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Adherence to Daily, Weekly, and Monthly Dosing Regimens of Bisphosphonates for Osteoporosis Treatment in Postmenopausal Women in Japan: A Retrospective Study Using Claims Data

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Poor medication adherence of osteoporosis patients is a major global medical problem because of its negative impact on health outcomes and quality of life. The aim of this study was to evaluate how differences in dosing regimens influence adherence to oral bisphosphonates using data from a large health insurance provider in Japan. This was a retrospective observational study using claims data obtained between October 2012 and January 2018, from the community-based National Health Insurance program of a large city in Japan. The data included in the analysis were obtained from women 60 to 74 years old whose oral bisphosphonate prescription was detected between April 2013 and February 2017. Treatment adherence was monitored from the initial prescription for one year, i.e., up to January 2018. Primary comparisons among the daily-dosing, weekly-dosing, and monthly-dosing groups were based on the mean medication possession ratio (MPR). Data from a total of 3,958 patients were analyzed. The numbers of patients aged 60-64, 65-69, and 70-74 were 425, 1,400, and 2,133, respectively. The highest mean MPR was 69.4% for the monthly-dosing of bisphosphonates, followed by the weekly-dosing at 63.5%, and daily-dosing at 57.2%. Using the Kruskal-Wallis test with Dunn-Bonferroni correction, there were significant differences in mean MPR for daily versus weekly ($p < 0.01$), daily versus monthly ($p < 0.001$), and weekly versus monthly dosing regimens ($p < 0.05$). These results suggest significantly more patients adhere to a monthly or weekly regimen of bisphosphonates in the treatment of osteoporosis than to a daily regimen.

Keywords: adherence; bisphosphonates; claims data; dosing regimens; Japan
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Introduction

Osteoporosis is a global chronic disease characterized by low bone mineral density and poor bone quality that reduces bone strength and increases fracture risk (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy 2001; Woolf and Pfleger 2003). More than 50% of women experience osteoporosis during their lives (Ross 1996). Osteoporotic fractures can increase pain, disability, total health care costs, and mortality (Tu et al. 2018). Bisphosphonates are used in the treatment of osteoporosis and have been shown to increase bone strength and reduce the risk of fracture (Lewiecki 2010). A study of more than 58,000 osteoporosis patients who initiated drug therapy for osteoporosis showed that one year of continuous therapy was associated with a reduced risk of hip fracture, compared to discontinuous therapy (McCombs et al. 2004).

However, adherence to oral bisphosphonate therapy is not adequately high (Tosteson et al. 2003; Kinov and Boyanov 2012; Fatoye et al. 2019; Nakatoh et al. 2021). Poor adherence to osteoporosis therapy can be motivated by several factors such as adverse drug effects, drug cost, and inconvenience (Rossini et al. 2006; Carr et al. 2006). Particularly, after taking the drug, patients are required to remain upright for at least 30 min to minimize gastroesophageal reflux, and refrain from food, medications, and liquids other than tap or filtered water for at least 30-45 min to

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optimize absorption (Favus 2010). This is a major limitation, especially since the medication is taken every day (Cotte et al. 2010). For this reason, various oral bisphosphonate regimens with less frequent dosing than daily administration (e.g., once-weekly and once-monthly oral regimens) have been developed to reduce the constraints associated with dosing (Cotte et al. 2010). Most of the previous studies have focused on adherence to and comparison between daily and weekly administration (Cramer et al. 2005; Recker et al. 2005; Cramer et al. 2006; Tafaro et al. 2013). However, very few studies have focused on adherence to monthly administration (Cotte et al. 2010; Kishimoto and Maehara 2015).

A study using prescription data in France (Cotte et al. 2010) reported that adherence to oral bisphosphonate treatment was significantly higher with monthly dosing compared to weekly dosing. However, the study used prescription data collected from general practitioners (GPs); therefore, it is difficult to verify whether patients continued their treatment with oral bisphosphonates in other settings (i.e., hospitals) with the GPs' referral letters during the follow-up period. A study using a prescription database in Japan also reported that those on a monthly regimen showed better adherence to treatment compared to those on weekly and daily regimens (Kishimoto and Maehara 2015). However, the study only included data from patients who visited university hospitals for the treatment of osteoporosis, and, therefore, it is difficult to generalize regarding whether monthly administration leads to better adherence to oral bisphosphonate therapy due to limited data. Another study in Japan, which was conducted in a cluster-randomized, multicenter crossover trial, demonstrated a strong patient preference for the convenience of the monthly bisphosphonate regimen over the weekly regimen, but did not report adherence (Iwamoto et al. 2016).

