

Proportion of Osteoporotic Women Remaining at Risk for Fracture Despite Adherence to Oral Bisphosphonates

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Abstract:

Background: Adherence to oral bisphosphonates is often low, but even adherent patients may remain at elevated fracture risk. The goal of this study was to estimate the proportion of bisphosphonate-adherent women remaining at high risk of fracture.

Methods: A retrospective cohort of women aged 50 years and older, adherent to oral bisphosphonates for at least two years was identified, and data were extracted from a multi-system health information exchange. Adherence was defined as having a dispensed medication possession ratio ≥ 0.8 . The primary outcome was clinical occurrence of: low trauma fracture (months 7-36), persistent T-score ≤ -2.5 (months 13-36), decrease in bone mineral density (BMD) at any skeletal site $\geq 5\%$, or the composite of any one of these outcomes.

Results: Of 7435 adherent women, 3110 had either pre- or post-adherent DXA data. In the full cohort, 7% had an incident osteoporotic fracture. In 601 women having both pre- and post-adherent DXA to evaluate BMD change, 6% had fractures, 22% had a post-treatment T-score ≤ -2.5 , and 16% had BMD decrease by $\geq 5\%$. The composite outcomes occurred in 35%. Incident fracture was predicted by age, previous fracture, and a variety of co-morbidities, but not by race, glucocorticoid treatment or type of bisphosphonate.

Conclusion: Despite bisphosphonate adherence, 7% had incident osteoporotic fractures and 35% had either fracture, decreases in BMD, or persistent osteoporotic BMD, representing a substantial proportion of treated patients in clinical practices remaining at risk for future fractures. Further studies are required to determine the best achievable goals for osteoporosis therapy, and which patients would benefit from alternate therapies.

Highlights:

- In women adherent to oral bisphosphonates 7% had incident osteoporotic fracture.
- In those with DXA pre and post adherence, 22% had persistent osteoporotic T-scores.
- In those with DXA pre and post adherence, 16% had BMD declines $\geq 5\%$ at any site.
- A third of patients had one or more of these outcomes despite adherence to oral bisphosphonates.

1. Background:

Osteoporosis is a condition of low bone density leading to fracture. Each year over 1.3 million fractures occur in the United States, the majority of which are due to age-related osteoporosis [1]. In 2010, 54 million adults age 50 and older in the United States were estimated to have osteoporosis or osteopenia as defined by BMD measurement [2]. Though the age-specific rates of hip fractures have been reported to be decreasing in some, albeit not all, countries [3, 4], osteoporosis remains a major public health problem that will continue to increase in prevalence as the population ages.

Despite the availability of highly efficacious treatments for osteoporosis such as oral bisphosphonates, low treatment initiation rates [5] and low adherence among patients in clinical settings [6] limits the benefits. In clinical trials, osteoporosis agents decrease hip fractures by up to 50%, vertebral fractures by 30-70% (depending on whether detected based on clinical symptoms or morphometry), and nonvertebral fractures by up to 30% [7, 8]. When patients are adherent and persistent in their treatments, the reduction in fracture rates has been reported to be similar between clinical trials and observational cohorts [9]. However, no osteoporosis treatment eliminates fractures and some patients that are adherent and persistent in their osteoporosis treatments may remain at elevated risk for future fractures.

A group of clinician/researchers have suggested a goal-directed strategy to initiate or change osteoporosis treatments based on targets to achieve a certain BMD value or level of fracture risk [10]. Concerns regarding difficulties in setting achievable goals have been raised [11], and these difficulties were later demonstrated empirically by showing that the FRAX Score was not responsive enough to treatment to be reliably used as target [12].

A working group for the International Osteoporosis Foundation (IOF) proposed a set of criteria for defining inadequate clinical treatment response (which may or may not be due to low adherence) that included the occurrence during osteoporosis treatment, of two or more incident fragility fractures, a significant decrease in bone mineral density

(BMD), (i.e. beyond the LSC of the measurement method), or change in bone turnover markers in the opposite direction of that induced by the treatment agent's mechanism [8]. It was suggested that although these patients may have had some benefit from their osteoporosis drug regimen, that the occurrence of any of these criteria may indicate a need to consider altering treatment in such patients to optimize risk reduction. The occurrence of one or more fractures is a risk factor for additional future fractures in both untreated patients [13], and in those treated with bisphosphonates [14]. Furthermore persistence of osteoporotic T-scores or further decrease in BMD after treatment indicates a higher risk of subsequent fracture compared to those with higher post treatment T-scores, and potential to benefit from additional treatment [15]. Thus the outcomes of fracture, or the surrogate outcomes of decline in BMD or persistent low BMD, are often used by practitioners to guide decisions regarding continuing or switching therapies, because the occurrence of each of these is associated with an elevated risk of fracture relative to other treated patients [16, 17].

The various criteria proposed for inadequate response can be adapted and applied to electronic medical records to identify patients remaining at high risk for fractures despite treatment. Based on readily available data in the clinical records, patients on treatment can be assessed for whether 1) they incur one or more fractures while adherent to treatment, 2) their BMD remains low, or 3) their BMD decreases significantly while adherent to treatment. The primary objective of this analysis was to estimate the proportion of osteoporotic women in a large clinical medical records system who, despite having been adherent to oral bisphosphonate therapy, remain at high risk of fracture, as indicated by the occurrence of one of these three outcomes. We also identified clinical and demographic factors associated with remaining at high risk.

2. Methods

2.1 Overview and Study Design

This is a retrospective cohort study of women aged 50 years and older, who have been adherent to oral bisphosphonates for at least two years. The cohort was

identified and all study data were extracted from a health information exchange as described below.

2.2 Data Source and Definitions

The study cohort and data were extracted from the Indiana Network for Patient Care (INPC), a leading operational regional Health Information Exchange formed in 1994 by the Regenstrief Institute and the five major hospital systems in Indianapolis, later joined by dozens more institutions around the state. Data types available from different institutions include diagnoses (ICD-9 codes), procedures (CPT codes), pharmacy transactions, orders, imaging studies, and laboratory results, though data completeness varies across INPC institutions. The study was approved by the Institutional Review Board of Indiana University. The study subjects were restricted to only those patients who had been adherent to at least one oral bisphosphonate for two years (see inclusion criteria below). Data from all hospitalizations including emergency room visits within the participating health systems are included in this dataset. In 2004 a program was initiated to send data from all emergency room visits in the state of Indiana to the INPC (including emergency room visits at hospitals that do not send other data), which would increase the capture of fractures.

