ORIGINAL ARTICLE

Long-term persistence with anti-osteoporosis drugs after fracture

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Abstract

Summary Long-term persistence with anti-osteoporosis drugs and determinants for discontinuation among fracture patients were examined. Persistence was 75.0 and 45.3 % after 1 and 5 years, respectively. Those aged ≥80 years were at increased risk of early discontinuation. Within 1 year after discontinuation, 24.3 % restarted therapy, yet 47.0 % persisted for 1 year.

Introduction The risk of osteoporotic fracture can effectively be reduced with use of anti-osteoporosis drugs. However, little is known about persistence with these drugs after fracture where subsequent fracture risk is high. The aims were to determine long-term persistence with anti-osteoporosis drugs among fracture patients, including its determinants, and to describe restart and subsequent persistence.

Methods A cohort study was conducted within the Dutch PHARMO Database Network. Patients aged ≥50 years (n=961) who received anti-osteoporosis drugs within 1 year after fracture, but not in the preceding year, were included (2002–2011). Persistence (defined as the proportion on treatment) and the proportion restarting after discontinuation were estimated using Kaplan-Meier analyses. Time-dependent Cox regression was used to identify determinants of non-persistence including age, sex, initial dosage regime, fracture type, comorbidities, and drug use.

Results Persistence with anti-osteoporosis drugs was 75.0 % (95 % confidence interval (CI) 72.0–77.7) and 45.3 % (95 % CI 40.4–50.0) after 1 and 5 years, respectively. A significant determinant of non-persistence was age ≥80 years (reference

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50–59 years: adjusted hazard ratio [adj. HR] 1.65; 95 % CI 1.15–2.38). This effect was not constant over time (≤360 days following initiation: adj. HR 2.07; 95 % CI 1.27–3.37; >360 days: adj. HR 1.08; 95 % CI 0.62–1.88). Within 1 year after discontinuation, 24.3 % (95 % CI 20.1–29.2) restarted therapy, yet 47.0 % persisted for 1 year.

Conclusions This study identified suboptimal persistence with anti-osteoporosis drugs among fracture patients. Major target groups for measures aimed to improve persistence may be those aged >80 years and those restarting therapy.

Keywords Epidemiology · Fracture prevention · Osteoporosis · Persistence · Therapeutics

Introduction

Osteoporotic fractures are a major burden for the patient in terms of increased morbidity, mortality, and a reduction in quality of life [1]. Prior fractures are strong predictors of fracture risk. Indeed, the fracture risk is two-fold higher following a non-vertebral fracture and is quadrupled after a vertebral fracture [2]. This risk is not constant over time with a five-fold higher risk in the year after the first fracture followed by a gradual waning off [3]. Within 5 years after the initial fracture, up to one third of the patients will sustain a new fracture [4, 5].

Anti-osteoporosis drugs, of which bisphosphonates are the most commonly prescribed, have shown to reduce the relative risk of osteoporotic fractures by 20–70 % in clinical trials, depending on the drug and fracture type [6–8]. Persistence with therapy is an important determinant for the anti-fracture efficacy of anti-osteoporosis drugs in clinical practice [9–12]. A meta-analysis with data of 219,676 patients indicated that non-persistence with anti-osteoporosis drugs increased fracture risk by 32 % (hazard ratio (HR) 1.32; 95 % confidence interval (CI) 1.23–1.42) where follow-up between studies varied between 40 and 159 weeks [9]. The effectiveness of oral bisphosphonates in relation to duration of use was more specifically identified in a Dutch observational study; persistent use of oral bisphosphonates for 1–2 and 3–4 years reduced fracture risk by 12 and 46 %, respectively, compared to <1 year of use (OR 0.88, 95 % CI 0.66–1.18 and OR 0.54, 95 % CI 0.35–0.84, respectively) [12]. Real-world persistence with osteoporosis therapy is, however, poor. One-year persistence ranged from 18 to 78 % between studies where differences were at least partly arising from non-uniformity used for the operational definition of persistence, including data-derived persistence and self-report [13–20].

