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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Influence of refill adherence method when comparing level of adherence for different dosing regimens

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Abstract
Purpose To examine the impact of two methods when estimating refill adherence in patients using bisphosphonates with different dosing regimens.
Methods In the Swedish Prescribed Drug Register, 18,203 new users of bisphosphonates aged 18–85 years were identified between 1 July 2006 and 30 June 2007 and followed for a maximum of 2 years. The patients were categorised based on dosing regimen: one tablet daily, one tablet weekly, switching between these regimens, and other regimens. Refill adherence was estimated with Continuous measure of Medication Acquisition (CMA, adherent if CMA≥80 %) and the maximum gap method (adherent if gaps <45 days). Differences in adherence between patients in the groups were assessed with logistic regression models controlling for confounding factors.
Results The proportion of patients classified as adherent was higher using CMA compared with patients classified as adherent using the maximum gap method. Patients on one tablet weekly had significantly lower adherence compared with patients on one tablet daily in the main analyses of both methods (the maximum gap method: 73 % vs. 80 %; adjusted OR=0.71; 95 % CI 0.57–0.89 and CMA: 84 % vs. 88 %, adjusted OR=0.75; 95 % CI 0.57–0.99). Patients using the other two dosing regimens had significantly lower adherence compared with patients on one tablet daily using both methods.
Conclusion Choice of method has an impact on the estimates of refill adherence to bisphosphonates. Patients on one tablet weekly dosing had lower adherence compared with patients on one tablet daily dosing using both methods.

Keywords Medication adherence · Swedish Prescribed Drug Register · Dosing regimen · Bisphosphonates

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Introduction

Oral bisphosphonates are a group of medications prescribed to reduce the risk of osteoporotic fractures [1], which afflict 40–50 % of the female population and 13–22 % of the male population during their lifetime [2]. The effectiveness of preventing osteoporotic fractures is compromised by low adherence.

Refill adherence can be measured using registers on purchased prescription medicines [3, 4]. This is an indirect measure of adherence [5, 6] that focuses on drug availability or gaps in treatment. Available methods to study refill adherence have previously been evaluated [6–12]. Refill adherence is sensitive to differences in regulations and reimbursement

systems [13], thus an evaluation of available methods used in different countries is necessary. Two methods measuring refill adherence have been compared in Sweden in statin users [14], a lipid lowering medication with a once-daily dose regimen. The study showed that the level of adherence differed depending on the method chosen to measure refill adherence.

One reason for low adherence to oral bisphosphonates is that they are supposed to be taken after overnight fasting and the patients have to be in an upright position for 30 min afterwards [15]. To improve adherence, tablets that can be taken less often have been developed. Refill adherence of oral bisphosphonates has been previously studied in Sweden [16]. However, differences in adherence estimates due to different methods to assess refill adherence were not estimated, nor were differences in refill adherence between patients on different dosing regimens.

The aim of this study was to analyse and compare two methods of estimating refill adherence among patients using different dosing regimens of bisphosphonates in Sweden; daily or weekly dosing, as well as switching between these dosing regimens.

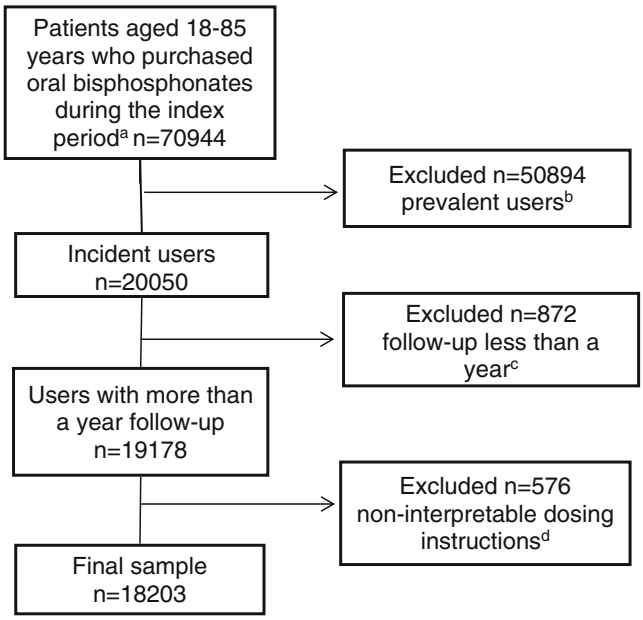

Fig. 1 Exclusion criteria. *a* Patients on multi-dose dispensed drugs (ApoDos) were not eligible for inclusion. *b* Excluding patients who refilled prescriptions of bisphosphonates during 12 months prior to index date. *c* Patients who emigrated or died within 12 months after index were excluded. *d* Patients were excluded if the first dosing instruction or none of the dosing instructions were interpretable

