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ORIGINAL ARTICLE

Trajectories of oral bisphosphonate use after hip fractures: a population-based cohort study

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Abstract

Summary Bisphosphonates prevent future hip fractures. However, we found that one in six patients with hip fractures had a delay in bisphosphonate initiation and another one-sixth discontinued treatment within 12 months after discharge. Our results highlight the need to address hesitancy in treatment initiation and continuous monitoring.

Purpose Suboptimal antiresorptive use is not well understood. This study investigated trajectories of oral bisphosphonate use following first hip fractures and factors associated with different adherence and persistence trajectories.

Methods We conducted a retrospective study of all patients aged ≥ 50 years dispensed two or more bisphosphonate prescriptions following first hip fracture in Victoria, Australia, from 2012 to 2017. Twelve-month trajectories of bisphosphonate use were categorized using group-based trajectory modeling. Factors associated with different trajectories compared to the persistent adherence trajectory were assessed using multivariate multinomial logistic regression.

Results We identified four patterns of oral bisphosphonate use in 1811 patients: persistent adherence (66%); delayed dispensing (17%); early discontinuation (9%); and late discontinuation (9%). Pre-admission bisphosphonate use was associated with a lower risk of delayed dispensing in both sexes (relative risk [RR] 0.28, 95% confidence interval [CI] 0.21–0.39). Older patients (≥ 85 years old versus 50–64 years old, RR 0.38, 95% CI 0.22–0.64) had a lower risk of delayed dispensing. Males with anxiety (RR 9.80, 95% CI 2.24–42.9) and females with previous falls had increased risk of early discontinuation (RR 1.80, 95% CI 1.16–2.78).

Conclusion Two-thirds of patients demonstrated good adherence to oral bisphosphonates over 12 months following hip fracture. Efforts to further increase post-discharge antiresorptive use should be sex-specific and address possible persistent uncertainty around delaying treatment initiation.

Keywords Antiresorptive medication · Bisphosphonate · Hip fracture · Osteoporosis

Introduction

Osteoporotic fractures are associated with significant disability, morbidity, and mortality. Hip fractures are responsible for considerable clinical and economic burden to individuals and the society [1, 2]. A recent projection based on data from 20 countries suggested the number of hip fractures will double from 2018 to 2050 [3]. The absolute number of hip fractures increased by 20% from 2012 to 2018 in Victoria, Australia [4].

Bisphosphonates are recommended as first-line treatment for patients with radiologically confirmed osteoporosis or following a minimal trauma fracture [5–7]. However, despite their established cost-effectiveness, bisphosphonates remain under-utilized [8, 9]. Undertreatment may arise from fear of possible negative impacts on fracture healing [10] or low treatment adherence and persistence [11]. Delayed

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dispensing may result in a missed opportunity for fracture prevention because the risk of second fracture is highest soon after the first fracture [12, 13], whereas non-adherence and non-persistence have been associated with up to a 40% increase in fracture risk [14]. Understanding the different trajectories of bisphosphonate use following fractures allows clinicians and policy makers to develop targeted strategies to address the longstanding problem of bisphosphonate underutilization.

Most studies on bisphosphonate adherence have used the medication possession ratio to dichotomize patients as adherent or non-adherent using various cut-offs [11]. More granular longitudinal understanding of bisphosphonate use after hip fracture is lacking. Group-based trajectory modeling is a useful agnostic epidemiological tool for identifying different trajectories of medication use based on similarities in actual dispensing patterns [15, 16].

The objective of our study was to investigate trajectories of oral bisphosphonate use following first hip fractures and factors associated with different adherence and persistence trajectories by using population-based linked datasets. The factors investigated included patient demographics, residence, comorbidities, polypharmacy, previous falls, osteoporosis diagnosis, and prior bisphosphonate use [11, 17, 18].

Methods

Data sources

Our population-based cohort study used linked data from the Victorian Admitted Episodes Dataset (VAED), Pharmaceutical Benefits Scheme (PBS), and National Death Index (NDI). VAED are routinely collected administrative data for all public and private hospital episodes in Victoria, Australia. The dataset contains comprehensive information on demographics, diagnoses, admission sources, and discharge destinations. Records for readmission within 1 day of discharge were combined with original admission as a single continuous hospitalization to account for transfers between hospitals. Hip fracture ascertainment using Australian administrative hospital data has a sensitivity (i.e., proportion of hip fractures captured in administrative data) around 95% and positive predictive value (i.e., proportion of recorded hip fractures were a new hip fracture) above 70% [19]. We restricted our investigation to first hip fracture to minimize false positives due to misclassification of subsequent episodes of care as new hip fractures. The PBS dataset contains information on pharmacy claims made by all Australian residents for medications subsidized by the Australian Government. This dataset contains records of medications dispensed at all community pharmacies, outpatient clinics and at hospital discharge. The PBS dataset does not contain information of medications dispensed during a hospitalization. NDI contains information on all deaths registered across Australia. Data from VAED and PBS were available from 1 July 2006 to 30 June 2018, whereas data from NDI were available from 1 July 2012 to 30 June 2018. Details on the datasets have been published previously [4].