Medical and pharmaceutical claims information from large insurance organizations offer the opportunity to efficiently identify and evaluate patients receiving pharmacological and medical care for osteoporosis. Refill patterns and details of individual prescription refills in claims databases allow for the longitudinal tracking of prescription activity of patients even after they move to other settings, if they remain enrolled in the same insurance plan. The aim of the present study was to evaluate the influence of dosing regimen (daily, weekly, or monthly) on adherence to oral bisphosphonates, using data from a large insurance provider in Japan.

Material and Methods

Data Source

We used longitudinal claims data from the National Health Insurance program, a community-based health insurance program managed by local municipalities, of a large city within the Tokyo metropolitan area in Japan. This type of health insurance covers the self-employed, the irregularly employed, pensioners, and their dependents, who were younger than 75 years old and live in the municipality (Ikegami et al. 2011). Data were provided in a fully anonymized form. Patient's prescription activity, including historical information, was tracked for a rolling 64-month period from October 2012 to January 2018. The claims data contains the inpatient and outpatient claims history of approximately 260,000 insured individuals between 0 and 74 years old. The data contains patient-level prescription information. The data elements include the brand and generic names of the prescription dispensed, dosage strength, quantity, and date of prescription fill or refill, as well as patient demographic characteristics such as age and sex. Other features of the data have been reported elsewhere (Sugiyama et al. 2019; Fukunishi et al. 2020; Iba et al. 2020). The study was approval by the Research Ethics Committee, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (No. 10834) and performed in compliance with relevant laws and institutional guidelines.

Study Population

For this study, we first selected women 60 to 74 years old, whose oral bisphosphonate medication usage was measured between April 2013 and February 2017 (N = 10,811). Treatment adherence was monitored from the initial prescription for one year up to January 2018. The initial prescription was determined by the absence of any bisphosphonate doses in the six months prior to the start of the newly prescribed bisphosphonates. Therefore, among the chosen women, those prescribed any bisphosphonate in the six months prior to the start of the newly prescribed bisphosphonates were excluded (N = 4,389). In the analysis, we only included women prescribed oral bisphosphonates at doses used for the treatment or prevention of osteoporosis (i.e., alendronate at 5 mg and 35 mg; risedronate at 2.5 mg, 17.5 mg, and 75 mg; minodronate at 1 mg and 50 mg; brand-name or generic). Information on every prescribed bisphosphonate is recorded on the claims data because in Japan, oral bisphosphonates are only available with a prescription; therefore, patients must visit a clinic or hospital regularly to receive treatment.

Women who were not continuously enrolled in the same health insurance program between October 2012 and twelve months after the initial prescription (N = 2,027) were excluded from the analysis. It is unknown whether they relocated to other cities, were enrolled in other types of health insurance programs, or otherwise. Women prescribed bisphosphonate injections for the twelve months after the initial prescription (N = 61) were excluded. We also excluded the women who were hospitalized with a batch payment system (N = 73), in which drug fees are included in the payment. This is because there is no data about anti-osteoporosis, and therefore adherence would be underestimated.

Women in the database were placed into three groups based on their dosing regimens, those whose first bisphos-