While previous studies have been conducted among first-time users of anti-osteoporosis drugs, there is a lack of understanding on fracture history with few studies identifying patients who had (recently) sustained an osteoporotic fracture. As a previous fracture is one of the most important risk factors for a subsequent fracture, it is important to investigate persistence with anti-osteoporosis drugs in this patient group and to understand its determinants. Furthermore, little is known about restart and subsequent persistence with these drugs after first discontinuation. Therefore, the aims of this study were (1) to identify long-term persistence with anti-osteoporosis drugs and its determinants in patients who had recently sustained a major osteoporotic fracture (hip, clinical vertebrae, humerus, forearm), (2) to determine the frequency of restarting treatment among patients who discontinued use, and (3) to assess persistence after restarting anti-osteoporosis treatment.

Methods

Data source

A cohort study was performed within the Dutch PHARMO Database Network [PHARMO Institute for Drug Outcome Research, www.pharmo.nl]. This data source contains primary care data linked to outpatient pharmacy dispensing data, hospitalizations from the Dutch Hospital Data Foundation (DHD, www.dutchhospitaldata.nl), and death registration data for approximately 660,000 community-dwelling individuals in the Netherlands. Almost every individual in the Netherlands is registered with a single community pharmacy, which results in a high degree of completeness with regard to dispensed drugs [21]. Drug-dispensing records contain information concerning the dispensed drug according to the Anatomical Therapeutic Chemical (ATC) Classification system codes including amount, dose, dosage regime, and date of dispensing. Primary care diagnoses are coded according to the International Classification of Primary Care (ICPC) coding system. Hospital records include dates of hospital admission and discharge, diagnoses, and procedures recorded according to the International Classification of Disease, 9th or 10th revision codes (ICD-9 or ICD-10).

Study population

All patients ≥50 years with a first record of a hip, humerus, clinical vertebral, or forearm fracture since the start of data collection were identified. Fractures were extracted from primary care records and hospitalization data between 1 January 2002 and 31 December 2011. In the Netherlands, drugs available for the treatment of osteoporosis include bisphosphonates (alendronic acid, risedronic acid, etidronic acid, ibandronic acid, zoledronic acid), selective estrogen receptor modulators (SERMS; raloxifene, bazedoxifene), strontium ranelate, teriparatide, and denosumab.

Patients were included at the date of first dispensing for an anti-osteoporosis drug in the year following the first fracture but not in the preceding year to include incident users only. The date of the first dispensing of an anti-osteoporosis drug after the fracture was set as the index date. Patients who were dispensed clodronic acid, pamidronic acid, tiludronic acid, or risedronic acid 30 mg once daily were not included since these drugs are not registered for osteoporosis but for hypercalcemia during malignancy or Paget's disease, which may also increase fracture risk. In the Netherlands, repeated weekly dispensing of medications is an indicator of medication delivery by a "weekbox," suggesting that patient persistence is monitored by a health care professional, and thus, any discontinuation is likely not patient driven. To control for physician-directed discontinuation, patients with repeated weekly (7-day) dispensing records were excluded.

Study outcomes

The outcome of interest was persistence with any anti-osteoporosis drug. Persistence was defined as the proportion of patients who were on treatment since treatment initiation [22]. Assessment of persistence was based on the calculation of the total duration of use where switching between drugs and dosage regimes was permitted [23]. The total duration of use was calculated on the basis of subsequent prescriptions for anti-osteoporosis drugs that were collected by (i.e., dispensed to) the patient at the community pharmacy. For each pharmacy dispensing, the theoretical duration of use was calculated by dividing the amount dispensed by the prescribed dosage regime. In the event of overlap between two dispensings (i.e., a repeat dispensing within the duration of use of a previous dispensing), the overlap days were added to the duration of the repeat dispensing. A gap of 90 days between the theoretical end date of a pharmacy dispensing (defined as the date of dispensing plus the theoretical duration of use) and the subsequent dispensing date was allowed. A patient was therefore classified as having discontinued with anti-osteoporosis treatment when either a gap of >90 days occurred between two dispensings, or when no further dispensing was issued and at least 90 days were available to the right censoring date. A 90-day permissible gap is consistent with prior literature [14, 15], and the maximum amount dispensed is a 90 days' supply in the Netherlands for chronic treatment, which is required for osteoporosis [23, 24]. In sensitivity analyses, permissible treatment gaps of 180, 270, and 365 days were applied.