Study population

All patients aged 50 years or above and discharged from any public or private hospital in Victoria between 1 July 2012 and 30 June 2017 following hip fractures were included. Patients with a principal diagnosis of hip fracture (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification [ICD-10-AM] S72.0-S72.2) [19–22] were included. Patients with a hip fracture or cancer diagnosis (ICD-10-AM C00-C99) within 5 years prior to the index hip fracture were excluded to ensure we investigated incident hip fractures and their bisphosphonate use were not affected by other indications (e.g., bone metastases or hypercalcemia). To avoid including patients who discontinued due to intolerance after their first dose, our study included patients with at least 2 dispensings of any oral bisphosphonates (World Health Organization Anatomical Therapeutic Chemical Classification [ATC] M05BA04, M05BA07, M05BB02-M05BB07) within 12 months after discharge. Patients dispensed other osteoporosis medications (i.e., denosumab [ATC M05BX04], zoledronic acid [ATC M05BA08, M05BB08], and raloxifene [ATC G03XC01]) within the follow-up period were excluded. Patients dispensed denosumab within 6 months before discharge were also excluded to avoid including patients not initiated on bisphosphonates at discharge for this reason. Patients who died within 12 months after discharge were excluded [23, 24]. Patients who were hospitalized for more than 1 month in the 12 months post-discharge were also excluded to avoid missing data from lack of inpatient dispensing data.

Trajectories determination

Dispensings of oral bisphosphonates were ascertained for each 30-day period after discharge for 12 months. Each oral bisphosphonate dispensing in Australia represents 30 days' supply. If there were two or more bisphosphonate dispensings in a 30-day period, the extra prescriptions were carried forward to the subsequent months for which there was no dispensing. Trajectories of oral bisphosphonate use were identified by group-based trajectory modeling with SAS PROC TRAJ [25]. The number of trajectories was first determined using the highest order possible with the procedure, which allows the maximum number of inflection points thus flexibility in fitting each trajectory [15]. Bayesian

information criterion (BIC) across all models was compared and models with less negative BIC were preferred (Supplemental Table 1) [15]. A model with 4 trajectories was chosen as any larger number of trajectories did not provide stratification of clinical significance. Different orders for each trajectory were then explored (Supplemental Table 2). Average posterior probability of group membership (AvePP) and odds of correct classification (OCC) for each trajectory were calculated to evaluate adequacy of the models [15]. The final best-fitting model was chosen based on the following criteria: (a) AvePP > 0.7, (b) OCC > 5, (c) the highest order parameter of each trajectory was statistically significant, (d) the group proportions estimated by the model was similar to the actual proportions of individuals assigned to each group based on their maximum posterior probability, (e) the BIC, (f) parsimony principle, and (g) clinical judgement (Supplemental Table 2) [15].

Factors associated with trajectories

We investigated factors that have been associated with adherence and persistence to oral bisphosphonates in previous research, including selected comorbidities related to cognitive, mental, and gastrointestinal health [11]. We also investigated factors that were associated with 1-year mortality following hip fracture in our previous research [4]. These factors included age, sex, discharge to residential aged care facilities (RACF), and frailty [4]. Frailty was assessed using the validated Hospital Frailty Risk Score (HFRS), a weighted score of 109 diagnoses recorded within 2 years prior to discharge [26]. Patients were categorized as having low frailty risk (HFRS < 5), intermediate frailty risk (HFRS 5–15), and high frailty risk (HFRS > 15) [26]. Comorbidities were identified from ICD-10-AM diagnosis codes recorded within 5 years prior to discharge. Previous falls and previous osteoporosis were identified from ICD-10-AM diagnoses recorded within 5 years prior to admission. A 5-year look-back period was used to improve the detection of comorbidities across multiple hospitalizations for each patient. This was because not all comorbidities may have been recorded at the index hospitalization. Pre-admission bisphosphonate use (any oral bisphosphonate dispensing within 6 months prior to admission) and pre-admission polypharmacy (5 or more different medications dispensed within 60 days prior to admission) were also assessed. Factors associated with different trajectories compared to the persistent adherence trajectory were assessed using multivariate multinomial logistic regression. The model was adjusted for age, sex, discharge to RACF, HFRS, comorbidities, previous falls, previous osteoporosis diagnosis, pre-admission bisphosphonate use, and pre-admission polypharmacy. Statistical significance was defined as p-value < 0.05. All analyses were performed using SAS (version 9.4) and R (version 4.0.0). As management of osteoporosis is sex-specific, sex-stratified subgroup analysis was performed to examine any differences across sex in bisphosphonate use after hip fractures. Sensitivity analysis was conducted to explore the possible effect of subsequent fractures on the analysis by excluding patients with second hip fractures from the multivariate multinomial logistic regression.