Methods

This study is a part of the Refill Adherence in REgisters (RARE) project [14, 17]. The project has been approved by the regional ethics board in Gothenburg, Sweden (No. 284–09).

Study population

New users of bisphosphonates (Anatomical Therapeutic Chemical classification system code: M05BA), initiating use between 1 July 2006 and 30 June 2007 in the Swedish Prescribed Drug Register (SPDR) [3], aged 18–85 years were included in the study. Individuals with multi-dose dispensed drugs (ApoDos) were excluded, since ApoDos is dispensed automatically; subsequently, these individuals fall outside the aim of the study. Detailed exclusion criteria are presented in Fig. 1. The index date for each participating patient was defined as the first purchase of a bisphosphonate from 1 July 2006 to 30 June 2007 (the index period). Individuals were followed until date of emigration, death or until 2 years after their index date, whichever occurred first.

Data collection

Data on dispensed drugs were collected from the SPDR, which includes individual-based information on all purchased prescribed drugs in Sweden since July 2005 [18]. This register includes information on the purchased drug, drug type and amount, date of dispensing, dosing instructions, age, and sex of the patient. The SPDR was linked with the National Patient Register to include information on duration of hospital admissions, as well as hospital discharge diagnoses classified according to the International Classification of Diseases, 10th revision. Date of death or emigration and sociodemographic variables were collected from the Longitudinal Integration Database for Health Insurance and Labour Market Studies. The record linkage was performed by the register holders using the unique person identification number. The data was de-identified by the register holders before delivery to the investigators.

Exposure variables

The type of bisphosphonate dosing regimen was the exposure variable in this study. This variable was estimated based on the dosing instructions from the prescriber available in the SPDR. Since the dosing instructions are in free text format, an algorithm for the interpretation of these instructions was developed by A.K.J. The algorithm was validated in one round where the authors (E.L., A-C.M., A.K.J. and K.A.S.) reviewed equal parts of all unique dosing instructions (n= 20,348). The algorithm was then adjusted to correct for inaccuracies. Dosing instructions were regarded as non-interpretable if the number of tablets was not stated (e.g. once weekly), the dosing varied over time (e.g. one tablet per week during the first 2 weeks and two tablets per week thereafter), if

the dosing was unclear (e.g. one to two tablets weekly), or if the frequency was unclear (e.g. one tablet with a glass of water). If a dosing instruction was not interpretable, the preceding interpretable dosing instruction was used. If no dosing instruction was interpretable, the patient was excluded. Based on the dosing instructions the study population was divided into four groups: patients using one tablet daily, patients using one tablet weekly, patients switching between these two dosing regimens during the study period, and patients using other regimens.

Number of days supply was calculated by dividing the number of dispensed units, e.g. 12 tablets, by the number of prescribed units (one tablet per week) as interpreted by the algorithm, in this example yielding 84 days' supply. Thereafter, treatment episodes were estimated based on date of purchase and days' supply. Bisphosphonates were assumed to be provided by the hospital during hospital admissions. In Sweden it is possible to have medicines dispensed for a maximum of 90 days within the reimbursement system by each purchase. Refill is possible when two-thirds has been consumed. It is hence possible to accumulate large amounts of medicines. When dispensed prescriptions overlapped, the overlapping days were therefore added to the next prescription.

Outcome variables

Refill adherence was the outcome variable in this study. It was estimated based on two methods: Continuous measure of Medication Acquisition (CMA) and the maximum gap method [5, 6, 8, 11, 14]. CMA measures the proportion of days' supply obtained during a given time period (number of days supply/number of days in the observation period). The results on refill adherence when using CMA is equivalent to Medication Possession Ratio (MPR) in this study, since fixed study periods were used [10]. Drug supplies extending beyond the end of the 2-year follow-up period were truncated (i.e., maximum CMA=100 %). The maximum gap method identifies gaps in drug supply that exceed a predetermined time period, a figure that often is presented in persistence analyses [19]. We also evaluated the time from initiation of therapy to the first gap in treatment.

