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Adoption of Once-monthly Oral Bisphosphonates and the Impact on Adherence

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Abstract

Background—The extent of the adoption of once-monthly bisphosphonates into general clinical practice is not known, nor is it known if the novel formulation improves adherence.

Methods—We analyzed administrative claims 2003-2006 from a large employer-based health insurance database for incident use of oral bisphosphonates and stratified users by daily, weekly and monthly dosing regimen. We measured adherence as the medication possession ratio (MPR) during the first year of therapy. We compared patient characteristics by dosing regimen and evaluated how the dosing regimen influenced the MPR.

Results—We identified 61,125 incident users of bisphosphonates (n=1034 daily, n=56,925 weekly, n=3166 monthly). Monthly bisphosphonate users were, on average, slightly older than the other groups (mean age 66 years monthly vs. 65 weekly or 66 daily, $p<.05$.) and more often lived in the U.S. North Central or South (76% vs. 72% weekly or 69% daily users, $p<.05$). There were no detectable differences among the dosing groups in the history of serious GI risk, comorbidity burden, or prior osteoporotic fractures. During the first year of bisphosphonate therapy, 49% of monthly users had $MPR \geq 80\%$ compared to 49% weekly users (N.S.) or 23% daily users ($p<.0001$).

Conclusions—We found little evidence of preferential prescribing of monthly bisphosphonates to certain types of patients. Furthermore, we found no evidence of improved bisphosphonate adherence with monthly dosing relative to weekly dosing, although adherence with either weekly or monthly dosing was significantly better than with daily dosing.

Keywords

patient compliance; bisphosphonates; novel formulation

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Background

In April 2005, the Food and Drug Administration approved the first once-monthly oral tablet for the treatment of a chronic disease. The once-monthly ibandronate sodium is a bisphosphonate, a class of drugs that inhibit bone resorption and are commonly prescribed for the treatment and prevention of osteoporosis in postmenopausal women.[1,2] The efficacy and safety of once-monthly bisphosphonates were demonstrated in a 1-year, double-blind study of postmenopausal women with osteoporosis whose treatment with 150 mg once-monthly ibandronate (n=327) was shown to be noninferior to 2.5 mg daily ibandronate (n=318) in increasing the bone mineral density in the lumbar spine.[3,4]

Previous to the monthly formulation, oral bisphosphonates were available in daily and weekly formulations, although the weekly formulation has dominated the market since its introduction in 2000. For instance, in a 2002-2003 observational cohort study, 84% of 211,319 patients were taking once-weekly bisphosphonates.[5] Once-weekly oral bisphosphonates have been associated with higher adherence over the once-daily formulations, although overall adherence has remained suboptimal in that drug class.[5-7] Between 52% to 87% of patients starting daily or weekly oral bisphosphonates discontinue the therapy within 1 year or do not fill enough prescriptions to cover 80% of a year of therapy.[5,8]

The extent of the adoption of once-monthly bisphosphonates into general clinical practice is not known, nor is it known if the novel formulation improves adherence. Research finds consistently that reducing the dosing demands of medications increases medication adherence, although this relationship has not been tested with once-monthly formulations.[9] In addition, recent surveys report conflicting results on patient preferences for the once-monthly formulation over the weekly, which might also influence adherence.[10,11] Furthermore, it is unclear if prescribers channel the once-monthly bisphosphonates to certain kinds of patients, such as those with gastrointestinal disorders. The adoption patterns of these medications and the impact of a once-monthly dosing schedule on adherence is especially important as once-monthly bisphosphonate costs approximately 40% to 60% more than the generic forms of the daily and weekly oral bisphosphonates, which have been available since early 2008. The objectives of this study were to assess whether once-monthly bisphosphonates are preferentially channeled to certain patients, and whether the monthly dosing schedule is associated with improvements in adherence.