Ethics

The study was approved by Australian Institute of Health and Welfare Ethics Committee (EO2018-4–468) and Monash University Human Research Ethics Committee (14,339).

Results

Among 13,112 patients hospitalized for hip fractures and eligible for evaluation of oral bisphosphonate use, 1811 patients dispensed ≥ 2 prescriptions were included for trajectories evaluation (Supplemental Fig. 1). Among these included patients, 80% ($n = 1439$) were females, 77% ($n = 1395$) were 75 years or older, and 14% ($n = 244$) were discharged to RACF. The majority (72%, $n = 1300$) had intermediate frailty risk (HFRS 5–15) at discharge, while 16% ($n = 290$) had low frailty risk (HFRS < 5) and 12% ($n = 221$) had high frailty risk respectively. Overall, 43% ($n = 775$) had oral bisphosphonates dispensed within 6 months pre-admission. The median (interquartile range) number of medications dispensed within 60 days pre-admission was 6 (3–8) and 62% ($n = 1117$) of patients had pre-admission polypharmacy (Table 1).

Trajectories of bisphosphonate use

The four trajectories identified by group-based trajectory modeling were labelled as "persistent adherence," "delayed dispensing," "early discontinuation," and "late discontinuation." The proportions of patients that were categorized into the different trajectories were 66% ($n = 1191$), 17% ($n = 305$), 9% ($n = 161$), and 9% ($n = 154$) respectively. Patients with "persistent adherence" had > 80% probability of monthly bisphosphonate dispensing throughout the 12 months. The probability of dispensing bisphosphonates for patients with "delayed dispensing" was low initially and increased to 50% at 6 months after discharge. The probability of bisphosphonate dispensing for patients with "early discontinuation" and "late discontinuation" decreased to 50% at around 3 and 8 months respectively (Fig. 1 and Supplemental Table 3).

Table 1 Characteristics of study cohort by trajectories

	Overall ($n=1811$)	Persistent adherence ($n=1191$)	Delayed dispensing ($n=305$)	Early discontinuation ($n=161$)	Late discontinuation ($n=154$)
Age, *n* (%)					
50–64	115 (6.4)	56 (4.7)	36 (11.8)	12 (7.5)	11 (7.1)
65–74	301 (16.6)	187 (15.7)	67 (22.0)	24 (14.9)	23 (14.9)
75–84	756 (41.7)	484 (40.6)	134 (43.9)	69 (42.9)	69 (44.8)
≥ 85	639 (35.3)	464 (39.0)	68 (22.3)	56 (34.8)	51 (33.1)
Sex, *n* (%)					
Males	372 (20.5)	236 (19.8)	62 (20.3)	38 (23.6)	36 (23.4)
Females	1439 (79.5)	955 (80.2)	243 (79.7)	123 (76.4)	118 (76.6)
Discharge destination, *n* (%)					
RACF	244 (13.5)	171 (14.4)	23 (7.5)	30 (18.6)	20 (13.0)
Home-dwelling and other[a]	1567 (86.5)	1020 (85.6)	282 (92.5)	131 (81.4)	134 (87.0)
HFRS, *n* (%)					
< 5	290 (16.0)	170 (14.3)	74 (24.3)	23 (14.3)	23 (14.9)
5–15	1300 (71.8)	873 (75.3)	203 (66.6)	116 (72.0)	108 (70.1)
> 15	221 (12.2)	148 (12.4)	28 (9.2)	22 (13.7)	23 (14.9)
Comorbidities					
Anxiety	126 (7.0)	78 (6.5)	20 (6.6)	18 (11.2)	10 (6.5)
Dementia	125 (6.9)	84 (7.1)	14 (4.6)	9 (5.6)	18 (11.7)
Depression	109 (6.0)	73 (6.1)	13 (4.3)	10 (6.2)	13 (8.4)
Gastroesophageal reflux	122 (6.7)	75 (6.3)	25 (8.2)	8 (5.0)	14 (9.1)
Previous falls	478 (26.4)	317 (26.6)	64 (21.0)	52 (32.3)	45 (29.2)
Previous osteoporosis diagnosis	226 (12.5)	144 (12.1)	36 (11.8)	21 (13.0)	25 (16.2)
Pre-admission medications					
Oral bisphosphonates	775 (42.8)	582 (48.9)	61 (20.0)	63 (39.1)	69 (44.8)
Polypharmacy	1117 (61.7)	768 (64.5)	153 (50.2)	92 (57.1)	104 (67.5)

