b. Denosumab vs Oral BP

Most baseline characteristics were similar between patients initiating denosumab and patients initiating oral BP with few exceptions. Characteristics with standardized mean differences (SMD) above 0.10 prior to weighting included mean age, calendar year of drug index date (2012), history of vertebral fractures, corticosteroid use, severe renal impairment, vitamin D deficiency, mean number of outpatient visits. After adjustment with IPTW, all characteristics were balanced between both treatment groups (i.e. SMD $\leq$ 0.1).

c. Denosumab vs ZA

Most baseline characteristics were similar between patients initiating denosumab and patients initiating zoledronic acid with few exceptions. Characteristics with standardized mean differences (SMD)s above 0.10 prior to weighting included mean age, geographic region, calendar year of drug index date, chronic kidney disease (CKD) stages III – V, severe renal impairment, Charlson Comorbidity Index. After adjustment with IPTW, all characteristics were balanced between both treatment groups (i.e. SMD $\leq$ 0.1).

2. Treatment experienced

a. Denosumab vs Alendronate

Most baseline characteristics were similar between patients initiating denosumab and patients initiating alendronate with few exceptions. Characteristics with standardized mean differences (SMD)s above 0.10 prior to weighting included geographic region, calendar year of drug index date, seasonality of index date, history of vertebral fractures during baseline, steroid use, vitamin D deficiency, osteoporosis diagnosis, use of bone density scan, wellness visit during baseline period, and mean number of physician office visits during baseline period. After adjustment with IPTW, all characteristics were balanced between both treatment groups (i.e. SMD $\leq$ 0.1).

b. Denosumab vs Oral BP

Most baseline characteristics were similar between patients initiating denosumab and patients initiating oral BP with few exceptions. Characteristics with standardized mean differences (SMD) above 0.10 prior to weighting included race, geographic region, seasonality, calendar year of drug index date (2012), history of vertebral fractures during baseline, corticosteroid use, stage III – V chronic kidney disease at baseline, severe renal impairment, use of bone density scan at baseline, osteoporosis diagnosis, vitamin D deficiency, wellness visits during baseline period, and total number of oral BP exposed days prior to the index date. After adjustment with IPTW, all characteristics were balanced between both treatment groups (i.e. SMD $\leq$ 0.1).

c. Denosumab vs ZA

Most baseline characteristics were similar between patients initiating denosumab and patients initiating zoledronic acid with few exceptions. Characteristics with standardized mean differences (SMD)s above 0.10 prior to weighting included mean age, race/ethnicity, geographic region, calendar year of drug index date, chronic kidney disease (CKD) stages III – V, severe renal impairment, Charlson Comorbidity Index. After adjustment with IPTW, all characteristics were balanced between both treatment groups (i.e. SMD $\leq$ 0.1).

Fracture outcomes

3. Treatment naïve (Figures 2, and 3)

a. MOP

A reduced risk of MOP fractures was observed when comparing denosumab to alendronate on and after 1 year of follow-up. Overall, patients using denosumab presented a 39% decreased risk of MOP fracture (RR: 0.61, 95% CI: 0.48, 0.74; p<0.05). We observed 9%, 12%, 18% and 31% reductions in MOP fracture risk at 1, 2, 3 and 5 years of follow-up (p<0.05 at 1, 2, 3, 5 yrs.). In absolute measures, patients treated with denosumab had 6.7 fewer MOP fracture cases per 100 patients, as compared to patients

treated with alendronate (RD: -6.74, 95% CI: -9.70, -3.77; p<0.05). Similar results were found when comparing denosumab to oral BP (RR: 0.61, 95% CI: 0.48, 0.75; p<0.05; RD: -6.71, 95% CI: -9.60, -3.82; p<0.05) and to zoledronic acid (RR: 0.74, 95% CI: 0.59, 0.89; p<0.05; RD: -2.87, 95%CI: -5.04, -0.70; p<0.05).