Dual-energy x-ray absorptiometry (DXA) measurements of bone mineral density (BMD) and their associated T-scores at the spine, femoral neck, and total hip were available in a subset of patients whose health systems submitted such data to the INPC. The BMD data included a combination of direct uploads from four DXA machines (11% of the total BMD data in this analysis) and data parsed from text reports (89%). The data directly uploaded from DXA machines (which included three machines used for medical research) incorporated both T-score and the BMD values in g/cm^2 . For quality control of data obtained from text reports, the T-scores were plotted against the BMD values in g/cm^2 , and compared to the equations for BMD measurement locations (total hip, femur neck, lumbar spine) according to different DXA machine manufacturers. Deviations from these equations triggered manual reviews of the reports and obvious typographical errors were corrected.

When the deviation could not be reconciled, the data were excluded. For the analysis of the complete-outcomes subcohort (having both pre and post index DXA), only reports listing BMD measures in g/cm^2 listed were included.

Clinical osteoporotic fractures were identified by ICD-9 codes (Supplemental Table 1). Fractures at the following sites not typically associated with osteoporosis were excluded: skull, craniofacial, phalangeal, carpal, metacarpal, tarsal, and metatarsal fractures. Fractures were excluded as outcome events if records indicated concurrent fractures at 5 or more different skeletal sites (coded within a 30 day window), suggesting a high trauma event. The arbitrary cutoff of 5 fractures was based on a limited chart review of occurrence of co-incident fracture codes and an estimate of the likely range in number of possible fractures occurring with low trauma vs high trauma events. However, in analysis no subject in our study had more than 3 concurrent fractures. Comorbidities were extracted from ICD-9 codes and medications were extracted from dispensing records.

2.3 Inclusion/exclusion Criteria

The study time period spanned 2000-2012, when bisphosphonates were widely used. Only women aged 50 years and over were included if they satisfied the criterion for adherence to at least one oral bisphosphonate over at least two years, regardless of whether they had any indications for treatment. Adherence was defined as “proportion of days covered” (PDC) [18] of at least 0.8 over 2 years, with no gap greater than 30 days between covered days. Only the first documentable continuous adherent period of at least 2 years for each subject was included in the study. The date at the beginning of the adherent period was considered the index date, and the woman’s age at the index date was her index age. Excluded were patients with osteogenesis imperfecta, hypercalcemia or Paget’s disease ICD9 codes. Patients that had a record of intravenous bisphosphonate treatments or denosumab from 2 years prior to the index date through the adherent period were excluded. Other pre-index osteoporosis treatments, including oral bisphosphonates that did not meet the criteria for adherence prior to the index date, and calcitonin or

teriparatide, were treated as covariates in modeling outcomes. Concurrent medications during the adherent period (which sometimes included calcitonin, estrogens or selective estrogen receptor modifiers, as well as medications for co-morbidities) were also treated as covariates. However, the use of teriparatide, intravenous bisphosphonates and denosumab were exclusionary if occurring during the adherent period.

2.4 Study outcomes

2.4.1 Outcome definitions

Outcomes for patients who had been adherent to oral bisphosphonates for at least 2 years (and may or may not be adherent in the third year) were measured through month 36 from the index date because the effects of bisphosphonates last beyond the treatment period [19]. Patients were considered to remain at high risk of fracture if they satisfied at least one of the following three criteria:

- 1) Low post-treatment T-score - defined as a T-score of ≤ -2.5 at any of the following skeletal sites (spine, femur neck or total hip) during months 13-36 from the index date.
- 2) Significant decline in BMD - defined as a decrease of $\geq 5\%$ (at any of the measured sites: spine, femur neck or total hip) these measured skeletal site from the pre-treatment BMD (latest value within 2 years prior to the index date) to any post-treatment value during months 13-36 from the index date.
- 3) Any clinically coded non-traumatic osteoporotic fracture (as defined above; codes listed in supplemental Table 1) occurring in months 7-36 from the index date.

Osteoporotic fractures were counted as events beginning after completing month 6 because fracture rates in treated and untreated patients begin to diverge between treatment and placebo arms in the first 6-12 months in randomized trials of oral bisphosphonates [20, 21]. In contrast, to allow adequate time for BMD response to oral bisphosphonates, post-index BMD measurements were counted only from the

beginning of month 13 onwards (i.e. from 13-36 months). While the fracture outcome could be ascertained on the entire cohort, the outcome of low post-treatment T-score could be ascertained only on the subset of subjects with BMD measurements in months 13-36 from the index date. The choice of -2.5 as a cutoff for the post-treatment T-score is based on the patient still meeting the definition of osteoporosis. The IOF recommends a decrease of 4-5% in BMD be generally considered a significant decline, depending on the precision of the individual machine [8]. Since the INPC data were received from multiple institutions with variable levels of quality control in their DXA measurements and the precision level for most contributing machines is not provided to INPC, the higher 5% value was chosen to indicate a significant decline. A composite outcome of “remaining at risk of fracture” was defined as a positive outcome in any one of the 3 individual outcomes. This could be ascertained only in the complete-outcomes subcohort.

2.4.2 The complete-outcomes subcohort

Within this subset, the outcome of a significant drop in BMD could be ascertained only in those subjects who also had at least one BMD measurement at the corresponding skeletal site(s) during the two years prior to the index date. This smallest subset of 601 subjects, having both pre- and post-treatment BMD during the defined periods, comprised the “*complete-outcomes subcohort*”.

2.5 Covariates

Patient demographics included age and race. Clinical characteristics included fractures and osteoporosis drug treatments prior to the index date, type of bisphosphonate and other co-medications used during the adherent period, and chronic comorbidities. Comorbidities were captured by ICD-9 codes. The Charlson Comorbidity Index was calculated, using a modified version excluding age as a factor [22]. The Charlson Comorbidity Index is generated from ICD9 codes to categorize burden of comorbidities. A higher score on the Charlson Comorbidity index indicates greater number or degree of comorbidities and is a predictor for mortality or for complications in a variety of disease states [22, 23]. In addition

codes for other major disease groups and selected conditions that may affect bone metabolism or risk of falls were also collected.

2.6 Statistical Analyses

Descriptive statistics were calculated for the entire cohort, and in the complete-outcomes subcohort (having both pre and post index DXA). Subject characteristics and fracture outcomes of the subcohort were compared to subjects not in the subcohort to identify how the subcohort might differ systematically from the remainder of the overall cohort. A p-value of <0.05 was considered statistically significant.

Logistic regression modeling was used to identify factors that predict outcomes. Predictors included demographic and clinical characteristics of the subjects. Preliminary analyses used only one predictor in each model to examine apparent associations. Then stepwise model selection was used to fit multivariable models. Predictors in the stepwise multivariable model were not pre-selected; however, pre-index T-score was excluded from the analysis because of strong relationship with post-treatment T-scores. For inclusion of a variable, p-values of 0.05 or less were required for inclusion versus elimination from the model at each step. A model was fitted to predict fractures since this outcome was available on the entire cohort, and the results could be compared to other studies. The model for predicting the composite outcome was then fitted to the complete-outcomes subcohort. Sensitivity analyses were also performed by using a 3% drop in BMD rather than 5% for the definition of a significant drop. Comparison between BMD change category and fracture occurrence was conducted using Mantel-Haenszel chi-square test (using the ordinal BMD change categories).