To facilitate comparison with previous studies and comparison between the two methods, we applied a cut-off for adherence. For CMA, patients with ≥80 % of days with bisphosphonates available during the entire observation period were defined as adherent. The cut-off at 80 % was chosen because a lower adherence rate has been associated with an increased risk for fractures [15]. The maximum gap method defined patients with gaps up to 45 days at any time during the observation period as adherent. This cut-off was based on the Swedish reimbursement system described above [20, 21].

Sensitivity analyses

To validate the methods and the definitions used in this study, a number of sensitivity analyses were performed: 1) The population was restricted to patients aged 60–85 years (where most women have entered menopause [22]) and 80–85 years (based on the median age of osteoporotic fractures [23]); 2) the patients were assumed to consume bisphosphonates from their own supply during hospital admissions, to analyse whether accounting for hospitalisations had an impact of the results; 3) overlapping supplies were disregarded, to assess the impact of accumulation; 4) the follow-up period was restricted to 1 year; 5) the maximum gap allowed was adjusted to 30 days and 60 days, respectively, to assess the stability of the selected cut-off.

Statistical analyses

Descriptive statistics were used to characterise the sample. Chi^2-tests were used to assess differences in categorical variables between adherent and non-adherent individuals. The unadjusted association between type of dosing regimens and adherence was assessed with logistic regression. To identify relevant covariates, the associations between adherence and each covariate were then assessed in separate regression models. All covariates yielding a p value≤0.25 in the global likelihood ratio test were subsequently included in a regression model [24]. Backward elimination was applied and covariates with p values>0.05 were dropped from the model. The final logistic regression model was adjusted for age, sex, country of birth, fractures within 2 years of index date, hospitalisation, education level, marital status, which bisphosphonate substances were used, use of calcium (A12AA, A12AX), use of anti-inflammatory and antirheumatic products (M01), and use of topical products for joint and muscular pain (M02). Kaplan-Meier curves and the log-rank test were used to assess differences in persistence between the groups. Data management and statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC).

Results

A total of 70,944 patients with at least one purchase of a bisphosphonate during the index period was identified. After applying the predetermined exclusion criteria (Fig. 1), the final study population included 18,203 patients. The majority of the patients (93 %, n=16,906) were assigned the dosing of one tablet weekly for their bisphosphonates, whereas 3 % (n=490) were assigned one tablet daily and 3 % (n=486) switched between one tablet daily and one tablet weekly. A majority were older than 60 years (82 %) and 85 % were women

(Table 1). Alendronic acid was the most commonly used substance (79 %, *n*=14,292).

Using the maximum gap method, patients on one tablet weekly had significantly lower adherence compared with patients on one tablet daily (73 % vs. 80 %; adjusted OR= 0.71; 95 % CI 0.57–0.89) (Table 2). The mean number of days on treatment was 657 days for patients on one tablet daily, 656 days for the patients on one tablet weekly, 607 days for those switching between dosing regimens, and 614 days on other dosing regimens. As seen in Fig. 2, the curve shows that

Table 1 Characteristics of the study population (*n*=18,208)