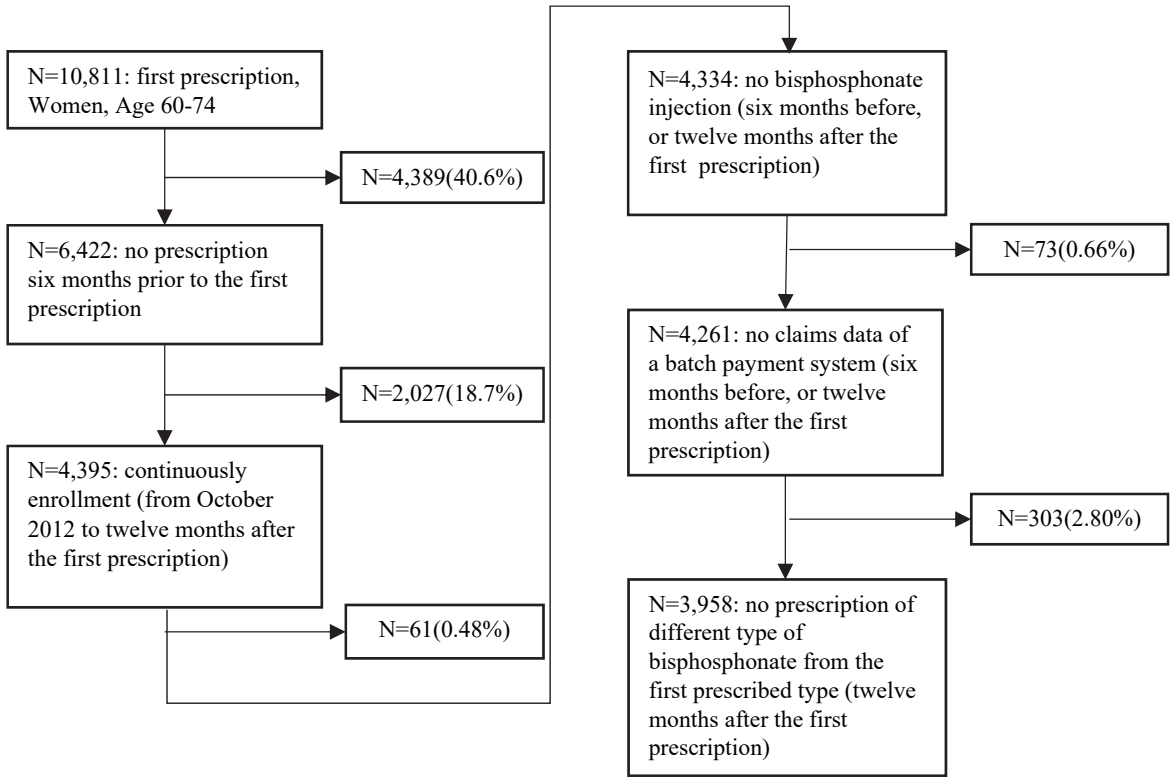

Fig. 1. Study flow diagram for the sample.

phonate prescription was based on (1) a daily regimen, (2) a weekly regimen, or (3) a monthly regimen, between April 2013 and February 2017. Women who were switched from a daily to a weekly regimen or from a weekly to a monthly regimen and vice versa after the initial prescription (N = 303) were excluded from the analysis. Finally, to achieve a more objective and stable measurement and comparison of medication adherence, only the subjects (N = 3,958) who were prescribed oral bisphosphonate medication were selected (Fig. 1).

Patients were included in the daily bisphosphonate group if they first received at least a one-day supply of a daily dose of a bisphosphonate (alendronate at 5 mg, risedronate at 2.5 mg, or minodronate at 1 mg) during the period between April 2013 and February 2017. Patients who first received at least a one-day supply of a weekly dose of a bisphosphonate (alendronate at 35 mg or risedronate at 17.5 mg) during the period from April 2013 to February 2017 were included in the weekly bisphosphonate group. Patients who first received at least a one-day supply of a monthly dose of a bisphosphonate (risedronate at 75 mg or minodronate at 50 mg) from April 2013 to February 2017 were included in the monthly bisphosphonate group.

Dosing regimens of bisphosphonates was classified into three types (Table 1). As a class, daily dosing regimens of alendronate, risedronate, and minodronate have comparable efficacy, tolerability, dosing requirements, dosing intervals, and cost within the daily bisphosphonate group. Thus, we did not separately analyze daily dosing regimens of alendronate, risedronate, and minodronate. Similarly, weekly dosing regimens of alendronate and risedronate were not analyzed separately within the weekly bisphosphonate group. For monthly dosing regimens of risedronate and minodronate, they also have comparable efficacy, tolerability, dosing requirements, and cost, but have different dosing intervals (risedronate for 30 days and minodronate for 28 days). This is because the recommended dosing frequency for 50-mg tablets of minodronate is 28 days. However, the recommended dosing frequency for 75-mg tablets of risedronate is once-a-month. It is difficult to define specific days for the dosing interval of the 75-mg risedronate tablets. In our study, we used a pre-specified dosing interval of 30 days for 75 mg of risedronate, because the dosing size of 75 mg of risedronate is 30 times the 2.5

Table 1. Classification of dosing regimens of bisphosphonates.