Among patients who discontinued use using a 90-day permissible gap, the proportion restarting therapy was identified. Persistence with any anti-osteoporosis drug upon restart of therapy was determined similarly as described above.

Definition of covariates

Potential determinants of non-persistence (discontinuation) with anti-osteoporosis drugs were included in univariate and multivariate Cox proportional hazards models. Age, drug exposure, and comorbidities were included as time-dependent covariates. Total follow-up time was divided into 30-day intervals, and covariates were evaluated before each interval. Covariates included age groups (50–59, 60–69, 70–79, ≥80 years), sex, type of fracture (hip, humerus, clinical vertebrae, forearm fracture), dosage regime of initial anti-osteoporosis drug (daily, weekly, or monthly), drug use in the 6 months before (systemic glucocorticoids, antidepressants, non-selective anti-inflammatory drugs [NSAIDs], opioids [tramadol or stronger], calcium supplements and/or vitamin D, and disease-modifying anti-rheumatic drugs [DMARDs]), comorbidities included a diagnosis of dementia/Alzheimer's disease ever before, and the occurrence of upper gastrointestinal disorders or a subsequent fracture (at any site) in the 6 months before [13, 16, 25]. The presence of alcoholism was also considered, expressed by diagnosis codes for alcohol dependence and alcoholic liver diseases (alcoholic acute hepatitis, alcoholic liver cirrhosis, alcoholic liver damage, alcoholic fatty liver) or exposure to drugs for alcohol abstinence (disulfiram, acamprosate, nalmefene, naltrexone). An incident diagnosis of renal failure (diagnosis for renal failure or stage 4/5 chronic kidney disease) was assessed but occurred too infrequent to include into the analysis ($n=3$).

Statistical analysis

All patients were followed from the index date until discontinuation, death, migration out of the data source, or end of study period [31 December 2011], whichever came first. Kaplan-Meier life table analyses were used to present persistence estimates (%) over time where discontinuation was the failure event. Analyses were completed using the whole study population and stratified by age groups and type of index fracture. Log-rank tests were used to test for significant differences between groups. In addition, Kaplan-Meier life tables were applied to determine the cumulative incidence of restarting any anti-osteoporosis drug after first 90-day discontinuation.

Determinants of non-persistence were estimated by time-dependent Cox proportional hazards regression (PHREG procedure) by entering all covariates into the regression model. The proportional hazards assumption was tested by including time interaction terms into the model. In case of violation (p value interaction <0.05), hazard ratios for the association between that covariate and non-persistence were calculated for two periods by restricting follow-up time to the first 12 30-day periods and the period thereafter (≤360 and

>360 days), to present the hazard ratio for "early" and "late" discontinuation, respectively.

All statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 1081 patients were identified as incident users of anti-osteoporosis drugs within 1 year after the first fracture. Of these, 120 patients had repeated 7-day dispensing indicating "weekbox" dispensing and were excluded. The final study cohort included 961 patients (81.3 % female) with a mean age of 69.8 years (SD=9.6 years). The vast majority initially received a bisphosphonate (96.5 %), most frequently alendronic acid (67.3 %) or risedronic acid (29.7 %). Alternatives for bisphosphonates, such as raloxifene and strontium ranelate, were rarely dispensed (Table 1). During follow-up, a total of 89 (9.3 %) patients switched between types of anti-osteoporosis drugs, where 67.4 % of all switches occurred between alendronic acid and risedronic acid. Bisphosphonates were predominantly prescribed in a weekly dosage regime (94.2 %). Of patients initiating on a daily dosage, 36.4 % switched to another dosage regime during follow-up.