HFRS, Hospital Frailty Risk Score; *RACF*, residential aged care facilities. [a]Including discharge to private residences, transition care program, mental health accommodation, and transfers from other health care organizations

Factors associated with trajectories

Patients aged 85 years or older and patients with intermediate frailty risk (HFRS 5–15) were more likely to have persistent adherence, as evidenced by their lower risk of delayed dispensing (≥ 85 years old versus 50–64 years old: relative risk [RR] 0.38, 95% confidence interval [CI] 0.22–0.64; HFRS 5–15 VS HFRS < 5: RR 0.66, 95% CI 0.47–0.93). In addition, patients who were on bisphosphonates pre-admission had a lower risk of delayed dispensing (RR 0.28, 95% CI 0.21–0.39). Patients with dementia were at higher risk of late discontinuation when compared with persistent adherence (RR 1.92, 95% CI 1.09–3.38), while patients with anxiety disorder had a higher risk of early discontinuation (RR 1.92, 95% CI 1.08–3.43) (Table 2).

When stratified by sex, females aged 85 years or older were more likely to have persistent adherence, as demonstrated by their lower risk of delayed dispensing (RR 0.39, 95% CI 0.21–0.72). However, there was no difference for males aged 85 years or older (RR 0.35, 95% CI 0.12–1.03). However, the estimates remained similar. Similarly, females but not males with intermediate frailty risk were more likely to display persistent adherence, as evidenced by their lower risk of delayed dispensing (females: RR 0.68, 95% CI 0.46–1.00; males: RR 0.57, 95% CI 0.26–1.24) with intermediate frailty risk. For patients who were on bisphosphonates pre-admission, decreased risks remained evident for delayed dispensing in both sexes (males: RR 0.17, 95% CI 0.06–0.49; females: RR 0.30, 95% CI 0.21–0.42). Higher risk of early discontinuation for patients with history of anxiety disorder remained significant for males (RR 9.81, 95% CI 2.24–42.9) but was not evident in females (RR 1.37, 95% CI 0.69–2.70). Additionally, females hospitalized for falls previously had higher risk of early discontinuation (RR 1.80, 95% CI 1.16–2.78). Higher risk of late discontinuation in patients with dementia became insignificant for both males (RR 1.82 95% CI 0.49–6.78) and females (RR 1.89 95% CI 1.00–3.58) (Tables 3 and 4).

Sex, type of residence, history of depression, gastroesophageal reflux, previous osteoporosis diagnosis, and

Table 2 Association between patient factors and different trajectories compared to persistent adherence

	Delayed dispensing		Early discontinuation		Late discontinuation	
	RR [95% CI][a]	*p*-value	RR [95% CI][a]	*p*-value	RR [95% CI][a]	*p*-value
Age, *n* (%)						
50–64	1		1		1	
65–74	0.71 [0.42–1.21]	0.210	0.69 [0.32–1.48]	0.342	0.62 [0.28–1.37]	0.240
75–84	0.67 [0.41–1.11]	0.119	0.81 [0.40–1.63]	0.555	0.70 [0.34–1.45]	0.340
≥ 85	0.38 [0.22–0.64]	< 0.001	0.66 [0.32–1.36]	0.266	0.55 [0.26–1.16]	0.117
Sex, *n* (%)						
Females	1		1		1	
Males	0.79 [0.57–1.11]	0.172	1.17 [0.78–1.76]	0.435	1.15 [0.76–1.74]	0.510
Discharge destination, *n* (%)						
Home-dwelling and other[b]	1		1		1	
RACF	0.68 [0.47–0.93]	0.119	1.42 [0.90–2.24]	0.136	0.84 [0.50–1.42]	0.511
HFRS, *n* (%)						
< 5	1		1		1	
5–15	0.66 [0.47–0.93]	0.019	0.97 [0.59–1.60]	0.902	0.89 [0.54–1.47]	0.645
> 15	0.64 [0.37–1.13]	0.124	0.93 [0.46–1.87]	0.831	0.94 [0.47–1.89]	0.864
Comorbidities						
Anxiety	1.30 [0.75–2.25]	0.351	1.92 [1.08–3.43]	0.027	0.88 [0.43–1.79]	0.725
Dementia	0.90 [0.49–1.67]	0.747	0.72 [0.35–1.50]	0.382	1.92 [1.09–3.38]	0.023
Depression	0.82 [0.43–1.56]	0.539	0.78 [0.38–1.63]	0.513	1.36 [0.71–2.61]	0.355
Gastroesophageal reflux	1.23 [0.75–2.03]	0.410	0.75 [0.35–1.60]	0.459	1.38 [0.75–2.54]	0.295
Previous falls	1.00 [0.71–1.41]	0.988	1.43 [0.97–2.11]	0.073	1.06 [0.70–1.59]	0.786
Previous osteoporosis diagnosis	1.22 [0.80–1.85]	0.354	1.10 [0.66–1.83]	0.719	1.38 [0.85–2.24]	0.189
Pre-admission medications						
Oral bisphosphonates	0.28 [0.21–0.39]	< 0.001	0.70 [0.49–1.00]	0.048	0.82 [0.57–1.18]	0.284
Polypharmacy	0.83 [0.62–1.09]	0.183	0.74 [0.51–1.06]	0.096	1.21 [0.82–1.77]	0.332