Dosing regimens	Bisphosphonates
Daily	Alendronate (5 mg) Risedronate (2.5 mg) Minodronate (1 mg)
Weekly	Alendronate (35 mg) Risedronate (17.5 mg)
Monthly*	Risedronate (75 mg) for 30 days Minodronate (50 mg) for 28 days

*Two types of a monthly-dosing bisphosphonates were analyzed separately in terms of the dosing interval.

mg dose of risedronate, which has a dosing frequency of once-a-day. For this reason, in regard to the dosing intervals, monthly dosing regimens of risedronate and minodronate were analyzed separately within the monthly bisphosphonate groups.

Analysis

The medication possession ratio (MPR) was calculated for each patient and used as an indicator of medication adherence (Recker et al. 2005; Cramer et al. 2005, 2006; Cotte et al. 2010; Tafaro et al. 2013; Kishimoto and Maehara 2015). The MPR was defined as the total number of days of supply of bisphosphonate for one year, starting after the first prescription of bisphosphonate, divided by the 365 potential days of supply (Lekkerkerker et al. 2007). The number of days of supply of bisphosphonate for each patient was calculated from all prescriptions filled and refilled according to drug name and dose (Recker et al. 2005). Each daily bisphosphonate dose was treated as a one-day supply; thus, for a prescription for 2.5 mg/day of risedronate, 30 tablets were treated as a 30-day supply for that patient. Each weekly bisphosphonate dose was treated as a 7-day supply; for example, a prescription for 35 mg/week of alendronate, 4 tablets were treated as a 28-day supply for that patient. Each monthly bisphosphonate dose was treated as a 28-day supply for a prescription of 50 mg of minodronate, and a 30-day supply for a prescription of 75 mg of risedronate. The MPR was capped at 100%, to prevent situations in which the total number of days of supply of bisphosphonate end up greater than 365 days (e.g., a patient who routinely refills their bisphosphonate prescription early and a patient who has used bisphosphonates for greater than the prescribed frequency) (Recker et al. 2005; Pittman et al. 2011).

Primary comparisons among the daily-dosing, weekly-dosing, and monthly-dosing groups were based on the mean MPR. The mean MPR was compared in all dosing regimen groups for all patients who met the study criteria. We also compared the mean MPR among the dosing groups as a function of the patients' age group (60-64, 65-69, and 70-74 years) in order to test the influence of the patients' age. The significance of the difference in MPR among the three dosing regimens for all patients and for each patient's age group was tested using the Kruskal-Wallis test by the "kruskalTest" function in the "PMCMRplus" package (Pohlert 2018). After the Kruskal-Wallis test, we did post-hoc pairwise comparisons among the three dosing types using Dunn's method (Dunn 1964) implemented by the "kwAllPairsDunnTest" function in the "PMCMRplus" package (Pohlert 2018), using the Bonferroni method to correct the p-values.

Furthermore, to check whether there were any differences over time in the mean MPR in this study period, we conducted the further analysis. First, we split the 47-month (April 2013 to February 2017) study period into 2 periods, the first period (24 months: April 2013 to March 2015) and the second period (23 months: April 2015 to February 2017). We calculated the mean MPR of monthly, weekly, and daily dosing of bisphosphonate for all age groups in each period. Then, the significance of the difference in the mean MPR between two periods for each dosing type was tested using the unpaired two-sample t-test. All analyses were conducted using the statistical software R, version 3.6.1 (R Core Team 2019).

Results

Patient Characteristics

Data from a total of 3,958 patients who met the study criteria were analyzed. Table 2 shows the number of patients in daily, weekly, and monthly dosing by age. Most patients received bisphosphonates weekly. The largest age group of patients treated with bisphosphonates was patients between 70-74 years old (10.7%, 35.4%, and 53.9% for the 60-64, 65-69, and 70-74 age groups, respectively). The proportion of patients for each age group was similar across dosing types.

Mean MPR

Fig. 2 shows that the mean MPR of bisphosphonates was different both as a function of dosing interval and age group; (i) daily: 40.4% [95% Confidence Interval (CI) = 21.2-59.5], 55.7% (46.3-65.1), 61.9% (53.9-70.0), and 57.2% (51.4-63.0) for each age group [60-64, 65-69, 70-74 years and all (60-74 years)], respectively; (ii) weekly: 60.5% (55.3-65.7), 63.2% (60.4-65.9), 64.3% (62.2-66.5), and 63.5% (61.9-65.1); and (iii) monthly: 62.9% (57.6-68.3), 69.8% (66.9-72.7), 70.5% (68.2-72.8), and 69.4% (67.7-71.1). Table 3 shows the details of the results.