Persistence estimates for treatment with anti-osteoporosis drugs are displayed in Fig. 1a for the total study population. Persistence decreased from 75.0 % (95 % CI 72.0–77.7) at 1 year to 45.3 % (95 % CI 40.4–50.0) at 5 years following initiation. The median time on treatment was 4.6 years [95 % CI 4.1–5.0]. Increasing the gap length showed increases in persistence (Table 2). When stratified by age groups, significant differences in persistence were identified ($p=0.003$), with those aged 80 years and older at index date having the lowest persistence (Fig. 1b), but no significant difference was noted between fracture types ($p=0.17$) (Fig. 1c). Of those aged 80 years and older, 63.9 % (95 % CI 55.8–70.9) persisted for 1 year following treatment initiation, as compared to 82.8 % (95 % CI 75.7–88.0) of those aged 50–59 years.

Table 3 presents associations between the covariates and non-persistence with anti-osteoporosis drugs. In a multivariate model, age ≥80 years was identified as a significant determinant of discontinuation (reference 50–59 years; adjusted [adj.] hazard ratio [HR] 1.65; 95 % CI 1.15–2.38). The effect of age, however, was not constant over time (p value interaction <0.05). When follow-up was restricted to the first 360 days following initiation, persistence was significantly lower for those ≥80years as compared to those 50–59 years (adj. HR 2.07; 95 % CI 1.27–3.37), while this was not observed beyond 360 days of follow-up (adj. HR 1.08; 0.62–1.88). The association between an initial daily versus weekly dosage regime and non-persistence was also not constant over time (≤360 days; adj. HR 1.49, 95 % CI 0.95–2.35, >360 days;

**Table 1** Characteristics of new anti-osteoporosis drug users who sustained a recent fracture

Characteristics	N=961
Follow-up time, mean (SD), years	3.0 (2.1)
Female sex	781 (81.3 %)
Age, mean (SD), years	69.8 (9.6)
Age categories	
50–59	161 (16.8 %)
60–69	308 (32.0 %)
70–79	322 (33.5 %)
≥80	170 (17.7 %)
Type of index fracture	
Hip	204 (21.2 %)
Humerus	127 (13.2 %)
Clinical vertebral	322 (33.5 %)
Forearm	308 (32.0 %)
Initial anti-osteoporosis drug	
Bisphosphonate	927 (96.5 %)
Alendronic acid	624 (67.3 %)
Risedronic acid	275 (29.7 %)
Other bisphosphonate[a]	28 (3.0 %)
Strontium ranelate	29 (3.0 %)
Other[b]	5 (0.5 %)
Dosage regime	
Daily	67 (7.0 %)
Weekly	873 (90.8 %)
Monthly	21 (2.2 %)
Diseases	
Upper gastrointestinal disorders 6 months before index date[c]	26 (2.7 %)
Dementia/Alzheimer's disease ever before index date[c] and during follow-up	25 (2.6 %)
Alcoholism ever before index date[c] and during follow-up	24 (2.5 %)
Fracture at any site during follow-up	80 (8.3 %)
Upper gastrointestinal disorders during follow-up	74 (7.7 %)
Drug use during 6 months before index date[c]	
Systemic glucocorticoids	78 (8.1 %)
Antidepressants	92 (9.6 %)
Opioids (tramadol or stronger)	97 (10.1 %)
Non-steroidal anti-inflammatory drugs	347 (36.1 %)
Calcium-supplements and/or vitamin D	64 (6.7 %)
Disease-modifying anti-rheumatic drugs	13 (1.4 %)

[a] Etidronic acid, ibandronic acid

[b] Raloxifene

[c] Index date defined as date of first dispensing for any anti-osteoporosis drug within 1 year after fracture

adj. HR 0.68; 95 % CI 0.35–1.30, p value interaction <0.05). Sensitivity analyses with increasing gap lengths provided similar results, where age ≥80 years remained the only

(a)

(b)