Methods

Study population and data sources

This study used the 2001-2006 MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases (Medstat: Ann Arbor, MI). This database contains over 500 million claim records per year from individuals with private health care insurance. Scientific studies based on this data source have been reported in more than 75 peer-reviewed articles.[12] The data come from approximately 45 large employers who self-insure their employees and dependents. The MarketScan database offers advantages over raw administrative claims because data file undergo validity and editing procedures to ensure high quality and consistency in fields across years.[13] The data are evaluated against population norms, previous year summaries, and validated data subsets. Outliers are flagged and reviewed for coding or processing errors. Encounter data are audited at the health plan level and plans submitting incomplete data are excluded. Diagnostic and procedural codes are compared against validity algorithms and set to missing values if inconsistent. The encounter files contain age, sex, geographic residence, and eligibility information. The prescription claims include the national drug codes, date of purchase, quantity, days' supply, and expenditure information. The medical

claims contain payment information, diagnoses, procedure codes, and type of provider. For this analysis, we pooled annual files to create a dataset of approximately 15 million people.

The study sample included individuals who were aged 50 years or older, had an osteoporosis diagnosis (ICD-9-CM 733.xx), an incident dispensing of an oral bisphosphonate (ibandronate, alendronate or risedronate), and least 2 years of observation. Incident use was defined as no bisphosphonate therapy for at least 12 months prior to initiating therapy. Individuals were excluded if they had Paget's disease (731.0) (n=242), received transplantations (n=321), or received an oral solution of bisphosphonates (n=1210). The institutional review board of the University of Massachusetts Medical School approved this research.

Measures—The main study variable was dosing schedule. We calculated the dosing schedule as the days supply divided by the metric quantity for each dispensing of the study drugs. Preliminary analyses showed evidence of prescribing outside of dosing guidelines, which made assignment by only tablet strength unreliable. We identified the modal value for each unique generic study drug dispensed to each individual, manually checked outliers for error (<0.5% of patients), and assigned individuals into mutually-exclusive dosing schedules based on set thresholds. For instance, if an individual's modal dosing schedule of alendronate dispensed during the year fell within the range of 1/2 to 2 tablets daily, then that individual was assigned to a daily dosing schedule. Individuals receiving more than one assignment were categorized by the earliest assignment (for example switching from weekly to monthly dosing), and all subsequent bisphosphonate use summed into 1 MPR value.

The dependent variable was adherence measured as Medication Possession Ratio (MPR). We estimated the MPR as the sum of the days supply of study medication dispensed during the year divided by the number of days in the year. Overlaps in the dispensing days of different generic drug therapies were eliminated, under the assumption that leftover supplies from earlier refills were discarded to begin the newer medication (e.g., a change in therapy). The value of the days supply was truncated if the supply extended beyond the time period of observation. Covariates included: age, sex, geographic residence, health plan type, any pre-period bone mineral density testing, serious gastro-intestinal risk[14], osteoporotic fractures of the hip, wrist, or humerus, acute care hospitalizations, and a comorbidity risk score from the Diagnostic Cost Group Hierarchical Condition Category (DCG/HCC) classification system (DxCg, Boston, MA).[15,16] The DCG/HCC risk adjuster creates a single score for each person based on the presence of 189 medical conditions in the diagnosis fields of claims records. Each person was assigned an index date based on the first dispensing of the incident study medication. Data from the year prior to the index date were used to construct pre-period measures of the covariates, most notably the comorbidity risk score.

Statistical analysis—Bivariate statistics were used to calculate 95% confidence intervals, unadjusted t-tests of means, and chi-square tests of frequency distributions. Stratified analyses by dosing frequency were conducted with all covariates.

Results

We identified 61,125 unique individuals who initiated an oral bisphosphonate for osteoporosis (n=1034 daily, n=56,925 weekly, n=3166 monthly). Approximately 4% switched dosing schedules, of which over 93% were from weekly to monthly dosing (data not shown). Figure 1 shows that in the year prior to the approval of once-monthly bisphosphonate, 98% of the study population was started on a weekly formulation. However, after 1 year on the market, the once-monthly bisphosphonate was the drug of choice for 10% of new users.