RR, relative risk; *CI*, confidence interval; *HFRS*, Hospital Frailty Risk Score; *RACF*, residential aged care facilities. [a]Adjusted for age, sex, discharge to RACF, HFRS, comorbidities, previous falls, previous osteoporosis diagnosis, pre-admission bisphosphonate use, and pre-admission polypharmacy. [b]Including discharge to private residences, transition care program, mental health accommodation, and transfers from other health care organizations

pre-admission polypharmacy were not associated with different trajectories in both main and sex-stratified analyses (Tables 2, 3, and 4). Sensitivity analysis excluding patients with second hip fractures from the analyses produced similar results for both overall and sex-stratified analyses. The study is reported in accordance with STROBE statement (Supplemental Table 4) [27].

Discussion

The main finding of our study was that two-thirds of patients demonstrated persistent adherence over 12 months following their first hip fracture. However, one-sixth of patients had delayed dispensing following discharge. Older age, increased frailty, and pre-admission bisphosphonate use were associated with lower risk of delayed dispensing. The remaining one-sixth of patients discontinued early or late over the 12-month post-discharge. Males with anxiety disorder and females with previous falls were associated with increased risk of early discontinuation.

The proportion of patients with persistent adherence was higher than for other chronic medications [28]. For example, 55% of older adults using statins in Australia were non-adherent and 45% discontinued their statins within 12 months [29]. Our study was comparable to a recent systematic review which revealed 12-month persistence was within the 18–75% range [11]. The high proportion of patients with persistent adherence may be because their recent hip fracture reinforced the need for adherence to prophylactic treatment. Another reason may be that patients at risk of non-adherence were preferentially prescribed denosumab, which has been shown to be associated with better adherence [30].

One in six patients had delayed dispensing. Primary non-adherence (i.e., a delay in having a prescription dispensed)