(c)
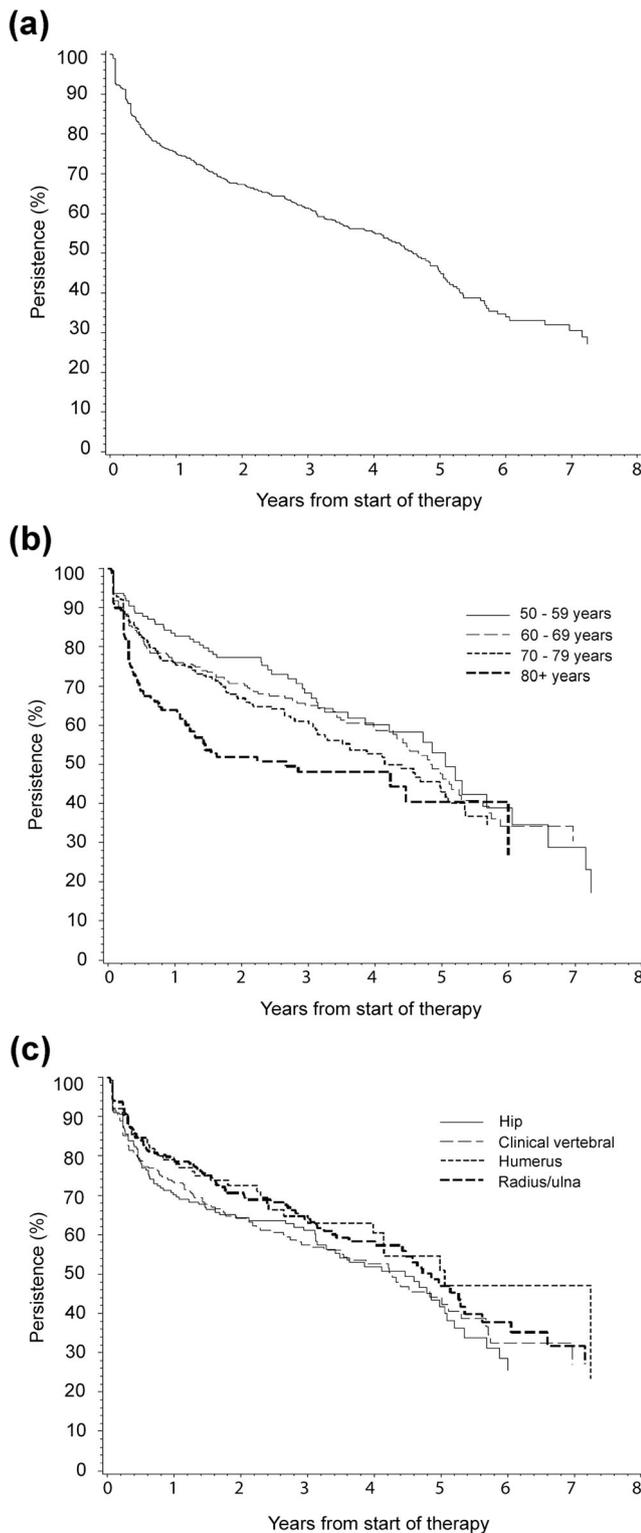
Fig. 1 Kaplan-Meier persistence curves for treatment with anti-osteoporosis drugs after a recent fracture for **a** the total study population, **b** stratified by age category, **c** stratified by type of fracture—discontinuation was defined as a treatment gap of >90 days and switching between anti-osteoporosis drugs or dosage regimes was allowed when this occurred within the treatment gap

Table 2 Kaplan-Meier estimates for persistence (%) at different time periods following initiation, by gap length

	Survival time		
	1 year	3 years	5 years
Gap length			
90 days	75.0 (72.0–77.7)	61.3 (57.6–64.8)	45.3 (40.4–50.0)
180 days	79.2 (76.3–81.7)	68.2 (64.7–71.5)	53.6 (48.6–58.4)
270 days	82.2 (79.5–84.6)	73.0 (69.6–76.1)	58.9 (53.7–63.6)
365 days	84.4 (81.9–86.6)	75.2 (71.9–78.3)	64.4 (59.5–68.9)

Patients were followed until first date of the following: discontinuation (non-persistence), death, migration out of data source, or end of study period

significant determinant of non-persistence (see supplementary Table S1/S2/S3).

Figure 2 shows the cumulative incidence of restarting any anti-osteoporosis drug after first discontinuation. Of all patients who discontinued treatment, 24.3 % (95 % CI 20.1–29.2) restarted therapy within 1 year, and this increased to 40.4 % (95 % CI 32.4–49.4) within 5 years. Patients who discontinued treatment were less likely to stay on treatment after restart; 47.0 % (95 % CI 36.4–56.9) persisted for 1 year. The median time on treatment was 0.92 years (95 % CI 0.61–1.47) (Fig. 3).