Table 1 shows relatively modest differences in the characteristics of the three groups, except for type of health insurance. Relative to the weekly or daily users, patients receiving once-monthly bisphosphonates were, on average, slightly older (66, vs. 65 or 65, $p < .05$), and more often female (93% vs. 90% and 90%, $p < .05$). In the year prior to initiating therapy, once-monthly users were more likely to have had bone mineral testing (72.7% vs. 65.3%, $p < .001$) and less likely to have been hospitalized than daily users (13.3% vs. 14.4%, $p < .02$), but slightly less likely to have bone mineral testing (72.7% vs. 74.9%, $p < .006$) than weekly users. Patients receiving once-monthly bisphosphonates more often lived in the North Central and South regions of the United States (76.5% vs. 72.0% or 69.3%, $p < .0001$) than those receiving weekly or daily formulations. Lastly, nearly all users of monthly bisphosphonates belonged to comprehensive or point-of-service health plans (85.5% vs. 81.4% or 44.0%, $p < .001$) compared to weekly users or daily users.

Figure 2 shows the adherence levels of newly started oral bisphosphonate users by dosing frequency. Approximately, 49% of once-monthly bisphosphonate users achieved an MPR of 80% or greater compared to 49% of once-weekly users (N.S.) or 23% of daily users ($p < .002$). Moving the MPR threshold to 60% or greater showed adherence was highest for weekly users (63%) compared to monthly users (60%, $p < .002$) or daily users (31%, $p < .0001$).

Figures 3A and 3B show the mean MPR adherence levels from the stratified analyses. In general, the adherence of monthly users varied little by the subgroups, and the MPRs of monthly users were nearly identical to those of weekly users although markedly different from those of daily users. For instance, among monthly users, males had an average MPR of 69.8% (95% CI: 65.4%-74.2%) compared to an average MPR of 68.6% (CI: 67.7%-69.5%) for weekly users, and 41.0% (CI: 34.1%-48.0%) for daily users. Average adherence of monthly users exhibited a slight decline in adherence after age 80 (63.2% MPR, 95% CI: 59.7%-66.8%) relative to those aged 50-59 (66.3% MPR, 95% CI: 64.3%-68.3%), a similar pattern to that of weekly users. Monthly users in HMOs (61.2% MPR, 95% CI: 56.8%-65.6%) or preferred provider organizations (61.8% MPR, 95% CI: 59.8%-63.9%) also had slightly lower MPRs than those in comprehensive plans (68.5% MPR, 95% CI: 66.9%-70.1%).

Testing for bone mineral density before initiating therapy was associated with a modest adherence improvement among monthly users (67.2% MPR, 95% CI: 65.9%-68.6% vs. 61.2% MPR, 95% CI: 58.9% vs. 63.5%) as well as weekly users, however not by daily users. No adherence improvement was found in monthly users with increased risk of serious gastrointestinal disorders, a prior fracture, or previous hospitalization. Lastly, adherence decreased slightly among monthly users with higher comorbidity burden (67.5% MPR for low burden, 95% CI: 65.2%-69.8% vs. 62.5% MPR for high burden, 95% CI: 59.7% vs. 65.2%). Again, this relationship also occurred with weekly users but not with daily users.

Discussion

In this large study of older adults with osteoporosis and newly-initiated on bisphosphonates, we found once-monthly dosing conferred no additional benefit in adherence compared to once-weekly dosing, although adherence with either weekly or monthly dosing was significantly better than with daily dosing. During the first year of therapy, 49% of monthly users had an MPR $\geq 80\%$ compared to 49% weekly users (N.S.) or 23% daily users ($p < .0001$). Furthermore, we found modest evidence of preferential prescribing of monthly bisphosphonates to certain types of patients. There were no detectable differences among the dosing groups in the history of serious gastrointestinal disorders, comorbidity burden, or prior osteoporotic fractures. Despite the unclear advantages of the novel formulation, the once-monthly bisphosphonates were prescribed to 10% of all newly-initiated patients on this class of drugs within the first year of availability.