For all age groups, the differences among daily, weekly, and monthly dosing regimens were statistically significant ($p < 0.001$). The highest mean MPR was observed in the monthly-dosing regimen of bisphosphonates, followed by the weekly-dosing and daily-dosing regimens. There were significant differences in MPR for daily versus weekly (Bonferroni adjusted $p < 0.01$), for daily versus monthly (Bonferroni adjusted $p < 0.001$) and for weekly versus monthly dosing regimens (Bonferroni adjusted $p < 0.05$).

Furthermore, the mean MPR was compared among the dosing types (daily, weekly, and monthly dosing types) for

Table 2. Number of patients in daily, weekly, and monthly dosing regimens by age between April 2013 and February 2017.

	Bisphosphonate dosing regimen		
Age	Daily (N = 180)	Weekly (N = 2,152)	Monthly (N = 1,626)
60-64	18 (10.0%)	217 (10.1%)	190 (11.7%)
65-70	73 (40.6%)	754 (35.0%)	573 (35.2%)
70-74	89 (49.4%)	1,181 (54.9%)	863 (53.1%)

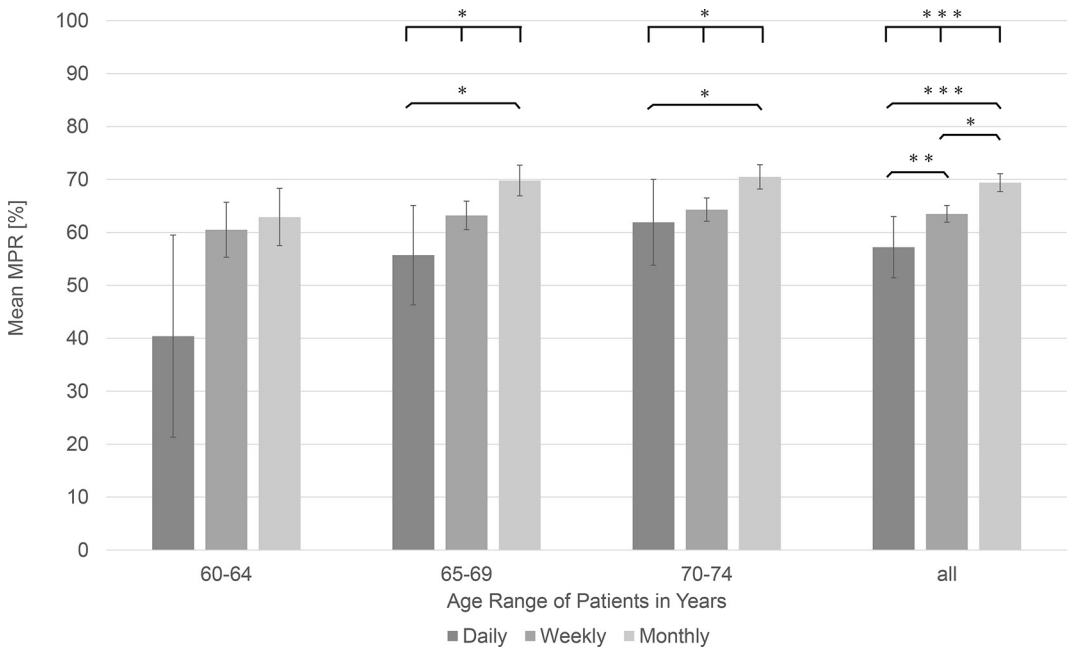

Fig. 2. Mean medication possession ratio (MPR) for each dosing regimen of bisphosphonates by age group between April 2013 and February 2017.
The numbers of patients in each group of dosing regimen by age group are the same as those in the corresponding group in Table 2. Error bars represent 95% Confidence Interval of mean MPR for each group.
Significance statistical differences shown as Kruskal-Wallis test or Bonferroni adjusted; *p < 0.05, **p < 0.01, ***p < 0.001.

Table 3. Mean medication possession ratio (MPR) in daily, weekly, and monthly dosing regimens by age between April 2013 and February 2017.