3. Results

The study cohort was selected from an initial set of 8,339 women who had been adherent to oral bisphosphonate treatments for at least 2 years. Figure 1 shows the application of the various exclusion criteria resulting in the final analysis cohort of

7435 women. Only 3110 in this cohort had any DXA data in the two-year pre-index period and/or months 13-36 post-index. In a small subset of reports, only T-scores were reported without the absolute BMD values (0.07% of reports at the total hip, 6.9% at the femur neck, 0.1% at the spine). Of the 620 subjects who had DXA measurements in both the requisite pre- and post-treatment periods, only 601 had BMD values at the same skeletal site (and measured in g/cm^2) in both periods so that percent change in BMD could be calculated, and these subjects comprised the “complete-outcomes subcohort.”

Table 1 shows the characteristics of subjects in the overall cohort, and in the complete-outcomes subcohort (having at least one pair of DXA measurements in the eligible pre- and post-treatment periods at the same skeletal site). Patients in the complete-outcomes subcohort were younger ($p < 0.01$), and were more likely to be white ($p < 0.0001$) compared to the rest of the cohort. Since the vast majority of patients in INPC are white (most likely including those with missing race), subsequent analyses used black and non-black categories, with proportions similar between the complete-outcomes subcohort and the entire cohort. Subjects in the complete-outcomes subcohort had a longer adherent period ($p < 0.001$), and were less likely to have diabetes ($p < 0.05$). During the pre-index period, subjects in the complete outcomes subcohort were also more likely to have received any previous osteoporosis treatment ($p < 0.01$), any previous bisphosphonate ($p < 0.05$), or alendronate ($p < 0.001$), than those in the full cohort.

Table 2 shows the different oral bisphosphonates dispensed during the adherent periods. In each cohort, a small subset received more than one oral bisphosphonate sequentially during the study period. Subjects in the complete-outcomes subcohort were more likely to have taken alendronate ($p < 0.01$) and less likely to have taken risedronate during the adherent period ($p < 0.01$). Other co-medications taken in the same period are also presented; only estrogens were taken by a smaller proportion of subjects in the complete-outcomes subcohort ($p < 0.05$).

Table 3 summarizes the study outcomes in the post-index period. Of the entire cohort of 7435 women, 499 (7%) had at least one coded clinical fracture event and 174 (2%) had 2 or more distinct fracture events between 7 & 36 months post-index. In our cohort most fracture events involved single fractures. Between the index date and 3 years after index there were 506 individual fracture events in patients with only 1 fracture at a time, 76 with 2 co-incident fractures, 13 with 3 co-incident fractures, and none with 4 or more co-incident fractures. However, only fractures occurring from months 7-36 were counted as outcomes in the analysis. From 7-12 months after index, 122 fracture events occurred; from 13-24 months, 288 fracture events occurred; and from 25-36 months, 367 fracture events occurred. The osteoporotic fracture rate was similar in the complete-outcomes subcohort (6%) to the entire cohort (7%).

A low post-treatment T-score ≤ -2.5 occurred in 20% of the full cohort having available DXA data, and in 22% of the complete-outcomes subcohort (having pre- and post-treatment DXA). Decline in BMD could only be assessed in the complete-outcomes subcohort. Pre-index, 152 women started with T-scores ≤ -2.5 , of which 55 (36%) had post-adherent T-scores > -2.5 . Of the remaining 449 women starting with pre-index T-scores > -2.5 , 34 (8%) ended with post-adherent T-scores ≤ -2.5 . Out of the 131 women who ended with T-scores ≤ -2.5 , 97 (74%) of them had started with pre-index T-scores ≤ -2.5 . The percent of subjects having BMD increases or decreases $\geq 5\%$, or with BMD remaining within $< \pm 5\%$ are listed in Table 3. Not every patient had data available for all 3 sites. In this subcohort, more patients had increases of BMD at the spine (37%), while more patients had decreased BMD at the femur neck (16%). When assessed for the worst BMD change at any measured site, 16% of adherent women had a decline in BMD $\geq 5\%$ during treatment at one or more sites.

The composite outcome of having at least one of the three outcomes is only assessable in the complete-outcomes subcohort having both pre- and post-adherent DXA. In this subgroup we identified 207/601 (35%) with positive composite

outcomes: of these 207 women, 64% had a T-score ≤ -2.5 ; 47% had a significant decline in BMD $\geq 5\%$; and 18% had a clinical fracture.

Table 4 shows the univariate estimates of association between the risk of a fracture outcome and each covariate, except for the use of thiazides, proton pump inhibitors, SSRIs/SNRIs, anticonvulsants, statin, antidiabetics, anticoagulants, and cyclosporins, which were not associated with any outcome in any analyses. The significant predictors of fracture include the well-known risk factors of age, previous fracture and low T-scores, as well as a number of chronic diseases. Black (versus non-black) race was not a predictor of fracture. The types of oral bisphosphonates were not associated with fracture outcomes, but the use of calcitonin before or concurrently with bisphosphonate treatment had an association with higher fracture risk, possibly due to providers treating those deemed at higher risk with dual therapy. Similarly those with previous treatment with teriparatide were also at higher risk of fracture during subsequent bisphosphonate adherence, likely identifying potent anabolic therapy being used in those at highest baseline risk. Higher Charlson Comorbidity Index and multiple individual comorbid conditions including AIDS, malignancy, chronic pulmonary diseases, chronic joint conditions, neurologic, cardiovascular, gastrointestinal and renal conditions and diabetes were all associated with increased risk of fracture despite bisphosphonates. Concomitant glucocorticoids were not predictive of fracture while adherent to bisphosphonates. Other co-medications during the adherent period did not predict fracture outcomes, though there was a nonsignificant trend for increased risk of fracture with use of tamoxifen.

When the univariate analyses in Table 4 were applied to the complete-outcomes analysis subcohort for associations with the composite outcome, the associations with individual predictors remained similar for the known osteoporosis factors of age, previous fracture and low T-scores, but weakened for most chronic conditions (as measured by odds ratio). However the associations with pre- and post-index use of calcitonin remained and had more extreme odds ratios, even though the p-values were larger due to the smaller sample size.