Prior research on adherence with once-monthly bisphosphonates is not entirely consistent with these findings. Cooper and colleagues found higher rates of persistence with the once-monthly users compared to once-weekly users in an open-label study of 1,103 postmenopausal women in the United Kingdom (56.6% vs. 36.6%, $p < .0001$).^[17] However, the simultaneous intervention of a patient support program for only the once-monthly users makes the independent influence of dosing on adherence impossible to evaluate. In contrast, two studies using only pharmacy dispensing records found no difference in the adherence or persistence of newly-initiated weekly versus monthly bisphosphonate users after the first refill.^[10,18] Although, in the one case the study lasted only 6 months, covered the period of initial market availability, and used nonconcurrent cohorts. Furthermore, in both prior studies, adherence may have been underestimated due to limited data capture on prescriptions filled outside the study pharmacy network and the .^[10]

Research is also mixed on patient preference for a once-monthly bisphosphonate, and how much this preference influences adherence. Two studies have reported conflicting findings on patient preference but both asked women who had experience in taking only the weekly or the monthly formulations but not both.^[10,19] A third study used a cross-over design of 298 women who initiated either weekly or monthly bisphosphonates for 3 months and then switched to the alternative treatment. That study found the majority (71% vs. 29%, $p < .0001$) preferred the monthly bisphosphonate, however no findings were reported on adherence.^[11]

Our study has several important limitations. First, we cannot assess the reasons for discontinued therapy, so some of our classification of noncompliance may have been in accordance with the advice of physicians. We also did not evaluate the use of estrogen therapy, etidronate, or nasal calcitonin, so patients who switched to these therapies would have been considered noncompliant. Secondly, we do not know if patients actually took the medication, only that they acquired the medication. Thirdly, we did not evaluate the effects of noncompliance on treatment outcomes, although the relationships between adherence and bone mineral density, as well as fracture risk has been demonstrated in other studies.^[20,21] Also, there may have been unmeasured confounders. For instance, we found few differences in the characteristics of patients by dosing formulation, but there may have been unmeasured differences, such as previous experiences with adverse drug events. Physicians may preferentially prescribe the monthly bisphosphonates to individuals believed to be at increased risk for nonadherence. Fourth, the patterns of monthly use come from the first year of market availability and these patterns may change over time. Lastly, the generalizability of our study is limited to insured patients who face fewer cost barriers to medications available in only branded versions.

Despite these limitations, this study offers one of the first assessments of the adoption of once-monthly bisphosphonates into general clinical practice. The similarity in patient characteristics between early adopters of the monthly formulations and the users of the established weekly formulation was notable; we found few differences and even those observed (e.g., slightly older age for monthly users) were statistically significant due to large sample size but not clinically meaningful. Instead, regional practice patterns and types of health plans appeared to be the stronger predictors of receipt of the monthly formulation, particularly in comparison to patients receiving daily bisphosphonates. Also, our dataset as drawn from comprehensive health insurance records provides a more complete assessment of prescription use than can be made using only the dispensing records of one pharmacy network.

The low adherence observed among all dosing groups suggests that merely reducing the dosing frequency of oral bisphosphonates is not enough to improve adherence. Instead, multimodal interventions may be needed, especially with a technology innovation in dosing schedule that may require a paradigm shift in adherence management. In the one study reporting an adherence advantage with monthly bisphosphonates, patients received a phone call reminder from a

trained nurse a few days before the next dose was due.[17] However, even with this support, the proportion of patients persisting with the once-monthly bisphosphonate was still only 57% after 6 months of therapy.[17] From research conducted on the older bisphosphonates, we know that compliance improves with regular bone mineral density testing and patient-physician discussions about how the results relate to the progression of osteoporosis.[22] All patients initiated on bisphosphonates, regardless of dosing schedule, require reinforcement in the importance of adherence.