	Bisphosphonate dosing regimen		
Age	Daily	Weekly	Monthly
60-64	40.4 (CI = 21.2-59.5)	60.5 (CI = 55.3-65.7)	62.9 (CI = 57.6-68.3)
65-70	55.7 (CI = 46.3-65.1)	63.2 (CI = 60.4-65.9)	69.8 (CI = 66.9-72.7)
70-74	61.9 (CI = 53.9-70.0)	64.3 (CI = 62.2-66.5)	70.5 (CI = 68.2-72.8)
all	57.2 (CI = 51.4-63.0)	63.5 (CI = 61.9-65.1)	69.4 (CI = 67.7-71.1)

The numbers of patients in each group of dosing regimen by age group are the same as those in the corresponding group in Table 2.
CI, Confidence Interval.

each age group. For the 65-69 and 70-74 age groups, the differences in MPR due to dosing type among daily, weekly, and monthly groups were statistically significant ($p < 0.05$). The highest mean MPR was observed with the monthly-dosing of bisphosphonates, followed by weekly and daily-dosing. There were significant differences in MPR between the daily and monthly (Bonferroni adjusted $p < 0.05$) dosing groups. However, for the 60-64 age group, differences in MPR among patients receiving a daily, weekly, or monthly regimen were not statistically significant ($p = 0.08$). The highest mean MPR was observed with the monthly dosing of bisphosphonates, followed by weekly and daily dosing.

Table 4 shows the number of patients in the first and second periods. Fig. 3 shows that the MPRs with daily, weekly, and monthly dosing bisphosphonate for all age groups were 56.9% (95% CI = 49.3-64.5), 63.0% (61.0-65.0) and 69.0% (66.7-71.1) in the first period, and 57.8% (95% CI = 48.6-66.9), 64.5% (61.8-67.3) and 70.0% (67.1-72.9) in the second period. The highest mean MPR was observed for the monthly-dosing regimen of bisphosphonates, followed by the weekly-dosing and daily-dosing regimens in the both periods. The differences among daily, weekly, and monthly dosing regimens were statistically significant for the first period ($p < 0.001$) and for the second period ($p < 0.05$). For the first period, there were significant differences in MPR daily versus weekly dosing groups (Bonferroni adjusted $p < 0.05$) and daily versus monthly dosing regimen (Bonferroni adjusted $p < 0.001$) were observed. The differences between two periods in each

Table 4. Number of patients in daily, weekly, and monthly dosing groups by age and period.

1st period (April 2013-March 2015)			
	Bisphosphonate doses		
Age	Daily (N = 109)	Weekly (N = 1,406)	Monthly (N = 1,058)
60- 64	16 (14.7%)	168 (11.9%)	131 (12.4%)
65-70	45 (41.3%)	468 (33.3%)	361 (34.1%)
70-74	48 (44.0%)	770 (53.5%)	566 (53.5%)
2nd period (April 2015-February 2017)			
	Bisphosphonate doses		
Age	Daily (N = 71)	Weekly (N = 746)	Monthly (N = 568)
60-64	2 (2.8%)	49 (6.6%)	59 (10.4%)
65-70	28 (39.4%)	286 (38.3%)	212 (37.3%)
70-74	41 (57.8%)	411 (55.1%)	297 (52.3%)