	Dosing regimen			
	Patients using one tablet daily % (n) *n*=490	Patients using one tablet weekly % (n) *n*=16,906	Patients switching between daily and weekly dosing regimens % (n) *n*=486	Patients using other regimens % (n) *n*=321
Age[a]				
18–39	3.1 (15)	1.7 (295)	1.6 (8)	2.7 (7)
40–59	24.3 (119)	16.3 (2,758)	17.9 (87)	18.1 (58)
60–69	29.8 (146)	29.9 (5,047)	31.3 (152)	29.0 (93)
70–79	30.0 (147)	35.8 (6,059)	36.8 (179)	34.3 (110)
80–85	12.9 (63)	16.2 (2,747)	12.3 (60)	16.5 (53)
Sex, women	81.6 (400)	84.7 (14,317)	84.6 (411)	76.9 (247)
Country of birth[a, b]				
The Nordic countries (Including Sweden)	89.6 (438)	92.4 (15,615)	92.8 (451)	88.7 (283)
Other European countries	5.9 (29)	4.7 (795)	3.7 (18)	7.5 (24)
Outside Europe	4.5 (22)	2.9 (4,888)	3.5 (17)	3.8 (12)
Education level[a, c]				
University or College	28.1 (98)	24.8 (2,683)	24.5 (81)	32.1 (67)
Secondary education	41.0 (143)	43.1 (4,661)	43.0 (142)	37.3 (78)
Primary Education	30.9 (108)	32.1 (3,474)	32.4 (107)	30.6 (64)
Marital status[a, d]				
Married	66.8 (272)	65.2 (8,581)	66.4 (259)	68.6 (177)
Single[e]	33.2 (135)	34.8 (4,581)	33.6 (131)	31.4 (81)
Hospital admissions				
Hospitalised during the study period	46.5 (228)	36.6 (6,180)	39.5 (192)	50.8 (163)
Number of admissions, mean (SD)	1.4 (2.3)	1.0 (2.1)	1.1 (2.2)	1.7 (2.7)
Length of stay per admission in days, mean (SD)	8.8 (30.5)	6.4 (5.7)	6.2 (5.5)	7.3 (7.6)
Fractures within 2 years of the index date	6.7 (33)	9.5 (1,598)	8.8 (43)	5.0 (16)
Type of medication (ATC code)				
Etidronic acid (M05BA01)	0.2 (1)	0.0 (2)	0.2 (1)	35.2 (113)
Clodronic acid (M05BA02)	1.0 (5)	0.0 (1)	0.6 (3)	23.4 (75)
Alendronic acid (M05BA04)	54.9 (269)	79.7 (13,470)	90.5 (440)	35.2 (113)
Ibandronic acid (M05BA06)	30.2 (148)	0.0 (2)	2.1 (10)	19.9 (64)
Risedronic acid (M05BA07)	14.9 (73)	24.8 (4,186)	24.5 (119)	17.8 (57)
Other medications (ATC code)				
Calcium (A12AA)	3.9 (19)	3.6 (607)	5.1 (25)	15.3 (49)
Calcium in combination with vitamin D (A12AX)	51.6 (253)	84.9 (14,351)	87.7 (426)	59.2 (190)
Topical products for joint and muscular pain (M02)	5.9 (29)	8.7 (1,466)	9.3 (45)	8.4 (27)
Anti-inflammatory and antirheumatic products (M01)	39.6 (194)	42.7 (7,226)	43.6 (212)	38.6 (124)

[a] The variables age, education level, marital status, were defined at the year of index date

[b] Information missing for 11 patients

[c] Information missing for 6,497 patients

[d] Information missing for 3,986 patients

[e] Unmarried, divorced and widow/er

Table 2 Refill adherence for 13,312 new bisphosphonate users on one tablet daily, one tablet weekly, patients switching between the two dosing regimens and other dosing regimens

Dosing regimen	CMA, proportion of days with bisphosphonates (median; q1, q3)	CMA, proportion adherent (%)[a]	CMA, unadjusted Odds ratio (95 % CI)	CMA, adjusted Odds ratio (95 % CI)[b]	Maximum gap, proportion adherent (%)[c]	Maximum gap, unadjusted Odds ratio (95 % CI)	Maximum gap, adjusted Odds ratio (95 % CI)[b]
Patients using one tablet daily (n=490)	100 (94, 100)	87.8	Reference	Reference	79.8	Reference	Reference
Patients using one tablet weekly (n=16,906)	98 (89, 100)	84.2	0.75 (0.57–0.98)	0.75 (0.57–0.99)	73.4	0.70 (0.56–0.87)	0.71 (0.57–0.89)
Patients switching between one tablet daily and one tablet weekly (n=486)	93 (75, 100)	70.6	0.34 (0.24–0.47)	0.34 (0.24–0.47)	54.3	0.30 (0.23–0.40)	0.31 (0.23–0.41)
Patients using other regimens (n=321)	95 (81, 100)	76.0	0.44 (0.31–0.64)	0.56 (0.37–0.87)	60.1	0.38 (0.28–0.52)	0.53 (0.37–0.76)

CMA, Continuous measure of Medication Acquisition

[a] Adherent: ≥80 %

[b] Logistic regression analysis adjusted for age, sex, country of birth, fractures within 2 years of index date, hospitalisation, education level, marital status, bisphosphonate substance used, use of Calcium (A12AA, A12AX), use of anti-inflammatory and antirheumatic substances (M01) and use of Topical products for joint and muscular pain (M02)

[c] Adherent: no gap ≥45 days

probability of ending treatment followed a similar pattern over time for patients on one tablet daily and one tablet weekly, respectively. Patients switching between one tablet daily and one tablet weekly had an increased probability of ending treatment after 3 months, and patients on other dosage regimens had an increased probability of ending treatment after 5 months.