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Bibliography

1. Chesnut IC, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004;19(8):1241–9. [PubMed: 15231010]
2. Delmas PD, Recker RR, Chesnut CH 3rd, et al. Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study. *Osteoporos Int* 2004;15(10):792–8. [PubMed: 15071723]
3. Boniva Product Labelling. Vol. v3.13. Mar. 2005
4. Miller PD, McClung MR, Macovei L, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res* 2005;20(8):1315–22. [PubMed: 16007327]
5. Recker RR, Gallagher R, MacCosbe PE. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. *Mayo Clin Proc* 2005;80(7):856–61. [PubMed: 16007889]
6. Cramer JA, Silverman S. Persistence with bisphosphonate treatment for osteoporosis: finding the root of the problem. *Am J Med* 2006;119(4 Suppl 1):S12–7. [PubMed: 16563936]
7. Cramer JA, Amonkar MM, Hebborn A, Altman R. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin* 2005;21(9):1453–60. [PubMed: 16197664]
8. Solomon DH, Avorn J, Katz JN, et al. Compliance with osteoporosis medications. *Arch Intern Med* 2005;165(20):2414–9. [PubMed: 16287772]
9. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med* 2007;167(6):540–50. [PubMed: 17389285]
10. Gold DT, Safi W, Trinh H. Patient preference and adherence: comparative US studies between two bisphosphonates, weekly risedronate and monthly ibandronate. *Curr Med Res Opin* 2006;22(12):2383–91. [PubMed: 17257452]
11. Emkey R, Koltun W, Beusterien K, et al. Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Boniva Alendronate Trial in Osteoporosis (BALTO). *Curr Med Res Opin* 2005;21(12):1895–903. [PubMed: 16368038]
12. Adamson, Dm; Chang, S.; Hansen, LG. Health Research Data for the Real World: The MarketScan Databases. White Paper. Thomson Medstat; Ann Arbor, MI: 2005.
13. MarketScan Research Databases User Guide and Database Dictionary. Thomson Medstat; Ann Arbor, MI: 2006.
14. Andrade SE, Gurwitz JH, Chan KA, et al. Validation of diagnoses of peptic ulcers and bleeding from administrative databases: a multi-health maintenance organization study. *J Clin Epidemiol* 2002;55(3):310–3. [PubMed: 11864803]
15. Ash AS, Ellis RP, Pope GC, et al. Using diagnoses to describe populations and predict costs. *Health Care Financ Rev* 2000;21(3):7–28. [PubMed: 11481769]
16. Zhao Y, Ellis RP, Ash AS, et al. Measuring population health risks using inpatient diagnoses and outpatient pharmacy data. *Health Serv Res* 2001;36(6 Pt 2):180–93. [PubMed: 16148968]

17. Cooper A, Drake J, Brankin E. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. *Int J Clin Pract* 2006;60(8): 896–905. [PubMed: 16800837]
18. Weiss TW, Henderson SC, McHorney CA, Cramer JA. Persistence across weekly and monthly bisphosphonates: analysis of US retail pharmacy prescription refills. *Curr Med Res Opin* 2007;23(9):2193–203. [PubMed: 17686228]
19. Simon J, Beusterien K, Kline Leidy N, Hebborn A. Women with postmenopausal osteoporosis express a preference for once-monthly ibandronate versus once-weekly bisphosphonate treatment. *Female Patient* 2005;30:31–36.
20. Briesacher BA, Andrade SE, Yood RA, Kahler KH. Consequences of poor compliance with bisphosphonates. *Bone*. 2007
21. Yood RA, Emani S, Reed JI, Lewis BE, Charpentier M, Lydick E. Compliance with pharmacologic therapy for osteoporosis. *Osteoporos Int* 2003;14(12):965–8. [PubMed: 14504697]
22. Tosteson AN, Grove MR, Hammond CS, et al. Early discontinuation of treatment for osteoporosis. *Am J Med* 2003;115(3):209–16. [PubMed: 12947959]