After all potential predictors (regardless of significance in univariate analyses) were entered stepwise into a multiple logistic model, age and previous fracture remained predictive of fractures in the study period, as did the modified Charlson Comorbidity Index and several individual chronic conditions. Pre-index (nonadherent) use of alendronate was associated with a lower fracture risk during subsequent oral bisphosphonate adherence, while pre-index use of calcitonin was associated with a higher subsequent fracture risk (see Table 5). Black race and pre-index T-score category (>-1 , -1 to -2.5 , <-2.5) did not predict fractures in multiple logistic regression. The OR for the composite outcome was increased by age, race (non-black), hyperparathyroidism, and use of estrogens.

As a secondary analysis, predictors of decline in BMD $\geq 5\%$ were analyzed in the complete-outcomes subcohort, having pre and post adherent DXA. In univariate analysis of association the type of oral bisphosphonates was not a significant predictor of BMD decline. Each oral bisphosphonate was individually compared to the other two. BMD decreased $\geq 5\%$ in 21% of patients treated with risedronate versus 15% of patients with other oral bisphosphonates ($p=0.08$); in 17% of patients treated with ibandronate versus 16% of patients with other oral bisphosphonates ($p=0.93$); and in 16% of patients treated with alendronate versus 18% of patients with other oral bisphosphonates ($p=0.60$). Variables increasing odds ratio for BMD decrease in stepwise multivariable analysis included age ($p=0.0377$, odds ratio 1.03 (1.00, 1.05)), chronic pulmonary diseases ($p=0.0270$, odds ratio 1.74 (1.07, 2.85)), and estrogen use ($p=0.0183$, odds ratio 2.39 (1.16, 4.93)). The type of bisphosphonate was not significant in stepwise multivariable models.

In the complete-outcomes subcohort, the occurrence of one or more fractures from month 7-36 was not related to different levels of change in BMD (Mantel-Haenszel chi square test $p=0.56$). Of 98 patients in whom BMD decreased by $\geq 5\%$, 8 (8%) sustained fracture. Of 434 patients without change in BMD (BMD within $\pm <5\%$), 22 (5%) of patients sustained fracture. In 69 patients BMD increased by $\geq 5\%$, and 8 (12%) had fracture. Similarly when BMD was treated as a continuous variable, there was no relationship with clinical fracture incidence ($p=0.73$).

When limiting to 2 or more clinical fractures as an outcome, for the multivariable analysis the significant variables and the odds ratios were similar and fairly stable (Supplemental Table 2) compared to those using 1 or more fractures as an outcome (Table 3). This was true for fractures as the endpoint, and also for the composite outcome. However in this analysis, risedronate use (compared to other bisphosphonates) was associated with the composite outcome including 2 or more fractures, while it was not associated with a composite outcome including 1 or more fractures.

4. Discussion

In a population of patients from a health information exchange network, we estimated that patients who have been adherent to oral bisphosphonates for at least two years have an absolute clinical fracture risk of 7% (including both vertebral and non-vertebral fractures) during months 13-36 from the beginning of the adherent period. These patients can be interpreted as remaining at high risk of fractures in part because past fractures predict future fractures. In the subset of patients with sufficient bone density measurements to determine declines in bone density, we estimated that 35% remained at risk for osteoporotic fractures based on the occurrence of either: one or more fractures while adherent to bisphosphonates, a T-score remaining in the osteoporotic range, or a significant decrease in BMD during two to three years of treatment.

The International Osteoporosis Foundation Inadequate Responders Working Group [7] proposed pragmatic criteria suggesting inadequate response to osteoporosis treatment including occurrence of two or more fractures, or a decrease in BMD, or change in bone turnover markers inconsistent with the specific drug mechanism of action. Unfortunately, this clinical patient care database did not have bone turnover marker data for analysis in this adherent population. Some authors have suggested that a persistent osteoporotic T-score indicates patients at higher fracture risk, who might not be candidates for drug holidays [23]. Similarly some authors have proposed considering a BMD target (such as achieving a non-osteoporotic T-score)

as a hypothetical goal of treatment [9], based on the finding that persistent BMD T-scores less than -2.5 after treatment with alendronate indicated a higher risk of subsequent fracture in the FLEX trial [14]. The occurrence of any fracture is still a risk factor for future fractures in both untreated patients [12], and in bisphosphonate treated subjects [13]. In a FIT trial analysis, out of 1841 patients receiving alendronate 248 (13.5%) sustained a first symptomatic fracture. Out of that subgroup of 248 subjects with first fracture, 51 (or 20.6%) sustained a second symptomatic fracture on treatment. Thus, even on oral bisphosphonates, the occurrence of one fracture indicated higher risk of subsequent fracture (compared to risk of first fracture on treatment) [13]. Of note the risk of a second fracture while on alendronate in that trial was still less than the risk of second fracture in the placebo group. We sought to apply a combination of these proposed factors as indicating a potential increased fracture risk, by collectively assessing the occurrence of one or more fractures while adherent to bisphosphonates, a T-score remaining in the osteoporotic range, or a significant decrease in BMD at either the hip or the spine.

The advantage of using health information exchange data is that it reflects real-life practice and patient behavior from a wide range of types of practices and patient backgrounds. Strengths of this study include its assessment of the effectiveness of actual treatment practices in our population, and the inclusion of clinical DXA and documented coded fractures as outcomes. However, there are limitations to using an administrative database to make inferences regarding the outcomes of clinical treatment modalities, and for determining which patients might require a change in therapy.

One limitation regarding outcome measurement includes that actual clinical practice may not result in the timing of sequential bone density measurements being on either side of clear time periods of treatment adherence and at appropriate intervals to assess the BMD outcomes in all subjects. The bone density related outcomes were limited to those patients whose BMD studies were performed at appropriate time intervals in relation to the actual adherent period. Thus not all subjects had both pre and post adherent period DXA scans. In clinical practice significant time intervals may occur between a diagnostic DXA scan, and the initiation of therapy,

while the actual adherence periods to therapy may be variable within an individual patient. In addition clinical DXA scans may not be timed around an adherent period, but may be planned based on payor coverage, or other factors. Likewise in clinical practice some patients may have had initial or post-treatment DXA scans at facilities that were outside the INPC networks. Another limitation of our study is that clinical DXA measurements are likely to have lower precision than DXA performed on research units, and for this study the least significant change information was not accessible. While we expect the T-score to be reasonably reliably measured in clinical practice, the measure of BMD change likely does not attain the precision expected from research trials. It is possible that the least significant change is higher than 5% in clinical practice facilities where some technicians may not be rigorously trained. However, it is important that we used the same information that the patient's treating clinician would have received, and which would impact clinical decision making. Thus the results seen in this study likely represent the situation faced by many treating clinicians.

Our study could only detect fractures that were clinically recognized and coded. Thus asymptomatic morphometric vertebral fractures are less likely to be included. Furthermore, some fractures will be missed if not evaluated or treated within the participating health systems. If such fractures occurred, our results would be an underestimate of the true fracture incidence in patients adhering to oral bisphosphonates. However, because of the robust statewide emergency room data and extensive hospitalization data, most clinical fractures occurring in the state are likely to be captured.