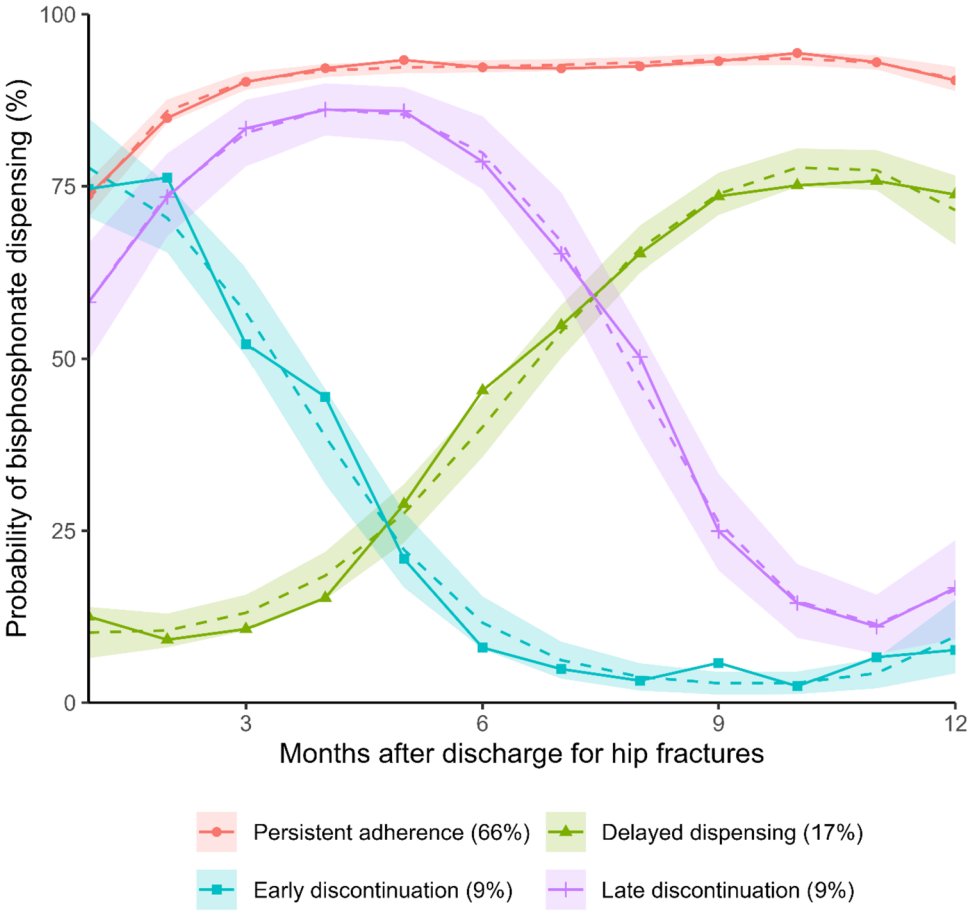

Fig. 1 Trajectories for oral bisphosphonate use over 12 months after discharge for hip fractures

may have contributed to this observed delay. However, despite a meta-analysis reporting that primary non-adherence was prevalent for osteoporosis medications [31], an Australian study reported that around 95% of patients filled their first antiresorptive prescription within 1 month [32]. Clinicians' fear of bisphosphonates slowing bone healing may have also contributed to the observed delay. However, recent systematic reviews suggest initiating bisphosphonates soon after fracture does not lead to adverse outcomes [33, 34]. During our study period, Australian guidelines recommended patients receive dental assessment prior to initiating bisphosphonates [6, 7]. This may have also contributed to the observed delay. Older Australians visit dentists more frequently than younger Australians [35], which may partly explain why older patients were less likely to have delayed dispensing. Clinical inertia (i.e., failure to initiate or intensify therapy when indicated) [36] may have also contributed to the observed delay. Higher perceived risk of fracture in patients with intermediate frailty may decrease clinical inertia. The absence of clinical inertia in patients already taking bisphosphonates may explain the reduced risk of delayed dispensing. Education addressing the risks of bisphosphonates and fractures following minimal-trauma fractures is needed to reduce apparent prescribing hesitancy.

Another one-sixth of patients did not persist with bisphosphonates over 12 months. More than half of these patients discontinued soon after discharge. Pre-admission bisphosphonate use had minimal effect on early or late discontinuation. This was largely consistent with a recent study that demonstrated pre-admission bisphosphonate users had different adherence patterns after fractures [37]. Males with history of anxiety were more likely to discontinue early, which is consistent with a previous study that reported anxiety was associated with medication non-adherence [38]. The greater disability experienced by males with anxiety may partly explain the differential effect across sex [39]. On the other hand, females, but not males, with previous falls had increased risk of early discontinuation. This may be because more osteoporosis guidelines focus on treating post-menopausal women [5], leading to more females than males being prescribed with bisphosphonates after a previous fall. Our results highlight the importance of sex-specific initiatives to improve bisphosphonate use during early post-fracture follow-up.

One-tenth of patients discontinued more than 6 months after discharge. Patients with dementia had increased risk of late discontinuation, which may result from cognitive impairment, lack of contact with medical specialists such as

Table 3 Association between patient factors and different trajectories compared with persistent adherence in males