Discussion

In this cohort of newly treated fracture patients, persistence with anti-osteoporosis drugs decreased from 75 % at 1 year to 45 % at 5 years following initiation. Patients aged 80 years and older were at increased risk of early discontinuation. A substantial proportion of patients restarted treatment following first discontinuation; yet, 47 % persisted with treatment for 1 year following restarting therapy.

Persistence estimates were higher than expected when compared to previously conducted studies among first-time users who did not initiate treatment specifically after fracture. A meta-analysis showed a pooled persistence estimate of 50 % (95 % CI 37–63 %) for treatment lasting 7 to 12 months as measured by treatment gaps that ranged from 30 to 120 days [19]. They also found increased persistence among patients allowed to switch medications (58 % [95 % CI 45–70 %] vs 46 % [95 % CI 38–55 %]). Another study that was conducted among new users irrespectively of fracture status and that similarly defined persistence as the present study (90-day gap and allowed switching between drugs) found a 1-year persistence estimate of 67 % (95 % CI 66–68), which was still lower as compared to the current study [15]. This suggests that the setting, where treatment was initiated after a recent

Table 3 Determinants of non-persistence (>90-day gap) with anti-osteoporosis drugs after fracture

	Cr. HR (95 % CI)	Adj. HR (95 % CI)
Gender		
Male	Reference	Reference
Female	0.91 (0.71–1.18)	0.97 (0.74–1.26)
Age categories		
50–59 years	Reference	Reference
60–69 years	1.05 (0.75–1.47)	1.06 (0.76–1.50)
70–79 years	1.15 (0.82–1.60)	1.13 (0.80–1.58)
≥80 years	1.70 (1.20–2.42)	1.65 (1.15–2.38)
Type of index fracture		
Forearm	Reference	Reference
Humerus	0.92 (0.65–1.31)	0.87 (0.61–1.24)
Clinical vertebral	1.22 (0.95–1.57)	1.13 (0.87–1.47)
Hip	1.24 (0.94–1.63)	1.08 (0.81–1.44)
Dosage regime		
Once daily	1.21 (0.84–1.74)	1.06 (0.73–1.54)
Once weekly	Reference	Reference
Once monthly	0.58 (0.24–1.40)	0.58 (0.24–1.41)
Drug use[a]		
Systemic glucocorticoids	1.21 (0.84–1.73)	1.18 (0.82–1.70)
Antidepressants	1.12 (0.81–1.55)	1.11 (0.80–1.54)
Opioids (tramadol or stronger)	1.00 (0.65–1.53)	0.83 (0.53–1.29)
Non-steroidal anti-inflammatory drugs	1.01 (0.79–1.31)	0.98 (0.76–1.27)
Calcium supplements and/or vitamin D	0.96 (0.77–1.19)	0.94 (0.76–1.17)
Disease-modifying anti-rheumatic drugs	1.01 (0.48–2.14)	1.10 (0.52–2.34)
Disease occurrence[b]		
Dementia/Alzheimer's disease	1.71 (0.94–3.11)	1.46 (0.79–2.70)
Subsequent fractures	1.70 (0.91–3.21)	1.64 (0.86–3.10)
Upper gastrointestinal disorders	1.54 (0.79–3.00)	1.40 (0.71–2.74)
Alcoholism	1.55 (0.80–3.01)	1.50 (0.76–2.96)

Cr crude, *Adj* adjusted, *HR* hazard ratio, *95 % CI* 95 % confidence interval

[a] Reference group is no use within 6 months prior within that drug category

[b] Reference group is no occurrence within 6 months prior (ever prior for dementia/Alzheimer's disease or alcoholism) within that disease category

fracture, may have influenced persistence. Indeed, studies that included patients who visited fracture liaison services (FLSs) showed 1-year persistence that ranged between 74 and 88 %, which were either based on self-report [25–28] or prescription claims [29]. These numbers may, however, have been biased upward by selection toward more motivated patients as only patients agreeing to participate in FLSs were included (response rate ranged between 38 and 88 %). To the best of our knowledge, the only previously conducted population-based study that assessed persistence after fracture (1997–2004) showed a 1-year persistence estimate of 80 % with alendronic acid weekly, etidronic acid, or raloxifene [30].