This study result may underestimate the risk of these outcomes in osteoporotic patients treated with bisphosphonates, as this was a subset of adherent patients [6]. Because patients may not become immediately adherent at the start of an initial prescription, patients were allowed to have oral bisphosphonates dispensed prior to the start of the recorded adherent period. Of note, this 'sub-adherent' treatment would still likely have some effect on bone turnover, thus inclusion of these subjects would tend to decrease the estimate of subjects having one or more of the outcome

events. Interestingly, those patients with 'sub-adherent' alendronate treatment prior to the adherent period did have lower fracture risk in multivariable analysis [OR 0.69 (95% CI 0.54, 0.89)], likely due to the cumulative effects of treatment with bisphosphonates even though initially used in a sub-adherent manner.

Compliance was assessed based on drug dispensing days covered, with the assumption that the medication once obtained was actually taken properly and reliably by the patient. However, neither appropriate provider instructions, nor correct administration by the patient (i.e. without food, etc.), can be assured in this study. Additionally, a comparator group of non-treated or non-adherent patients was not analyzed, in part because while dispensing of medications could be confirmed, lack of treatment is more difficult to ascertain with certainty, as patients may receive prescriptions at non-participating pharmacies. Of note, previous studies have suggested that bisphosphonate treatment as assessed in clinical databases indicates similar relative fracture risk reduction as in trials, which correlated to adherence rates [24, 25]. However prospective trials following adherent oral bisphosphonate treated subjects in clinical practices would better define the occurrences of these outcomes.

Our data cannot specifically guide treatment choices in subjects having one of these events, as we could not evaluate the effect of treatment changes in the subgroup having incident fractures, decreasing BMD or persistent osteoporotic T-scores. There are some published data from clinical trials of switching subjects from oral bisphosphonate to other agents (nicely reviewed by Eiken and Vestergaard [26]). Studies in prior bisphosphonate users have indicated BMD increases at the spine or total hip after switching to denosumab or teriparatide, although a transient decrease in areal BMD at the total hip occurred during the first 6 months of teriparatide. Switching from alendronate to zoledronate or raloxifene did not increase BMD further. However, the trials of treatment switching generally did not limit enrollment to subjects having fractures or one of the BMD outcomes listed in our trial, but rather included subjects on an oral bisphosphonate regardless of previous treatment response. Thus it is not certain whether patients with incident fractures, decreasing BMD or persistent low T-scores while adherent to oral bisphosphonates would

actually benefit from a switch to other osteoporosis agents. Prospective trials with these specific enrollment criteria would be needed to address this issue.

Since our study only included subjects during a period of time with adherence to oral bisphosphonates, the findings are not generalizable to subjects receiving intravenous bisphosphonates. Patients sustaining fractures on treatment may have been switched to intravenous bisphosphonates, in which case their potential eligible time in the study period would have ended, and they would not have been included in our study if the oral bisphosphonate treatment was for less than 2 years. Thus higher risk subjects might have been excluded from the study, which would likely lead to an underestimate of the incidence of fracture or the BMD outcomes. Furthermore patients with contraindication to oral bisphosphonate would be excluded from this study regardless of whether they had higher or lower risk of fracture compared to the studied population. Higher risk patients on oral bisphosphonates who may have refused other therapies also could have biased the results in favor of higher incidence of outcomes.

This study represents a cross-section of individual risk. Patients at higher baseline risk of fracture benefit the most from therapy targeted at reducing fracture risk, but also are most likely to remain at high fracture risk even after potent therapy, limiting attempts to treat to a specific desired target of BMD or fracture risk level [11, 12]. Interestingly pre-index treatment with calcitonin or teriparatide before the adherent bisphosphonate period, and co-treatment with calcitonin and bisphosphonates, were both associated with increased fracture risk during months 13-36. This may be explainable by a greater likelihood for providers to treat higher risk patients with teriparatide, or to attempt combination therapy in those at higher risk. However in univariate analysis, concomitant raloxifene did not influence risk of fractures or composite outcomes in bisphosphonate adherent subjects. Co-medication with raloxifene and bisphosphonates may occur due to the common practice of prescribing raloxifene for potential extra-skeletal benefits. In short term clinical trials, raloxifene and alendronate in combination have been shown to increase BMD

greater than either agent alone [27], although a fracture risk benefit from this combination therapy has not been demonstrated.

According to the findings of Hochberg et al, both absolute BMD and the magnitude of change on treatment had additive effect on the risk of fractures in bisphosphonate treated subjects in clinical trials[16]. A significant decline in BMD was observed in 16% of our subcohort having pre- and post-treatment DXA, which was considerably higher than in clinical trials[16, 17]. However the fracture rates were comparable between our study and clinical trials of oral bisphosphonates. In fact, in our study, change in BMD did not predict the occurrence of clinical fractures, whether BMD change was evaluated as a continuous variable or as categories of change. The incidence of clinical fracture was similar whether there was an increase or decrease in BMD. This would suggest that measurements of BMD change in the context of clinical practice may be a poor surrogate for clinical fracture risk prediction.

Sambrook showed that fractures could be predicted from relatively simple algorithms that performed as well as more complex ones.[28] Since older patients, non-black patients, and those with hyperparathyroidism or concomitant estrogen use tended to remain at higher risk of fracture despite being adherent to bisphosphonate treatment, these are the patients who may need to be considered early for alternative treatments or monitored more closely to decide whether they need alternative treatments. Exactly what those criteria would be beyond BMD or new fractures are uncertain, as algorithms such as FRAX are not responsive enough to therapy to reliably detect a change in risk with therapy [12].

In summary, despite adherence, a substantial proportion of patients in clinical practices treated with oral bisphosphonates remain at risk for fractures and a third of patients had one of the suboptimal clinical outcomes. Although clinical trials have indicated a decrease in fracture risk even with declines in BMD during bisphosphonate therapy, the benefit achieved by such patients is not likely to be optimal. Further studies are required to identify which patients require alternate therapies to maximize their fracture reduction

benefit, and how best to identify appropriate and achievable targets for goal-directed osteoporosis therapy.