	Delayed dispensing		Early discontinuation		Late discontinuation	
	RR [95% CI][a]	*p*-value	RR [95% CI][a]	*p*-value	RR [95% CI][a]	*p*-value
Age, *n* (%)						
50–64	1		1		1	
65–74	0.57 [0.20–1.64]	0.299	0.14 [0.02–0.83]	0.030	0.51 [0.12–2.06]	0.342
75–84	0.56 [0.21–1.51]	0.248	0.70 [0.21–2.37]	0.563	0.56 [0.16–2.05]	0.384
≥85	0.35 [0.12–1.03]	0.057	0.64 [0.18–2.30]	0.499	0.26 [0.06–1.11]	0.069
Discharge destination, *n* (%)						
Home-dwelling and other[b]	1		1		1	
RACF	0.48 [0.13–1.75]	0.265	1.93 [0.73–5.09]	0.183	1.35 [0.49–3.73]	0.562
HFRS, *n* (%)						
< 5	1		1		1	
5–15	0.57 [0.26–1.24]	0.155	0.88 [0.26–2.96]	0.840	1.26 [0.38–4.16]	0.706
> 15	0.47 [0.15–1.51]	0.204	0.90 [0.20–3.94]	0.887	0.63 [0.13–3.04]	0.561
Comorbidities						
Anxiety	3.75 [0.57–24.7]	0.169	9.81 [2.24–42.9]	0.002	2.31 [0.35–15.1]	0.381
Dementia	0.73 [0.15–3.52]	0.693	N.A	N.A	1.82 [0.49–6.78]	0.374
Depression	0.68 [0.18–2.57]	0.568	1.07 [0.30–3.87]	0.917	2.06 [0.68–6.22]	0.199
Gastroesophageal reflux	0.90 [0.26–3.18]	0.876	N.A	N.A	2.07 [0.58–7.31]	0.260
Previous falls	1.02 [0.47–2.23]	0.964	0.61 [0.24–1.60]	0.318	1.28 [0.55–3.00]	0.565
Previous osteoporosis diagnosis	0.68 [0.24–1.97]	0.482	1.35 [0.46–3.96]	0.580	0.67 [0.21–2.18]	0.506
Pre-admission medications						
Oral bisphosphonates	0.17 [0.06–0.49]	0.001	0.66 [0.27–1.59]	0.357	1.21 [0.54–2.70]	0.647
Polypharmacy	1.10 [0.59–2.05]	0.768	0.93 [0.42–2.05]	0.865	1.93 [0.81–4.59]	0.135

RR, relative risk; *CI*, confidence interval; *HFRS*, Hospital Frailty Risk Score; *RACF*, residential aged care facilities. [a]Adjusted for age, sex, discharge to RACF, HFRS, comorbidities, previous falls, previous osteoporosis diagnosis, pre-admission bisphosphonate use, and pre-admission polypharmacy. [b]Including discharge to private residences, transition care program, mental health accommodation, and transfers from other health care organizations

endocrinologists, or change in the goals of care [40, 41]. Our results underscore the importance of understanding the benefits and risks of ongoing treatment in people with dementia.

Strengths and limitations

Strengths of our study include the use of linked administrative health data for all patients with hip fracture in Victoria [42]. Our group-based trajectory modeling was based on 30-day dispensing rather than prescription data or 60-day or 90-day dispensing. Group-based trajectory modeling was an agnostic approach to identify trajectories which avoided potential bias arising from defining adherence using arbitrary cut-offs or dichotomization of patients [16, 43, 44]. Particularly, our model identified patients with delayed dispensing and late discontinuation. These dispensing patterns would not have been evident had we calculated the possession ratio (MPR), another adherence measure with common cut-offs of low (MPR < 0.5), moderate (MPR 0.5 to < 0.8), and high (MPR 0.80 to 1.00) adherence. Our study allowed identification of risks factors for bisphosphonate use patterns that would have been obscured otherwise. Another strength of our study is our stringent inclusion and exclusion criteria. By including only those with at least 2 dispensings of bisphosphonate and excluding patients who used other anti-osteoporosis medications during follow-up, our results are not biased by patients who discontinued due to intolerance or contraindications or those who switched to other anti-osteoporosis medications.

While this study included the entire population in Victoria, Australia, one limitation of our study is that it may not be generalizable to other populations. Patterns of bisphosphonate use may be different in other populations due to differences in guidelines around medication selection, initiation, availability of dental examination, and medication reimbursement criteria. Other limitations include we only included patients dispensed two or more oral bisphosphonate prescriptions and did not investigate the characteristics of patients not initiated on bisphosphonates. While we adjusted for pre-admission bisphosphonate use in our analysis, we did not account for the duration of previous use. Our study also did not investigate the use of parenteral

Table 4 Association between patient factors and different trajectories compared with persistent adherence in females