Overall, the proportion of patients classified as adherent was higher using CMA compared with patients classified as adherent using the maximum gap method. For example, among patients with a dosing regimen of once daily, a higher proportion was classified as adherent using CMA compared with maximum gap (88 % vs. 80 %). Of those classified as adherent using CMA, 87 % were also classified as adherent using the maximum gap method, whereas 100 % of those classified as adherent using the maximum gap were also classified as adherent using CMA. A significantly lower proportion of patients on one tablet weekly were classified as adherent compared with patients on one tablet daily using CMA (84 % vs. 88 %, adjusted OR=0.75; 95 % CI 0.57-0.99). Patients using the other two dosing regimens had significantly lower adherence compared with patients on one tablet daily using both methods (Table 2).

The sensitivity analyses performed had similar effects on the proportion of patients classified as adherent in most dosing regimens groups, irrespective of methods used to estimate refill adherence (Table 3). The proportion patients classified as adherent increased when the analyses were restricted to patients aged 80–85 years, except for patients on one tablet daily, and when the study period was restricted to 365 days. Moreover, when the gap length in the maximum gap method was extended, the proportion of patients classified as adherent increased; e.g. for patients on one tablet daily, the adherence was 75 % and 83 % for 30 and 60 days of gap, respectively. However, the proportion of patients classified as adherent decreased when accumulation was not allowed. Using the maximum gap method, patients on one tablet daily were significantly more adherent compared with patients on one tablet weekly in all sensitivity analyses, except when the analyses were restricted to patients aged 60–85 years, or patients aged 80–85 years, and when the follow-up was 365 days. In the CMA analyses, a significant difference was observed between patients on one tablet daily and patients on one tablet weekly when accumulated medicines were not allowed to fill future gaps.

Discussion

The choice of method used when estimating refill adherence had an effect on refill adherence to bisphosphonates in this study.

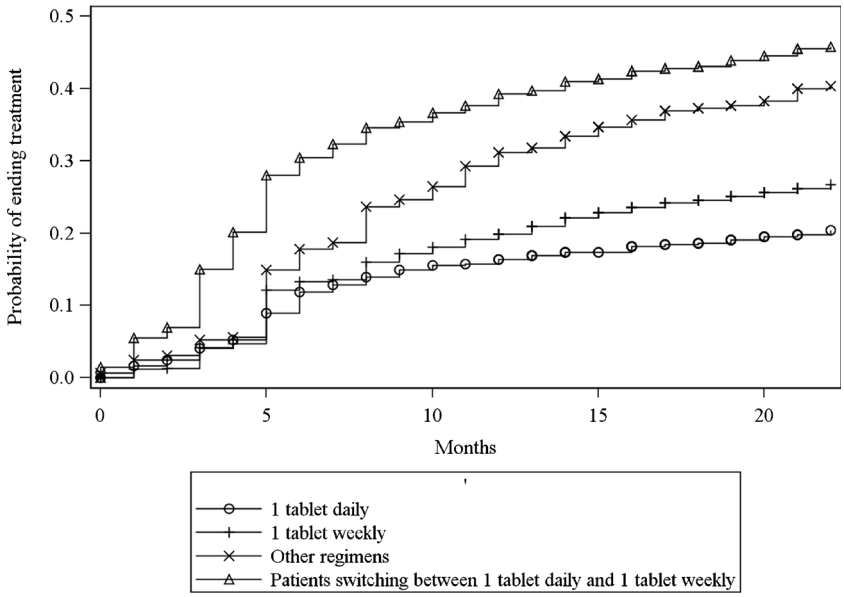

Fig. 2 Persistence over time for patients on one tablet daily, patients one tablet weekly, patients switching between one tablet daily and one tablet weekly, and patients on other dosing regimens. Each patient was followed from index date (zero months) until the end of follow-up (24 months) with a grace period of 45 days allowed. Log-rank test, $p<0.001$