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Figure 1: Cohort Inclusions (n=7435)

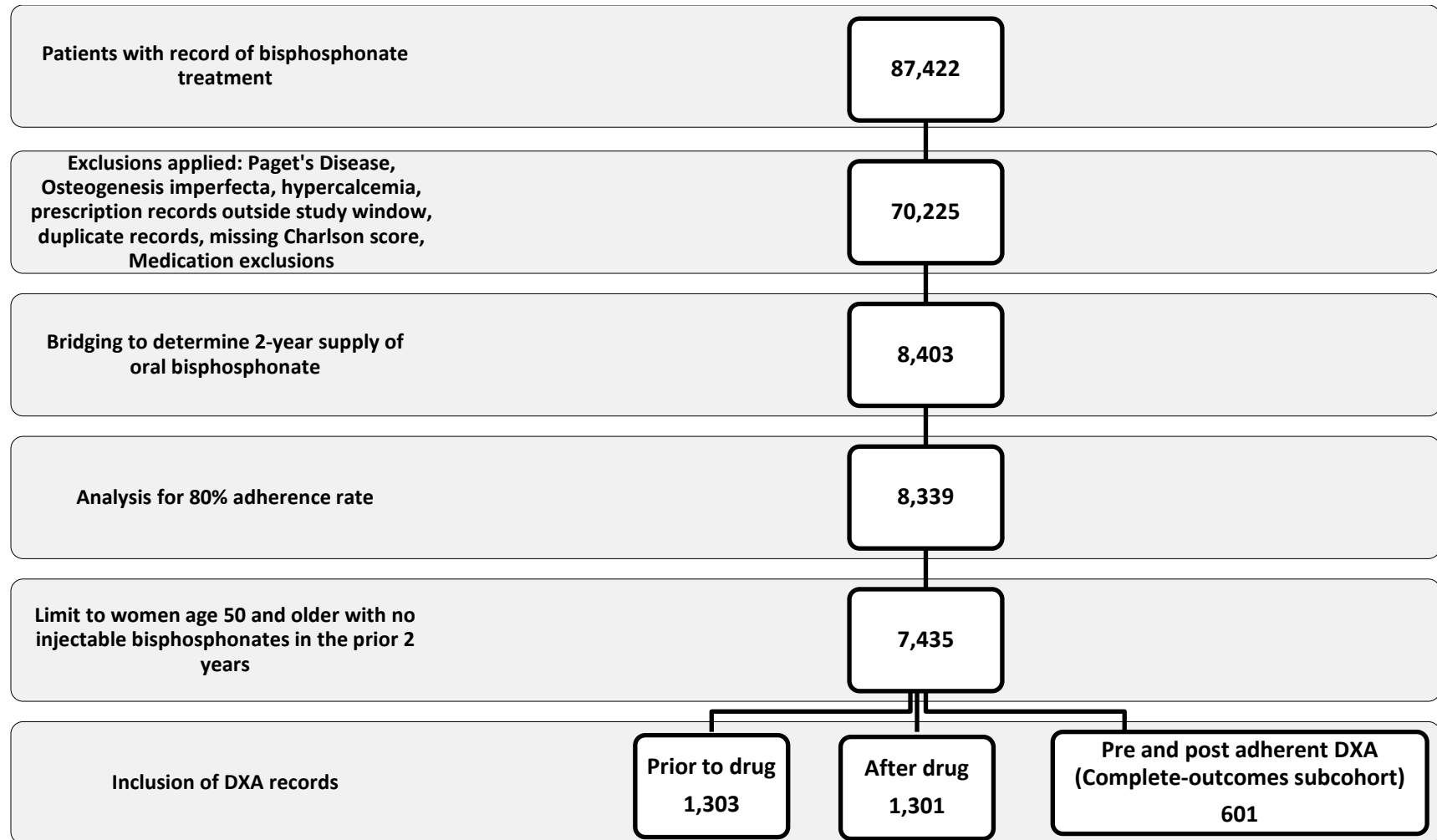


Table 1: Demographics, adherence and pre-index bone-related measures, and comorbidities of the cohort. Values are provided as mean (SD) or N (%)

	All (n=7435)	Complete-outcomes Subcohort having pre and post- adherent DXA (n=601)
<u>Demographics</u>		
Age at index	68 (10)	66 (9)
Race		
Black	493 (7%)	46 (8%)
Hispanic	23 (<1%)	5 (1%)
Missing	1228 (17%)	29 (5%)
White	5691 (77%)	521 (87%)
<u>Adherence Measures</u>		
Proportion of days covered	0.96 (0.04)	0.96 (0.04)
Length of Bisphosphonate Adherent Period (days)	1019 (272)	1053 (289)
Length of Bisphosphonate Adherent Period (years)		
2-2.224	1855 (25%)	104 (17%)
2.25-2.49	1336 (18%)	103 (17%)
2.5-2.74	1017 (14%)	91 (15%)
2.75-2.99	984 (13%)	95 (16%)
3+	2243 (30%)	208 (35%)
<u>Pre-index Bone Measures</u>		
Fracture pre-index	680 (9%)	62 (10%)
Minimum T-score within 2 years pre-index		
≤-2.5	350 (27%)	152 (25%)
>-2.5	953 (73%)	446 (75%)
Missing	6132	3 ^a
<u>Pre-index Osteoporosis Medications</u>		
Any osteoporosis drug	2249 (30%)	211 (35%)
Calcitonin	63 (1%)	6 (1%)
Teriparatide	33 (<1%)	4 (1%)
Any bisphosphonates	2215 (30%)	206 (34%)
Risedronate	692 (9%)	50 (8%)
Ibandronate	222 (3%)	23 (4%)
Alendronate	1441 (19%)	150 (25%)
<u>Comorbidities</u>		
Mean Modified Charlson Comorbidity Index (SD) ^b	1.26 (1.78)	1.23 (1.86)
AIDS	6 (<1%)	1 (<1%)
Any Malignancy	1089 (15%)	100 (17%)
Chronic pulmonary diseases	1599 (22%)	125 (21%)
Inflammatory and other chronic joint conditions	2733 (37%)	233 (39%)
Neurologic conditions	1805 (24%)	133 (22%)
Cardiovascular conditions (other than cerebrovascular)	4272 (57%)	348 (58%)
Diabetes	1035 (14%)	67 (11%)
Hyperparathyroidism	67 (1%)	6 (1%)
Vitamin D deficiency	401 (5%)	40 (7%)
Renal disease	369 (5%)	24 (4%)
Gastrointestinal disorders	1895 (25%)	159 (26%)

^a Three subjects in the complete outcomes cohort were missing pre-index T-scores, but BMD value (without listing T-score) was available from the existing reports.

^b The Charlson Comorbidity Index is a scale generated from ICD9 codes, and higher index values indicate greater comorbidities.