	Delayed dispensing		Early discontinuation		Late discontinuation	
	RR [95% CI][a]	*p*-value	RR [95% CI][a]	*p*-value	RR [95% CI][a]	*p*-value
Age, *n* (%)						
50–64	1		1		1	
65–74	0.77 [0.41–1.42]	0.395	1.05 [0.41–2.69]	0.918	0.66 [0.25–1.75]	0.407
75–84	0.71 [0.39–1.26]	0.239	0.89 [0.37–2.17]	0.801	0.76 [0.31–1.85]	0.547
≥ 85	0.39 [0.21–0.72]	0.002	0.69 [0.28–1.72]	0.426	0.67 [0.27–1.67]	0.392
Discharge destination, *n* (%)						
Home-dwelling and other[b]	1		1		1	
RACF	0.74 [0.43–1.24]	0.253	1.33 [0.78–2.27]	0.302	0.67 [0.35–1.26]	0.217
HFRS, *n* (%)						
< 5	1		1		1	
5–15	0.68 [0.46–1.00]	0.049	0.97 [0.56–1.69]	0.922	0.83 [0.48–1.45]	0.518
> 15	0.71 [0.37–1.36]	0.297	0.84 [0.37–1.93]	0.690	1.17 [0.53–2.58]	0.700
Comorbidities						
Anxiety	1.14 [0.64–2.04]	0.659	1.37 [0.69–2.70]	0.368	0.81 [0.37–1.79]	0.606
Dementia	0.95 [0.49–1.84]	0.868	0.95 [0.45–2.02]	0.897	1.89 [1.00–3.58]	0.051
Depression	0.91 [0.43–1.90]	0.793	0.61 [0.23–1.65]	0.333	1.15 [0.49–2.70]	0.749
Gastroesophageal reflux	1.33 [0.77–2.31]	0.305	0.96 [0.44–2.09]	0.914	1.30 [0.64–2.64]	0.475
Previous falls	0.98 [0.67–1.44]	0.913	1.80 [1.16–2.78]	0.008	0.92 [0.57–1.49]	0.738
Previous osteoporosis diagnosis	1.39 [0.87–2.20]	0.166	1.01 [0.55–1.84]	0.984	1.64 [0.96–2.81]	0.071
Pre-admission medications						
Oral bisphosphonates	0.30 [0.21–0.42]	< 0.001	0.68 [0.45–1.01]	0.058	0.74 [0.49–1.11]	0.147
Polypharmacy	0.77 [0.56–1.06]	0.110	0.69 [0.46–1.04]	0.076	1.06 [0.69–1.63]	0.788

RR, relative risk; *CI*, confidence interval; *HFRS*, Hospital Frailty Risk Score; *RACF*, residential aged care facilities. [a]Adjusted for age, sex, discharge to RACF, HFRS, comorbidities, previous falls, previous osteoporosis diagnosis, pre-admission bisphosphonate use, and pre-admission polypharmacy. [b]Including discharge to private residences, transition care program, mental health accommodation, and transfers from other health care organizations

antiresorptives (e.g., denosumab, zoledronic acid) because of their different dosing and dispensing frequencies. We did not exclude patients dispensed zoledronic acid within 1 year prior to discharge. However, we do not anticipate this would result in significant overestimation of delayed dispensing because oral bisphosphonates and denosumab are the most common antiresorptives in Australia [6]. Misclassification bias, common in administrative data, is also present in our study. However, data quality was maximized with regular Australian Government data integrity audits [45] and our frequent monthly data also minimized the effect of single dispensing on trajectory determination. It was a strength of our study that we used a 5-year lookback period to maximize detection of comorbidities. However, we acknowledge that this may have led to the inclusion of comorbid conditions that were no longer acutely symptomatic. We were also not able to investigate why patients exhibit their respective trajectories. However, this may be partly related to patients' beliefs regarding the benefits and harms of medications, which have been demonstrated to impact adherence [46].

Conclusion

In conclusion, two-thirds of patients had persistent adherence to oral bisphosphates over 12 months following hip fracture. However, one-sixth of patients had delayed dispensing and another one-sixth had early or late discontinuation. Efforts to further increase post-discharge antiresorptive use should be sex-specific and address possible persistent uncertainty around delaying treatment initiation.

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Data Availability Restrictions apply to the availability of all data generated and analyzed during this study to preserve patient confidentiality. By Australian legislation, individual patient level data cannot be made publicly available.

Declarations

Conflicts of interest MTYL, JPT, CM, and TT have nothing to declare. JI has received grant or consulting funds from the National Health and Medical Research Council, Medical Research Future Fund, Dementia Australia Research Foundation, Yulgilbar Foundation, National Breast Cancer Foundation, AstraZeneca, and Amgen unrelated to this work. JSB has received grant funding or consulting funds from the National Health and Medical Research Council, Medical Research Future Fund, Victorian Government Department of Health and Human Services, Dementia Australia Research Foundation, Yulgilbar Foundation, Aged Care Quality and Safety Commission, Dementia Centre for Research Collaboration, Pharmaceutical Society of Australia, Society of Hospital Pharmacists of Australia, GlaxoSmithKline Supported Studies Programme, Amgen, and several aged care provider organizations unrelated to this work. All grants and consulting funds were paid to the employing institution.

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