In a multivariable adjusted analysis, age of 80 years and older (reference 50–59 years) was identified as a significant determinant of non-persistence with anti-osteoporosis drugs early after initiation. This finding is in line with the, to the best of our knowledge, only previous study that explored determinants of non-persistence with these drugs when initiated after recent fracture (OR 1.008; 95 % CI 1.004–1.012 per year

of age) [30]. Although older age was identified as a marker for increased risk of early discontinuation, the underlying reasons remain unknown and may be multifactorial, including but not limited to the number of comorbid conditions, poly-pharmacy, physical inability or dependency of others to take medication, or willingness to take medication.

A weekly dosage regime has now been widely adopted in clinical practice and has been associated with increased persistence when compared to a daily regime although evidence is conflicting for the difference in persistence between weekly and monthly regimes [13, 17]. In the present study, we did not find evidence that daily and monthly dosage regimes of the initial drug were associated with increased or decreased risk of discontinuation compared to a weekly regime, respectively. However, switching between anti-osteoporosis drugs and dosage regimes was permitted and may have diluted the association. In addition, the number of daily and monthly users was limited (daily, 7 % of whom 3.4 % were daily bisphosphonate users; monthly, 2.2 %). Similarly, the occurrence of upper
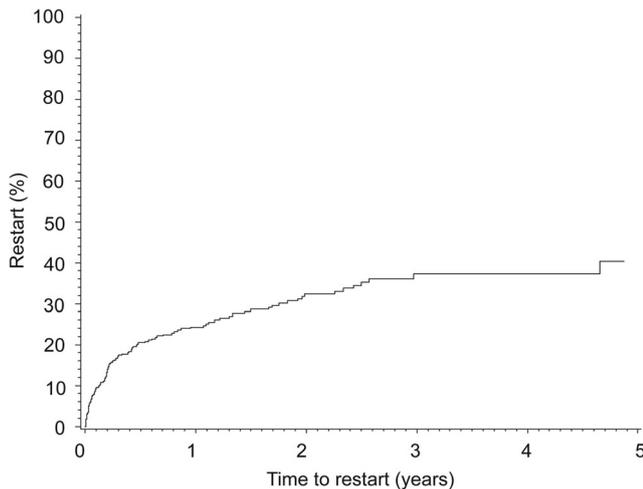
Fig. 2 Kaplan-Meier curve for cumulative incidence of restart with anti-osteoporosis drugs after first discontinuation (>90-day gap)

gastrointestinal disorders is a frequently cited reason for discontinuation of bisphosphonates, but this was not confirmed in the present study [31–33]. Again, switching between anti-osteoporosis drugs was allowed and may explain this finding. Furthermore, a qualitative study indicated that fear for side effects, while they did not occur yet, was enough to discontinue with treatment, which was not captured in our data [26].

Approximately 40 % of patients restarted therapy within 5 years after discontinuation, of whom the majority did so within the first 6 months. Previous studies showed proportions of restarting patients varying between 18 and 38 % within 6 months after first discontinuation [13, 18, 34–36]. Our finding of 20 % is at the lower end of this range and is in agreement with a Dutch study, where 18 % of osteoporotic patients restarted therapy within 6 months [13]. The substantial proportion of patients who restarted therapy was reflected by an increase in persistence over time when permissible treatment gaps became wider. The present study identified that
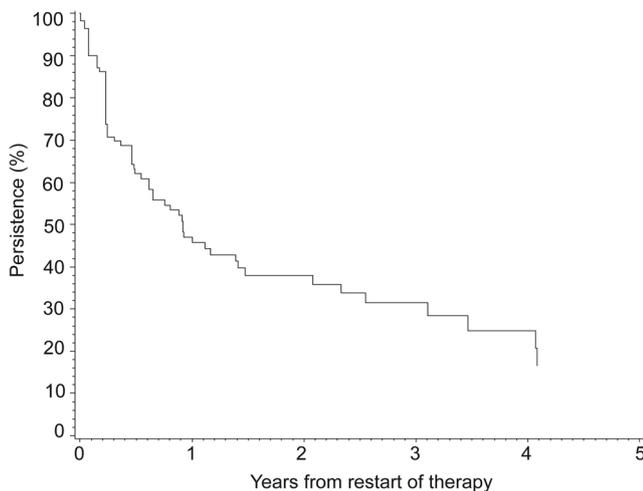
Fig. 3 Kaplan-Meier persistence curve for treatment with anti-osteoporosis drugs following restart of therapy (>90-day gap)