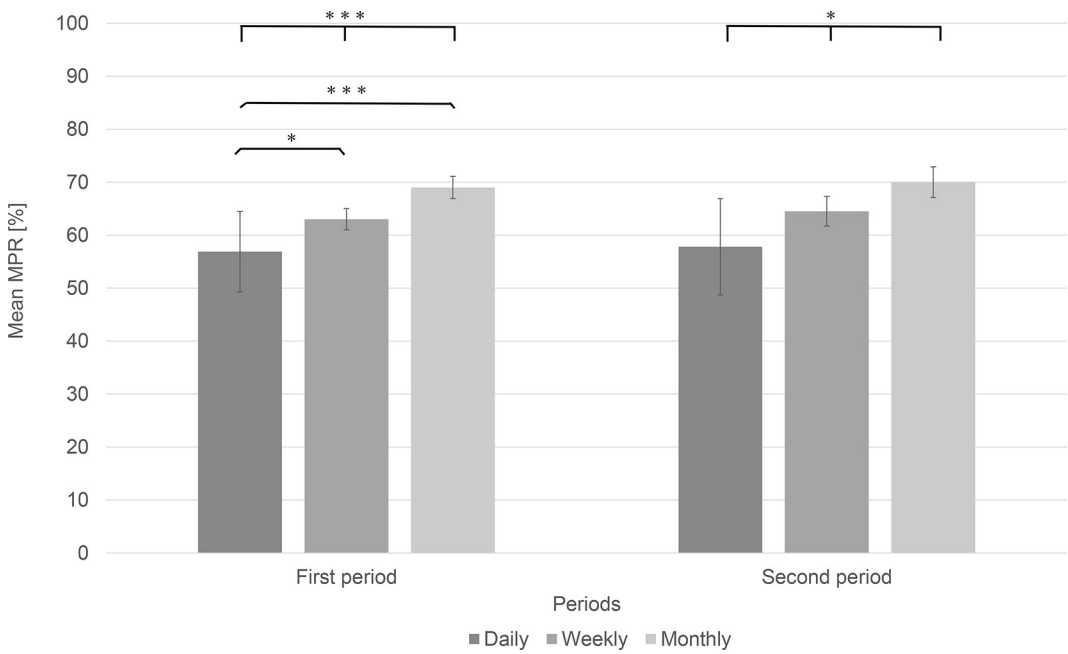

Fig. 3. Mean medication possession ratio (MPR) for each dosing regimen of bisphosphonates for all age groups in the first and second periods.
The numbers of patients in each group of dosing regimen for the two periods are the same as those in the corresponding group in Table 4. Error bars represent 95% Confidence Interval of mean MPR for each group.
Significance statistical differences shown as Kruskal-Wallis test or Bonferroni adjusted; *$p < 0.05$, ***$p < 0.001$.

dosing type were not statistically significant. This result means that there might be no difference over time of MPR.

Discussion

Patient adherence for all age groups (60-74 years) was highest for a monthly dosing regimen of bisphosphonates and lowest for a daily dosing regimen, with a weekly dosing regimen in between; statistically significant differences were observed between each pair groups. The improved adherence to monthly and weekly dosing suggests that less frequent dosing may be beneficial to postmenopausal women with osteoporosis in Japan.

In a previous study, in which adherence to two dosing intervals of bisphosphonates (weekly and monthly) was compared (Cotte et al. 2010), monthly regimens showed superior results. The results of our study are consistent with those of the previous study. Another study in Japan (Kishimoto and Maehara 2015) compared three dosing intervals of bisphosphonates (daily, weekly, and monthly) for all patients and found that the best adherence to the bisphosphonate therapy was in the monthly dosing group. The results for all age groups (60-74 years) in our study are

consistent with the results of the previous study. Furthermore, unlike in the previous studies, the present study analyzed adherence as a function of the patients' age [60-64, 65-69, 70-74 years, and all (60-74 years)]. Our study shows that there were significant differences between the daily and monthly dosing for the 65-69 and 70-74 age groups. For these age groups, patient adherence to the monthly dosing regimen of bisphosphonates was significantly higher than adherence to the daily regimen of bisphosphonates. This implies that monthly dosing of bisphosphonates will improve adherence for patients aged 65-74 over their adherence to a daily dosing of bisphosphonates.

However, there was no significant difference among daily, weekly, and monthly dosing for the 60-64 age group. One possible reason is the small sample size of the 60-64 age group, because the number of patients who start on medicine for osteoporosis at the age of 60-64 is assumed to be relatively small. In fact, clinical practice guidelines universally recommend bone mineral density screenings for women aged 65 and older (U.S. Preventive Services Task Force 2011; Gourlay et al. 2015). In addition, for the 60-64 age group, adherence to all the regimens was relatively low compared to the other age groups, which might be other possible reason why there was no difference. Younger patients generally have less severity of illness than older ones, which decreases their awareness about their health status, and this seems to have a negative effect on awareness of the importance of taking bisphosphonate medications. Therefore, it is more important to look for other means of improving adherence for younger patients than prescription of less frequent dosing of bisphosphonate.

Furthermore, from the adequate adherence point of view, adherence to monthly dosing was the highest, but the mean MPR for the monthly dosing of bisphosphonates did not exceed 80% in each age group. For monthly prescriptions, patients may be more likely to forget to take the medication itself because of the long interval between each treatment. Nevertheless, the 80% MPR has been associated with adequate medication adherence (Hurley et al. 1998; Recker et al. 2005) and an improved outcome of osteoporosis medication (Caro et al. 2004; Siris et al. 2006). A recent study using a Belgian database reported that the risk of hip fracture increased by 0.4% for each incremental decrease of the MPR by 1% (Rabenda et al. 2008). Therefore, it is important to recommend less frequent dosing and other treatment methods to increase the MPR to 80%.