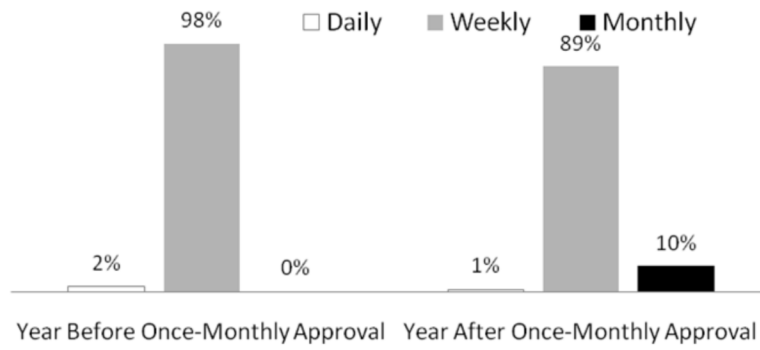


Figure 1. Adoption of Once Monthly Bisphosphonates by New Users

The percentage of new users on daily, weekly and monthly bisphosphonates 1 year before and 1 year after the approval of once-monthly bisphosphonates.

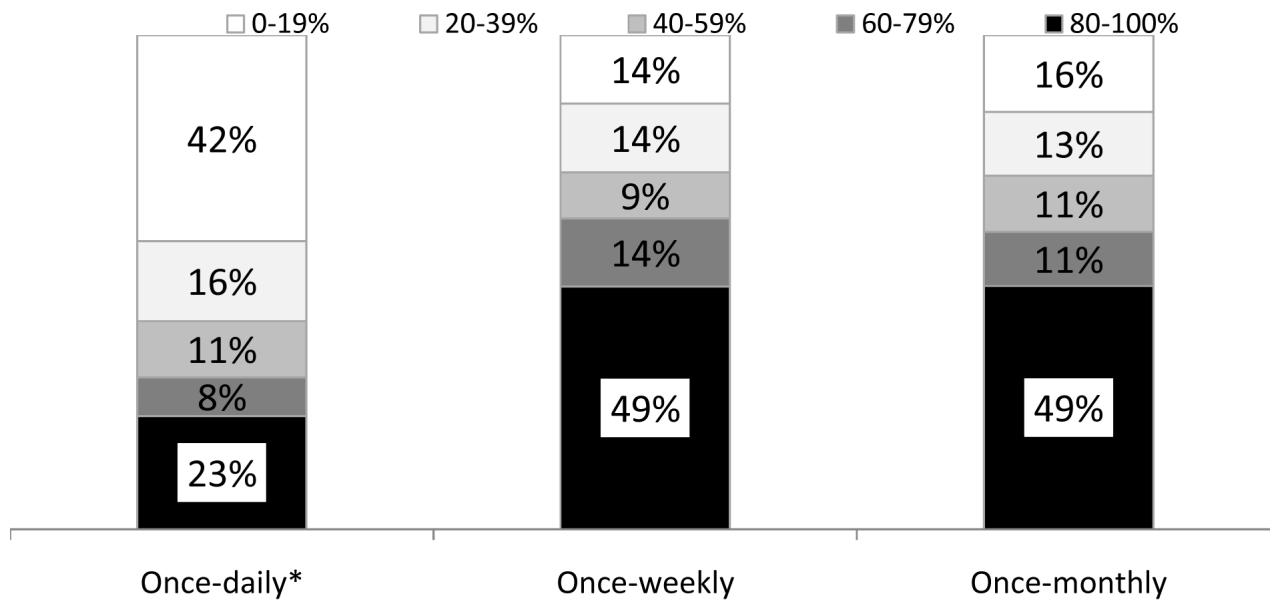
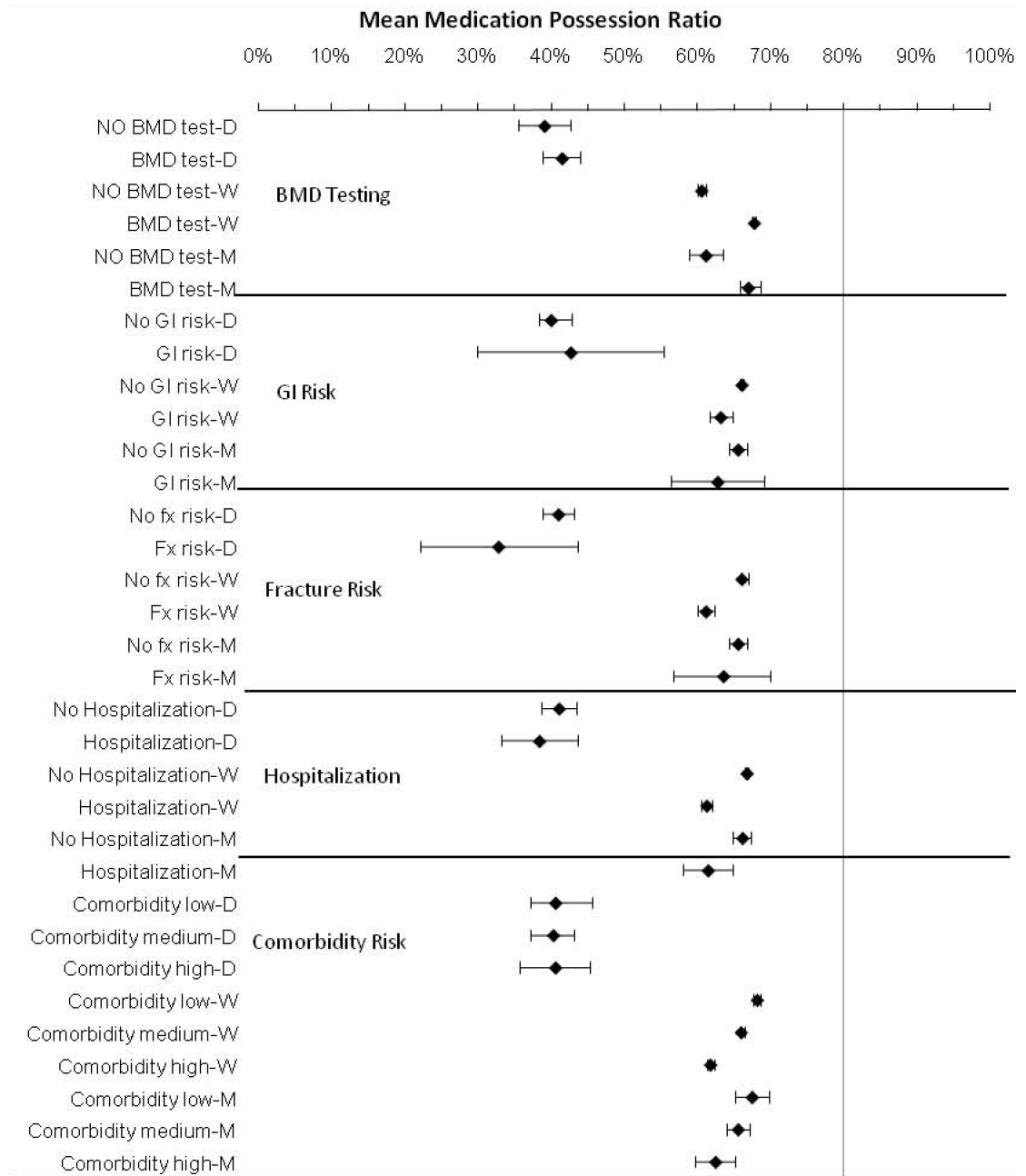
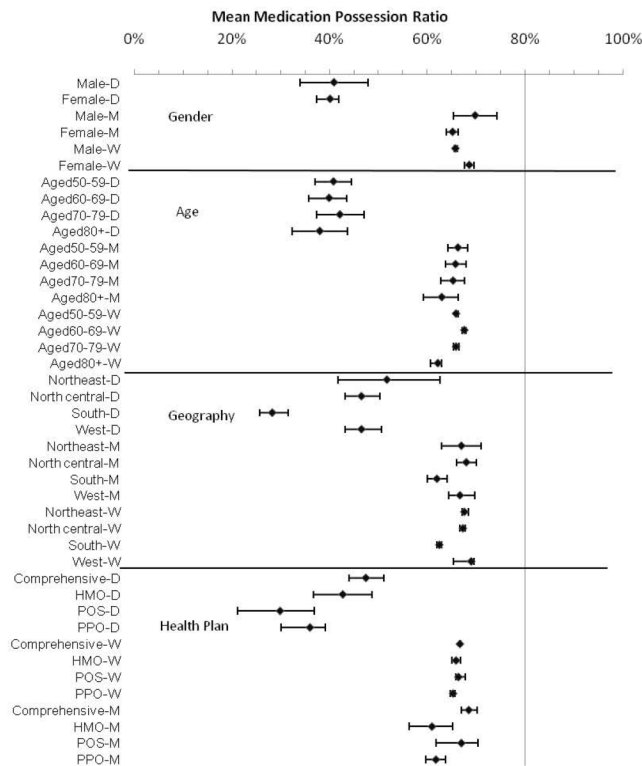