Table 2: Medications used during the adherent period

	All (n=7435)	Complete-outcomes subcohort having pre and post-adherent DXA (n=601)
<u>Bisphosphonates</u> ^a	N (%)	N (%)
Risedronate	2011 (27%)	131 (22%) ^b
Ibandronate sodium	774 (10%)	72 (12%)
Alendronate	5254 (71%)	454 (76%) ^b
<u>Other Medications</u>		
Calcitonin-salmon	66 (1%)	7 (1%)
Estrogens	718 (10%)	41 (7%) ^c
Tamoxifen	53 (1%)	6 (1%)
Aromatase inhibitor	222 (3%)	25 (4%)
Raloxifene	295 (4%)	28 (5%)
Thiazide diuretics	1273 (17%)	95 (16%)
Glucocorticoids	2602 (35%)	207 (34%)
Proton pump inhibitors	1662 (22%)	119 (20%)
SSRIs/SNRIs	1723 (23%)	143 (24%)
Anticonvulsants	1138 (15%)	97 (16%)
Statins	3283 (44%)	261 (43%)
Antidiabetics	191 (3%)	19 (3%)
Coumadin/anticoagulants	399 (5%)	27 (4%)
Cyclosporin cytotoxic agents	107 (1%)	7 (1%)

^a Some subjects changed oral bisphosphonate during the adherent period.

^b p<0.01

^c p<0.05

Table 3: Outcomes: Fracture, low T-score ≤ -2.5 , change in BMD (from corresponding pre- to post-index periods), and composite outcomes

Full cohort (n=7435)	N (%)
Fracture (7-36 months post-index)	499 (7%)
Low T-score (minimum T-score ≤ -2.5) BMD from 13-36 months post-index (n=1301)	264 (20%).
Complete-outcomes subcohort having pre and post-adherent DXA (n=601)	
Fracture (7-36 months post-index)	38 (6%)
Low T-score (minimum T-score ≤ -2.5) from 13-36 months post-index	131 (22%)
BMD change*	
Femur neck (n=236 patients)	
Mean (SD) of overall % change	0.71 (5.85)
Increase $\geq 5\%$	51 (22%)
Remained unchanged (within $\pm 5\%$)	148 (63%)
Decrease $\geq 5\%$	37 (16%)
Total hip (n=553)	
Mean (SD) of overall % change	1.28 (5.37)
Increase $\geq 5\%$	112 (20%)
Remained unchanged (within $\pm 5\%$)	393 (71%)
Decrease $\geq 5\%$	48 (9%)
Spine (n=506)	
Mean (SD) of overall % change	3.29 (7.58)
Increase $\geq 5\%$	185 (37%)
Remained unchanged (within $\pm 5\%$)	283 (56%)
Decrease $\geq 5\%$	38 (8%)
Worst BMD change at any site (n=601)	
Increase $\geq 5\%$	69 (11%)
Remained unchanged (within $\pm 5\%$)	434 (72%)
Decrease $\geq 5\%$	98 (16%)
Mean of minimum % change at any site, mean (SD)	-0.62 (5.55)
Composite outcome (one or more of the following: fracture, minimum T-score ≤ -2.5 , or BMD decrease $\geq 5\%$)	207 (35%)

*Due to rounding, percent of patients in categories at a BMD site may not add up to exactly 100%. Not every patient had data available for all 3 sites, so the numbers with DXA at each site varied.

Table 4: Prediction of 7-36 month post-index fracture by each individual predictor for entire cohort of 7435 women with 499 fracture outcomes: univariate estimates of association

		Fracture N (%)	No Fracture N (%)	OR (95% CI)	p-value
Total n= 7435		499 (6.7%)	6936 (93.3%)		
Age at index		72.77 (10.98)	67.31 (10.29)	1.27 (1.22, 1.33)	<0.0001 *
Black race	Yes	35 (7%)	458 (93%)	1.07 (0.75, 1.52)	0.7217
	No	464 (7%)	6478 (93%)		
Fracture pre-index	Yes	130 (19%)	550 (81%)	4.09 (3.29, 5.09)	<0.0001 *
	No	369 (5%)	6386 (95%)		
Minimum pre-index T-score of femoral neck, hip, spine \leq -2.5	Yes	29 (8%)	321 (92%)	1.22 (0.83, 1.81)	0.3162
	No	48 (5%)	905 (95%)	0.72 (0.53, 0.98)	0.0340 *
	missing	422 (7%)	5710 (93%)		
Co-morbidities					
Modified Charlson Comorbidity Index, mean (SD) (OR is given per 1 unit increase in index) ^a		2.36 (2.35)	1.18 (1.70)	1.29 (1.24, 1.34)	<0.0001 *
AIDS	Yes	2 (33%)	4 (67%)	6.97 (1.27, 38.17)	0.0251 *
	No	497 (7%)	6932 (93%)		
Any Malignancy	Yes	103 (9%)	986 (91%)	1.57 (1.25, 1.97)	0.0001 *
	No	396 (6%)	5950 (94%)		
Chronic pulmonary diseases	Yes	163 (10%)	1436 (90%)	1.86 (1.53, 2.26)	<0.0001 *
	No	336 (6%)	5500 (94%)		
Inflammatory and other chronic joint conditions	Yes	289 (11%)	2444 (89%)	2.53 (2.10, 3.04)	<0.0001 *
	No	210 (4%)	4492 (96%)		
Neurologic conditions	Yes	229 (13%)	1576 (87%)	2.89 (2.40, 3.47)	<0.0001 *
	No	270 (5%)	5360 (95%)		
Cardiovascular conditions (other than cerebrovascular)	Yes	383 (9%)	3889 (91%)	2.59 (2.09, 3.20)	<0.0001 *
	No	116 (4%)	3047 (96%)		
Diabetes	Yes	119 (11%)	916 (89%)	2.06 (1.66, 2.56)	<0.0001 *
	No	380 (6%)	6020 (94%)		
Hyperparathyroidism	Yes	5 (7%)	62 (93%)	1.12 (0.45, 2.80)	0.8051