This study showed that overall a higher proportion of patients on bisphosphonates were classified as adherent with CMA compared with the maximum gap method. This pattern confirms the results observed in our previous study on statin use [14], with a dosing regimen of one tablet daily, where a higher proportion (76 % vs. 65 %) was classified as adherent using CMA compared with maximum gap. This has also been observed for bisphosphonates in the US [25] and for glucose-lowering agents, antihypertensive drugs and lipid-lowering drugs in the Netherlands [11]. There is no consensus about the best approach to determine refill adherence [11]. CMA and the maximum gap method focus on different aspects of refill adherence; i.e., the average supply during the study period versus gaps in drug supply. Based on the pharmacokinetic properties of the medicines, one method to estimate refill adherence might have a higher clinical relevance. For example, due to the long half-life of bisphosphonates, occasionally missed doses are not as important as long gaps in the treatment.

In this study, a higher proportion of patients were classified as adherent compared with previous studies [26, 27]. In our previous study on statin users [14], a higher proportion of patients was also classified as adherent compared with previous studies. One possible explanation to these results is differences in country-specific policies. The Netherlands has a similar reimbursement system as Sweden and the adherence rates for bisphosphonates are similar to those in Sweden [28]. The high adherence rate in Sweden might be related to the 3-month supply that is generally dispensed at each occasion for continuous treatments. Refill is also possible when two-thirds has been consumed, making stockpiling likely. In previous studies, a large prescription size increased overall medication acquisition and reduced gaps in treatment [29, 30]. Moreover, the Swedish reimbursement system has a stepwise reduction in co-payment and an annual maximum accumulated co-payment, which have been positively related to refill adherence [17].

In our study, a higher proportion of patients was classified as adherent in patients on daily dosing compared with patients on weekly dosing using both methods. Previously, using CMA/MPR patients with daily dosing was continuously reported to have lower adherence rates compared with patients with weekly dosing with a MPR (mean) of 0.58–0.76 versus 0.46–0.64 [26]. However, no definitive conclusion could be drawn due to a small subset of data when data were pooled in a meta-analysis [27]. In the meta-analysis, 50 % (95 % CI 40–60 %) of patients on weekly dosing versus 37 % (95 % CI 30–44 %) of patients on daily dosing were considered adherent (MPR>80 %). To our knowledge, the maximum gap method has not been used to compare adherence rates between patients on weekly dosing and patients on daily dosing. However, in persistence analyses, most studies report the proportion of patients on treatment after a certain time (most often 365 days), and these results could be compared with ours. These studies have consistently observed a higher persistence among patients on weekly compared with daily dosing (35.7–69.7 % vs. 26.1–55.7 %) [26]. However, in a meta-analysis [27], no definitive conclusion could be drawn on the difference of the proportion of patients still on treatment after 12 months between patients on daily dosing compared with patients on weekly dosing. In these studies, the gaps allowed varied between 30 and 120 days.

The results from the sensitivity analyses in this study indicate that the results are robust. Most earlier studies [26] applied a study period of 365 days. In this study, adherence estimates increased with a shorter observation period (365 days vs. 730 days), as has been previously reported [14, 26, 31]. The adherence estimates decreased when overlapping supplies were not allowed to fill future gaps.

Table 3 Sensitivity analyses

	Patients using one tablet daily		Patients using one tablet weekly		Patients switching between one tablet weekly and one tablet daily		Patients using other dosing regimens	
	CMA, proportion adherent (%)[a]	Maximum gap, proportion adherent (%)[b]	CMA, proportion adherent (%)[a]	Maximum gap, proportion adherent (%)[b]	CMA, proportion adherent (%)[a]	Maximum gap, proportion adherent (%)[b]	CMA, proportion adherent (%)[a]	Maximum gap, proportion adherent (%)[b]
Main analysis	87.8	79.8	84.2	73.4*	70.6*	54.3*	76.0*	60.1*
Age 60–85 years (n=14,856)	86.0	78.4	85.3	74.5	74.2*	57.5*	76.2	59.8*
Age 80–85 years (n=2,923)	81.0	77.8	86.6	76.5	76.7	63.3	79.2	58.5
Drug NOT provided by hospital during admissions (n=18,203)	86.9	79.6	83.9	72.9*	70.0*	54.3*	74.8*	59.2*
No accumulation (n=18,203)	84.5	70.6	79.4*	61.6*	62.1*	40.3*	66.0*	50.2*
1-year follow-up (n=18,203)	87.5	85.2	88.2	85.1	75.9*	70.3*	81.5	76.7
Maximum gap <30 days (n=13,312)		74.5		66.5*		49.6*		55.1*
Maximum gap <60 days (n=13,312)		83.1		77.3*		59.3*		65.7*