Figure 2. Overall Year 1 Adherence of Bisphosphonate Initiators by Dosing Frequency
 The frequency distribution of the medication possession ratio for new users of daily, weekly and monthly bisphosphonates.





Figures 3a and 3b.

Stratified Year 1 Adherence of Bisphosphonate Initiators by Dosing Frequency and Key Baseline Characteristics. The mean medication possession ratio for new users of daily, weekly and monthly bisphosphonates stratified by gender, sex, health plan, geographic residence, bone mineral density testing, gastrointestinal disorder risk, hospitalization, and comorbidity risk. Footnote: D=daily dosing users, W=weekly dosing users, M=monthly dosing users

Table 1

Characteristics of Patients in Year Before Initiating Bisphosphonate Therapy by Dosing Schedule

Characteristics	Monthly	Weekly	Daily
No. of patients	n=3,166	N=56,925	N=1,034
Age, mean (SD)	66.0 (10.1)	65.4 (10.2)*	65.7 (10.4)*
Female sex (%)	93.1	90.1*	90.1*
Comorbidity risk score, mean (SD)	.754 (.63)	.743 (.66)	.754 (.65)
Selected diagnoses and medical care history			
Any bone mineral density testing, (%)	72.7	74.9*	65.3*
Any serious GI risk, (%)	3.7	3.2	2.5
Any osteoporotic fracture, (%)	3.3	3.7	3.8
Any hospitalization (%)	13.3	14.4	16.3*
Geographic residence (%)			
North East	8.7	9.5*	4.5*
North Central	38.9	37.8*	35.2*
South	37.6	34.2*	34.1*
West	14.5	18.5*	26.0*
Type of health plan (%)			
Comprehensive	49.9	44.6*	36.2*
Health maintenance organization	0.1	0.0	12.5*
Point-of-service	42.8	46.3*	7.8*
Preferred provider organization	6.6	7.8*	43.6*

* =p<.05 relative to monthly users