persistence with anti-osteoporosis therapy was poor among restarting patients. While there is little evidence of persistence after restarting therapy, the results of this study are similar to, to our knowledge, the only previous study to address this issue, which identified a median duration of persistence of 6 months following restart (>60-day gap) [18].

Strengths of this study include that persistence was determined over a long-term follow-up period and that linkage of longitudinal data of hospitalizations, diagnoses made by general practitioners, mortality, and drug dispensing was possible. The majority of studies on anti-osteoporosis drug persistence included a short 1-year follow-up with a focus on first treatment discontinuation. However, determining persistence for the initial drug or first treatment period may result in an underestimation of total exposure. Indeed, this study identified that up to a quarter of patients who discontinued therapy returned to treatment within 1 year of discontinuation which increased to 40 % within 5 years. Although it is encouraging that many patients may return to therapy, extended gaps in therapy may result in reduced effectiveness. This may, however, depend on the duration of prior exposure as limited evidence shows a residual anti-fracture effect during posttreatment follow-up that was inversely associated with time on treatment and may be explained by accumulation of bisphosphonates in the bone [37].

A limitation of this study was that persistence relied on pharmacy dispensing data where the actual intake remained unknown. However, several studies showed that repeated dispensing records are a good indicator of consumptions [38, 39]. Second, due to the coding system within general practitioner records, we were not able to disentangle proximal humerus fractures from those of the distal part and shaft. Proximal humerus fractures have been associated with osteoporotic BMD [40, 41] and fracture risk [40], while little is known for those of the shaft and distal part where benefits of treatment with anti-osteoporosis drugs may be less clear. We believe that the impact of this is limited as proximal humerus fractures are the dominant type of humerus fractures after the age of 50 years [42] and the study population was highly likely to have osteoporotic BMD since the Dutch primary care guideline primarily focusses on DXA-diagnosed osteoporosis when considering starting anti-osteoporosis drugs after non-vertebral fractures. Furthermore, this study only identified old age as a significant determinant of discontinuation and the results of several other determinants, including dementia, exposure to DMARDs, initial monthly dosage regime, and alcohol-related diagnoses, should be interpreted with caution due to the low numbers of patients exposed. An incident diagnosis of renal failure may as well be a determinant of discontinuation but could not be included in the analyses due to the fact that only three patients with this determinant were present. Another limitation was that intravenously administered anti-osteoporosis drugs (zoledronic acid) or

subcutaneous drugs (e.g., teriparatide, denosumab) prescribed by a specialist were not (completely) captured as they are either delivered to the patient in the hospital or frequently by special ambulatory pharmacies. A significant underestimation of persistence due to this limitation, however, is unlikely as zoledronic acid was not frequently administered during the study period [43], denosumab was introduced in the Netherlands in the year 2011, and teriparatide is only reimbursed under restricted conditions.

In conclusion, results identified suboptimal persistence among a cohort of patients with prior fracture, highlighting the need for additional research focused on improving persistence among patients at high risk for subsequent fractures, which includes a better understanding of the underlying reasons for non-persistence. The results of the present study further add to the literature by identifying the frequency of treatment re-initiation following an extended gap and the subsequent persistence with therapy. There are a number of opportunities for improving treatment persistence, including educational interventions targeted at physicians and/or patients as many physicians may be unaware of, and therefore unable to address, non-adherence [44, 45] and both physicians as patients may be sceptical or unaware of treatment benefits, other opportunities include telephone-based counselling [46], pharmaceutical intervention [47, 48], or use of patient decision aids [49]; yet, few have proven effective in clinical settings [50]. Major target groups for intervention after a recent fracture may be those aged 80 or more years and those restarting therapy following an extended gap.

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