Our study has two notable strengths compared to previous studies (Cotte et al. 2010; Kishimoto and Maehara 2015): 1) a general patient population and 2) a longer observation period between doses. Considering that a monthly bisphosphonate dosing regimen was relatively new, we were able to identify the study patients who received their first prescription of bisphosphonates. First, claims data from large insurance organizations offers the opportunity to track each patient's prescription activity longitudinally, even after patients move to other settings, if they remain enrolled in the same insurance plan. Second, a previous study in Japan (Kishimoto and Maehara 2015) included patients who received their first prescription of bisphosphonates during a 15-month period from November 2011 to January 2013. In Japan, monthly dosing of minodronate, oral bisphosphonate, was approved in September 2011. New drug diffusion is determined by the strategies of pharmaceutical companies, government policies, as well as the behavior of medical professionals (Lubloy 2014). The previous study (Kishimoto and Maehara 2015) may have been critically affected by the prescription behaviors of medical doctors at an early stage of adaptation to the market.

The present study included patients who received their first prescription of bisphosphonates during a 47-month period from April 2013 to February 2017. This extended period enabled us to derive a greater understanding of prescription behaviors of medical doctors and drug utilization behaviors of patients prescribed monthly doses of bisphosphonates in a real-world setting.

The differences over time in the mean MPR between all age groups (60-74 years) in this study period were not statistically significant. The highest mean MPR was observed in the monthly dosing regimen of bisphosphonates, followed by the weekly dosing and daily dosing regimens in both the first period (April 2013 to March 2015) and the second period (April 2015 to February 2017). The result is consistent with the result for the entire study period (April 2013 to February 2017).

Some limitations should be noted in this study. First, the patients were members of a National Health Insurance program in a large city in Japan. Therefore, there exist potential biases related to both physician prescribing practices and patient drug utilization behavior associated with different geographical areas of the country. Second, this study's data source covers the self-employed, the irregularly employed, pensioners, and their dependents, who were younger than 75 years old and live in the municipality. So, people insured by the employee insurance system and the elderly aged 75 years or older were not included. We thought the result of this study could be applicable to those insured by the employee insurance system, as shown in a previous study of 13 university hospitals in Japan (Kishimoto and Maehara 2015); however, it might be difficult to apply these results to those who are 75 years old or over because other factors would be involved, such as cognitive functioning. Third, reasons for discontinuation may not be determined only by adherence and may include recommendations by physicians to stop medication caused by unpleasant situations such as occurrences of adverse drug reactions. In addition, we were not able to use data from a patient's examination results, and communication between healthcare professionals and the patient. Some adverse reactions of bisphosphonate for each dosing type were reported (Favus 2010), but it is not substantiated whether

the dosing regimens of bisphosphonate influence the occurrence of adverse reactions. Recently, efficacy and safety of monthly doses of bisphosphonates in osteoporosis patients with mild kidney disease were reported (Sugimoto et al. 2019). Finally, MPR is the accepted standard evaluation measure for medication adherence using retrospective data (Choo et al. 1999; Hudson et al. 2007; Ho et al. 2009). However, it is possible that patients receive medication prescriptions regularly but do not actually take the drugs; this kind of behavior cannot be reflected in the MPR calculation. Therefore, adherence can be sometimes underestimated or overestimated when using MPR. MPR can be over 100% theoretically, if the patient gets refills close to one year after the initial prescription or early refills before the drug completely runs out; this can also lead to an overestimation of adherence. Nonetheless, MPR is one of the most commonly used methods for measuring medication adherence. Also, we capped MPR at 100% for MPRs over 100% to neutralize the possible overestimation in the same manner as many existing studies.

In conclusion, the results of this study, conducted using medical and pharmaceutical claims information obtained from a large community-based health insurance organization, suggest that monthly or weekly regimens are more effective in improving adherence to the bisphosphonate treatment of osteoporosis than a daily regimen. This increase in compliance to oral bisphosphonates may lead to more effective fracture risk reduction.

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Author Contributions

All authors made substantial contributions to conception and design or analysis, interpretation of data, and drafting of the article or critical revision for important intellectual content. Y.K. and Y.K. designed the study. Y. Kosaka wrote the first draft of the manuscript and analyzed the data. T.S., K.H., and Y. Kobayashi reviewed and edited the manuscript. Y. Kobayashi is the guarantor of this article.

Conflict of Interest

The authors declare no conflict of interest.

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