b. Hip

A reduced risk of hip fractures was observed when comparing denosumab to alendronate on and after 2 years of follow-up. Overall, patients using denosumab presented a 36% decreased risk of hip fracture (RR: 0.64, 95% CI: 0.39, 0.90; p<0.05). We observed 11%, 18% and 39% reductions in hip fracture risk at 2, 3 and 5 years of follow-up (p<0.05 at 2, 3, 5 yrs.). In absolute measures, patients treated with denosumab had 2.0 fewer hip fracture cases per 100 patients, as compared to patients treated with alendronate (RD: -1.99, 95% CI: -3.57, -0.41; p<0.05) over the entire study period. Similar results were found when comparing denosumab to oral BP (overall: RR: 0.63, 95% CI: 0.36, 0.90; p<0.05; RD: -2.16, 95% CI: -3.86, -0.45; p<0.05) and to zoledronic acid (RR: 0.66, 95% CI: 0.43, 0.90; p<0.05; RD: -1.22, 95% CI: -2.47, 0.03).

c. Non-vertebral

A reduced risk of non-vertebral fractures was observed when comparing denosumab to alendronate on and after 1 year of follow-up. Overall, patients using denosumab presented a 43% decreased risk of non-vertebral fractures (RR: 0.57, 95% CI: 0.42, 0.71; p<0.05). We observed 9%, 13%, 20% and 34% reductions in non-vertebral fracture risk at 1, 2, 3 and 5 years of follow-up (p<0.05 at 1, 2, 3, 5 yrs.). In absolute measures, patients treated with denosumab had 6.2 fewer non-vertebral fracture cases per 100 patients, as compared to patients treated with alendronate (RD: -6.24, 95% CI: -9.08, -3.41; p<0.05). Similar results were found when comparing denosumab to oral BP (RR: 0.57, 95% CI: 0.43, 0.72; p<0.05; RD: -6.18, 95% CI: -8.94, -3.42; p<0.05) and to zoledronic acid (RR: 0.67, 95% CI: 0.52, 0.82; p<0.05; RD: -2.99, 95% CI: -5.02, -0.96; p<0.05).

d. Non-hip, non-vertebral

A reduced risk of NHNV fractures was observed when comparing denosumab to alendronate on and after 1 year of follow-up. Overall, patients using denosumab presented a 50% decreased risk of NHNV fracture (RR: 0.50, 95% CI: 0.35, 0.64; p<0.05). We observed 11%, 16%, 22% and 32% reductions in NHNV fracture risk at 1, 2, 3 and 5 years of follow-up (p<0.05 at 1, 2, 3, 5 yrs.) In absolute measures, patients treated with denosumab had 5.4 fewer NHNV fracture cases per 100 patients, as compared to patients treated with alendronate (RD: -5.42, 95% CI: -7.93, -2.91; p<0.05). Similar results were found when comparing denosumab to oral BP (RR: 0.50, 95% CI: 0.36, 0.64; p<0.05; RD: -5.36, 95% CI: -7.71, -3.02; p<0.05) and to zoledronic acid (RR: 0.69, 95% CI: 0.50, 0.88; p<0.05; RD: -1.94, 95% CI: -3.59, -0.28; p<0.05).

e. Hospitalized vertebral

Overall, patients using denosumab presented a 30% decreased risk of hospitalized vertebral fractures (RR: 0.70, 95% CI: 0.40, 1.01), however this reduced risk did not reach statistical significance. We observed 15% and 17% reductions in hospitalized vertebral fracture risk at 3 and 5 years of follow-up ($p<0.05$ at 3, 5 yrs.). In absolute measures, patients treated with denosumab had 1.4 fewer hospitalized vertebral fracture cases per 100 patients, as compared to patients treated with alendronate (RD: -1.37, 95% CI: -3.08, 0.35), although these differences were also not statistically significant. Similar results were found when comparing denosumab to oral BP (RR: 0.72, 95% CI: 0.41, 1.02; RD: -1.29, 95% CI: -2.94, 0.36) . When compared to zoledronic acid, no statistically significant differences were found in the risk of hospitalized vertebral fractures (RR: 0.90, 95% CI: 0.56, 1.24; RD: -0.27, 95% CI: -1.26, 0.71).