CMA Continuous measure of medication acquisition

[a] Adherent: ≥80 % of days

[b] Adherent: gap <45 days

* Compared with patients on one tablet daily $P<0.05$ using a logistic regression analysis adjusted for age, sex, country of birth, fractures within 2 years of index date, hospitalisation, education level, marital status, bisphosphonate substances used, use of Calcium (A12AA, A12AX), use of anti-inflammatory and antirheumatic products (M01) and use of Topical products for joint and muscular pain (M02)

Interestingly, using the CMA, patients on one tablet daily had significantly higher adherence than patients on one tablet weekly when accumulated medicines were not allowed to fill future gaps. It is, however, important to take accumulated medicines into account in studies of refill adherence, since there is a risk of misclassification [31].

In our previous study [14], a trend of increased adherence with increasing age was observed using both methods. This was also observed in this study for patients on one tablet weekly and for patients switching between one tablet daily and one tablet weekly when the analyses were restricted to patients aged 80–85 years. However, the proportion classified as adherent decreased for patients with daily dosing when the analyses were restricted to this age group. This might be related to the fact that the tablets should be taken after overnight fasting and that patients have to be in an upright position for 30 min afterwards, which might be a greater problem in older ages.

When estimating refill adherence using the maximum gap method, the gap length has a substantial impact on the proportion classified as adherent. Since the proportion considered adherent increases with the gap length chosen, it is important to analyse the gap length used. When extending the gap length in this study, the proportion classified as adherent never exceeded the proportion classified as adherent using CMA. In this study, as in previous studies [5, 19], the gaps allowed were based on the number of days that one dispense covered. In Sweden, 90-day supplies are dispensed. There is, however, an ongoing discussion on whether it is appropriate to allow the same gap when you compare different dosing regimens, since the clinical impact of a 45-day gap may differ if using one tablet daily or one tablet weekly due to pharmacokinetic differences. As can be seen in Table 3, if patients on one tablet weekly would have been allowed a 60-day gap, and patients on one tablet daily a 30-day gap, the proportions classified as adherent in the two groups would have been comparable (77 % vs. 75 %).

Refill adherence rates were not affected when hospitalised days were not taken into account, which is in line with our previous findings [14]. However, other studies have shown that it is important to consider periods of hospitalisation [5]. Whether the number of days patients are hospitalised affect refill adherence is probably related to the healthcare system, and the length of hospital stays and hospitalisations should be considered.

An important strength in this study is the use of data from a population-based register including all medicines, irrespective of reimbursement status. The study also includes all individuals in Sweden who fulfil the inclusion criteria of the study, regardless of their socioeconomic background and geographical site. Moreover, a novel approach of building an algorithm for interpreting dosage instructions in free text in the SPDR was used. The algorithm was manually validated and subsequently corrected.

The main limitation of this study is the lack of information on whether the purchased medicines were actually taken. Previous studies have, however, found that refill adherence correlates well with other methods to measure adherence, such as self-reported adherence [32–34], pill counts [12], presence of drug in blood/urine, or effect [6]. Refill adherence has also been shown to be more sensitive concerning identification of non-adherent individuals compared with electronic monitoring [7]. Moreover, if patients do not purchase their prescribed medicines (i.e., primary non-adherence), they are not included in the register and hence were not included in this study.

Conclusion

Choice of method has an impact on the estimates of refill adherence to bisphosphonates. The proportion of patients classified as adherent was higher using CMA compared with the maximum gap method. A difference in adherence between patients on daily dosing and weekly dosing was observed in the main analyses of both methods, when the analyses were restricted to patients aged 60–85 years or patients aged 80–85 years, or when the follow-up was 365 days in the maximum gap method, and when accumulated medicines were not allowed to fill future gaps in the CMA analyses.

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Conflict of interest The authors declare that they have no conflict of interest.

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