	No	494 (7%)	6874 (93%)		
Vitamin D deficiency	Yes	31 (8%)	370 (92%)	1.18 (0.81, 1.72)	0.4021
	No	468 (7%)	6566 (93%)		
Renal disease	Yes	69 (19%)	300 (81%)	3.55 (2.68, 4.69)	<0.0001 *
	No	430 (6%)	6636 (94%)		
Gastrointestinal disorders	Yes	160 (10%)	1387 (90%)	1.89 (1.55, 2.30)	<0.0001 *
	No	339 (6%)	5549 (94%)		
Pre-index treatments					
Risedronate pre-index	Yes	51 (7%)	641 (93%)	1.12 (0.83, 1.51)	0.4675
	No	448 (7%)	6295 (93%)		
Ibandronate sodium pre-index	Yes	17 (8%)	205 (92%)	1.16 (0.70, 1.92)	0.5676
	No	482 (7%)	6731 (93%)		
Alendronate pre-index	Yes	90 (6%)	1351 (94%)	0.91 (0.72, 1.15)	0.4314
	No	409 (7%)	5585 (93%)		
Any bisphosphonate treatment pre-index	Yes	149 (7%)	2066 (93%)	1.00 (0.82, 1.22)	0.9725
	No	350 (7%)	4870 (93%)		
Calcitonin pre-index	Yes	12 (19%)	51 (81%)	3.33 (1.76, 6.28)	0.0002 *
	No	487 (7%)	6885 (93%)		
Teriparatide pre-index	Yes	7 (21%)	26 (79%)	3.78 (1.63, 8.76)	0.0019 *
	No	492 (7%)	6910 (93%)		
Any osteoporosis treatment pre-index	Yes	152 (7%)	2097 (93%)	1.01 (0.83, 1.23)	0.9148
	No	347 (7%)	4839 (93%)		
Drugs during adherent period.					
Bisphosphonate type					
Risedronate during adherent period	Yes	135 (7%)	1876 (93%)	1.00 (0.82, 1.23)	1.0000
	No	364 (7%)	5060 (93%)		
Ibandronate sodium during adherent period	Yes	51 (7%)	723 (93%)	0.98 (0.73, 1.32)	0.8866
	No	448 (7%)	6213 (93%)		
Alendronate during adherent period	Yes	368 (7%)	4886 (93%)	1.18 (0.96, 1.45)	0.1179
	No	131 (6%)	2050 (94%)		
Additional concomitant medications during bisphosphonate adherent period					
Calcitonin during adherent period	Yes	10 (15%)	56 (85%)	2.51 (1.28, 4.96)	0.0078 *
	No	489 (7%)	6880 (93%)		
Glucocorticoids during adherent period	Yes	178 (7%)	2424 (93%)	1.03 (0.85, 1.25)	0.7443

	No	321 (7%)	4511 (93%)		
Tamoxifen during adherent period	Yes	7 (13%)	46 (87%)	2.13 (0.96, 4.75)	0.0638
	No	492 (7%)	6890 (93%)		
Aromatase inhibitor during adherent period	Yes	18 (8%)	204 (92%)	1.24 (0.76, 2.02)	0.3990
	No	481 (7%)	6732 (93%)		
Raloxifene during adherent period	Yes	22 (7%)	273 (93%)	1.13 (0.72, 1.76)	0.6014
	No	477 (7%)	6663 (93%)		
Estrogens during adherent period	Yes	52 (7%)	666 (93%)	1.10 (0.81, 1.48)	0.5506
	No	447 (7%)	6269 (93%)		

^a The Charlson Comorbidity Index is a scale generated from ICD9 codes, and higher index values indicate greater comorbidities.

* Marks significant p values.

Table 5: Multivariable prediction of outcomes: Fractures in entire cohort and composite outcome in the complete-outcomes subcohort

Outcome	Predictor	OR (95% CI)	p-value
Entire cohort (n= 7435)			
Fractures (1 or more)	Age at index	1.03 (1.02, 1.04)	<0.0001
	Charlson Comorbidity Index ^a	1.14 (1.09, 1.20)	<0.0001
	Inflammatory and other chronic joint conditions	1.64 (1.34, 2.00)	<0.0001
	Neurologic conditions	1.55 (1.25, 1.91)	0.0001
	Cardiovascular conditions (other than cerebrovascular)	1.33 (1.04, 1.68)	0.0206
	Alendronate pre-index	0.69 (0.54, 0.89)	0.0037
	Calcitonin pre-index	2.10 (1.07, 4.12)	0.0318
	Fracture pre-index	2.59 (2.05, 3.28)	<0.0001
Complete-outcomes subcohort having pre and post-adherent DXA (n=601)			
Composite outcome (Fractures, T-score ≤-2.5, BMD decrease ≥5%)	Age at index	1.05 (1.03, 1.08)	<0.0001
	Black race	0.37 (0.17, 0.79)	0.0105
	Hyperparathyroidism	7.01 (1.18, 41.7)	0.0322
	Estrogens during adherent period	2.41 (1.23, 4.71)	0.0100

^a The Charlson Comorbidity Index is a scale generated from ICD9 codes, and higher index values indicate greater comorbidities.

Supplemental Table 1: ICD-9 codes used in the study

<i>Osteoporosis and fracture codes</i>	
Osteopenia and Osteoporosis	2317, 3846, 733.0-733.03, 733.09, 733.9, 733.90
Fracture codes used for outcome events	733.1-733.16, 733.19, 805-808, 812-813, 818-821, 823, 827-828
<i>Exclusion criteria</i>	
Hypercalcemia	275.42
Pagets Disease of Bone	731.0
Osteogenesis Imperfecta	756.51
<i>Charlson comorbidity score components</i>	
Any Malignancy	140-172, 174-195, 200-205
Chronic Pulmonary Disease	490-496, 500-505, 506.4
Diabetes (and Complications)	250
Hemiplegia or Paraplegia	342, 344.1
Mild Liver Disease	571.2, 571.4-571.6
Myocardial Infarction	410
Peptic Ulcer Disease	531-534
Renal Disease	582-583, 585-586, 588
Rheumatologic Disease	710, 714, 725
<i>Additional comorbidities included</i>	
Celiac Disease	579
Chronic Inflammatory Bowel	555-556
Chronic Inflammatory Joint	714-715
Depression	311
Gastrointestinal & Urination	788
Glucocorticoid therapy	255.41
Hyperparathyroidism	252
Hypertension	401-405
Neurologic Conditions	326, 330-336, 340-345, 355-359
Renal Impairment	585-585.6, 585.9
Vitamin D Deficiency	268, 268.9

Supplemental Table 2; Secondary analysis using 2 or more fractures as an outcome.

Outcome	Predictor	OR (95% CI)	p-value
Entire cohort (n= 7435)			
Fractures (2 or more)	Age at index	1.04 (1.03, 1.06)	<0.0001
	Charlson Comorbidity Index	1.16 (1.09, 1.24)	<.0001
	Black race	0.43 (0.20, 0.93)	0.0316
	Inflammatory and other chronic joint conditions	2.49 (1.78, 3.49)	<0.0001
	Neurologic conditions	1.80 (1.29, 2.53)	0.0006
	Alendronate pre-index	0.59 (0.39, 0.91)	0.0164
Complete-outcomes subcohort having pre and post-adherent DXA (n=601)			
Composite outcome (2 or more fractures, T-score≤-2.5, or BMD decrease ≥ 5%)	Age at index	1.05 (1.03, 1.08)	<0.0001
	Black race	0.40 (0.18, 0.90)	0.0272
	Diabetes	0.51 (0.27, 0.96)	0.0374
	Hyperparathyroidism	9.58 (1.62, 56.74)	0.0128
	Risedronate during adherent period	1.74 (1.15, 2.66)	0.0096
	Estrogens during adherent period	2.20 (1.12, 4.33)	0.0227