4. Treatment experienced (Figure 4)

a. MOP

A reduced risk of MOP fractures was observed when comparing denosumab to alendronate at 1 year, 2 years, 3 years and 5 years of follow-up, where a 25% risk reduction was observed (RR: 0.75, 95% CI: 0.67, 0.82; $p<0.05$). In absolute measures, patients treated with denosumab had 3.49 fewer MOP fracture cases per 100 patients, as compared to patients treated with alendronate (RD: -3.49, 95% CI: -4.84, -2.14; $p<0.05$). Similar results were observed when comparing denosumab to oral BP and zoledronic acid.

b. Hip

A reduced risk of hip fractures was observed when comparing denosumab to alendronate at 1, 3, and 5 years of follow-up, where a 37% risk reduction was observed (RR: 0.63, 95% CI: 0.51, 0.75). When comparing denosumab to oral BP, a reduced risk of hip fractures was observed at 2 years, 3 years and 5 years of follow-up, where a 45% risk reduction was observed (RR: 0.55, 95% CI: 0.42, 0.68, $p<0.05$). When comparing denosumab to zoledronic acid, a reduced risk of hip fractures was observed at 1 year and 5 years of follow-up, where a 38% risk reduction was observed (RR: 0.62, 95% CI: 0.32, 0.91; $p<0.05$). In absolute measures, patients treated with denosumab had 1.99 fewer hip fracture cases per 100 patients, as compared to patients treated with alendronate (RD: -1.99, 95% CI: -2.99, -1.00) over 5 years. Similar results were found when compared denosumab to oral BP and zoledronic acid.

c. Non-vertebral

A reduced risk of non-vertebral fractures was observed when comparing denosumab to alendronate on and after 2 years of follow-up. At 5 years, patients using denosumab presented a 28% decreased risk of non-vertebral fractures (RR: 0.72, 95% CI: 0.64, 0.81; $p<0.05$). In absolute measures, patients treated with denosumab had 3 fewer non-vertebral fracture cases per 100 patients, as compared to patients treated with

alendronate (RD: -3.14, 95% CI: -4.40, -1.89; p<0.05). Similar results were found when comparing denosumab to oral BPs and zoledronic acid.

d. Non-hip, non-vertebral

A reduced risk of NHNV fractures was observed when comparing denosumab to alendronate on and after 2 year of follow-up. At 5 years, patients using denosumab presented a 26% decreased risk of NHNV fracture (RR: 0.74, 95% CI: 0.64, 0.85; p<0.05). In absolute measures, patients treated with denosumab had 2 fewer NHNV fracture cases per 100 patients, as compared to patients treated with alendronate (RD: -1.94, 95% CI: -2.92, -0.95; p<0.05). Similar results were found when comparing denosumab with oral BP and zoledronic acid.

e. Hospitalized vertebral

A reduced risk of hospitalized vertebral fractures was observed when comparing denosumab to alendronate at years 2 and 5 of follow-up, where a 23% risk reduction was observed (RR: 0.77, 95% CI: 0.59, 0.95; p<0.05). When comparing denosumab to oral BP, a reduced risk of hospitalized vertebral fractures was observed at years 1, 2, 3 and 5 of follow-up, where a 37% risk reduction was observed (RR: 0.63, 95% CI: 0.49, 0.77; p<0.05). Similar results were found when comparing denosumab to zoledronic acid.
In absolute measures, patients treated with denosumab had 0.84 fewer hospitalized vertebral fracture cases per 100 patients, as compared to patients treated with alendronate (RD: -0.84, 95% CI: -1.66, -0.01), 1.59 fewer cases as compared to patients treated with oral BP (RD: -1.59, 95% CI: -2.49, -0.68; p<0.05), and 1.42 fewer cases when comparing denosumab to zoledronic acid (RD: -1.42, 95% CI: -2.48, -0.36; p<0.05).

- **Discussion**

  We observed a robust and significant treatment effect. Among treatment-naïve patients, we observed reduced risks of of hip, non-vert, NHNV, hospitalized vertebral (inpatient), and major osteoporotic fracture with Prolia compared with alendronate/oral BP, and reduced risks of of major osteoporotic, hip, non-vert, and NHNV fracture with Prolia compared with with zoledronic acid. Among treatment-experienced post-menopausal women, Prolia significantly reduced the risk of major osteoporotic, hip, non-vert, NHNV, and hospitalized vertebral fracture compared with alendronate, oral BPs and zoledronic acid. In all analyses, we observed a larger difference in treatment effect with longer duration of therapy: The longer the patient remains on Prolia, the greater the fracture risk-reduction benefit.

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