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Hip fracture risk and safety with alendronate treatment in the oldest-old

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Abstract. Axelsson KF, Wallander M, Johansson H, Lundh D, Lorentzon M (Skaraborg Hospital, Skövde; University of Gothenburg, Gothenburg; Karolinska Institute, Stockholm, Sweden; Catholic University of Australia, Melbourne, Vic., Australia; University of Skövde, Skövde, Sweden; Sahlgrenska University Hospital, Mölndal). Hip fracture risk and safety with alendronate treatment in the oldest-old. *J Intern Med* 2017; **282**: 546–559.

Background. There is high evidence for secondary prevention of fractures, including hip fracture, with alendronate treatment, but alendronate's efficacy to prevent hip fractures in the oldest-old (≥80 years old), the population with the highest fracture risk, has not been studied.

Objective. To investigate whether alendronate treatment amongst the oldest-old with prior fracture was related to decreased hip fracture rate and sustained safety.

Methods. Using a national database of men and women undergoing a fall risk assessment at a Swedish healthcare facility, we identified 90 795 patients who were 80 years or older and had a prior fracture. Propensity score matching (four to one) was then used to identify 7844 controls to 1961 alendronate-treated patients. The risk of incident hip fracture was investigated with Cox models and the interaction between age and treatment was investigated using an interaction term.

Results. The case and control groups were well balanced in regard to age, sex, anthropometrics and comorbidity. Alendronate treatment was associated with a decreased risk of hip fracture in crude (hazard ratio (HR) 0.62 (0.49–0.79), $P < 0.001$) and multivariable models (HR 0.66 (0.51–0.86), $P < 0.01$). Alendronate was related to reduced mortality risk (HR 0.88 (0.82–0.95) but increased risk of mild upper gastrointestinal symptoms (UGI) (HR 1.58 (1.12–2.24). The alendronate association did not change with age for hip fractures or mild UGI.

Conclusion. In old patients with prior fracture, alendronate treatment reduces the risk of hip fracture with sustained safety, indicating that this treatment should be considered in these high-risk patients.

Keywords: alendronate, efficiency, elderly, fracture, osteoporosis, treatment.

Introduction

In the United States alone, the population of oldest-old (over 80 years of age) is expected to increase from 11.7 million in 2012 to more than 20 million in 2030 [1]. As the risk to fracture increases exponentially with age [2], the number of fractures is expected to increase dramatically as a consequence. At the age of 50, the risk of sustaining a fragility fracture (low energy trauma fracture) during the remaining lifetime is 50% for women and 20% for men [2]. Already today, patients with fragility fractures require more in-hospital days than breast and prostate cancer combined, a figure exceeded only by those with stroke [3]. The increase in fracture rates will result in enormous health care cost; already the yearly fracture-related cost of osteoporosis in the United States is estimated to $17 billion [4]. Hip fracture is the most severe fracture and associated with increased morbidity and mortality [5]. Between 40% and 60% of hip fracture, survivors are not likely to recover their

prefracture level of mobility [6], and the one-year mortality is increased by 8–36% [7, 8].

There is strong evidence for secondary fracture prevention with the bisphosphonate alendronate, a treatment that results in a 40% relative risk reduction (RRR) of hip fractures in postmenopausal women [9]. However, as older patients often suffer from multiple comorbidities preventing the participation in clinical trials, none of the large randomized trials (RCTs) included a significant proportion of patients above the age of 80 years [10]. An RCT investigating the effect of risedronate on old women (n = 3886, aged 80–89) found no clear hip fracture risk reduction [11]. However, that study included women with one nonskeletal risk factor for hip fracture or low BMD, whereas a previous fracture was not required. Thus, there is insufficient evidence regarding the effectiveness and safety of oral bisphosphonate treatment amongst the oldest-old.

The purpose of this study was to investigate whether alendronate (which accounts for 93% of all oral bisphosphonate use in Sweden [12]) prescribed to older patients (≥80 years) with prior fracture was related to a reduced risk of hip fracture and sustained safety in a large cohort of older men and women.

Materials and methods

Study design

The risk of hip fracture and expected adverse events in older alendronate users and nonusers was investigated in a prospective observational register-based study, using four to one propensity score matching and multivariable Cox models.

Study population

The 'Fractures and fall injuries in the elderly cohort' (FRAILCO, [13]) is a national cohort based on information from several Swedish national registers, linked in order to study associations regarding fractures, fall injuries, morbidity, mortality and medications. Patients were initially selected from the Senior Alert register, consisting of men and women ≥65 years, who underwent a fall risk assessment in connection to a visit to a healthcare facility in Sweden between 2008 and 2014 [14]. All patients were included in the register, without exclusion criteria. Senior Alert was originally designed to follow and support improvements in preventive care for older adults and encompasses more than 90% of all municipalities and counties throughout Sweden [14]. In 2014, it included approximately 22% of the Swedish population over 65 years of age [15].

After excluding patients with probable registry errors as well as immigrants with insufficient background data, patients aged 80 years or older were selected. In order to emulate a secondary prevention setting, only patients with a prior fracture (index fracture) were included in the present study. Patients with severe kidney failure (N184-N185), that is not eligible for alendronate treatment, were excluded (Fig. 1).

Ascertainment of alendronate treatment

Medication data were collected from the Drug Dispensation Register (2005–2014). Only patients being treatment naïve at the time of the index fracture were included in the analysis either as case or control. Patients starting alendronate treatment after fracture were included as cases and compared to patients who never received any osteoporosis treatment after index fracture (controls). All patients with other known osteoporotic treatments (risedronate, zoledronic acid, denosumab, testosterone, systemic oestrogens, strontium ranelate, PTH-analogues and selective oestrogen receptor modulators) before the risk assessment were excluded from the analyses. Alendronate patients with <3 months of treatment or not currently treated (last dispensation expected to be consumed but not renewed) were also excluded. Currently treated was here defined as having access to alendronate for at least three months immediately before the risk assessment. In order to balance the groups, controls with <3 months between index fracture and risk assessment were excluded. Thus, the resulting alendronate variable represents use in the interval between index fracture and risk assessment and ongoing (current) at the time of the risk assessment (Figs 1 and 2). Apart from the dichotomous alendronate variable, others were defined: alendronate treatment time was measured from the date of the first prescription after the index fracture to the date when the last prescription was used, truncated at the fall risk assessment date (time zero). Medication possession ratio (MPR) was calculated as the sum of the defined daily doses during the treatment time,

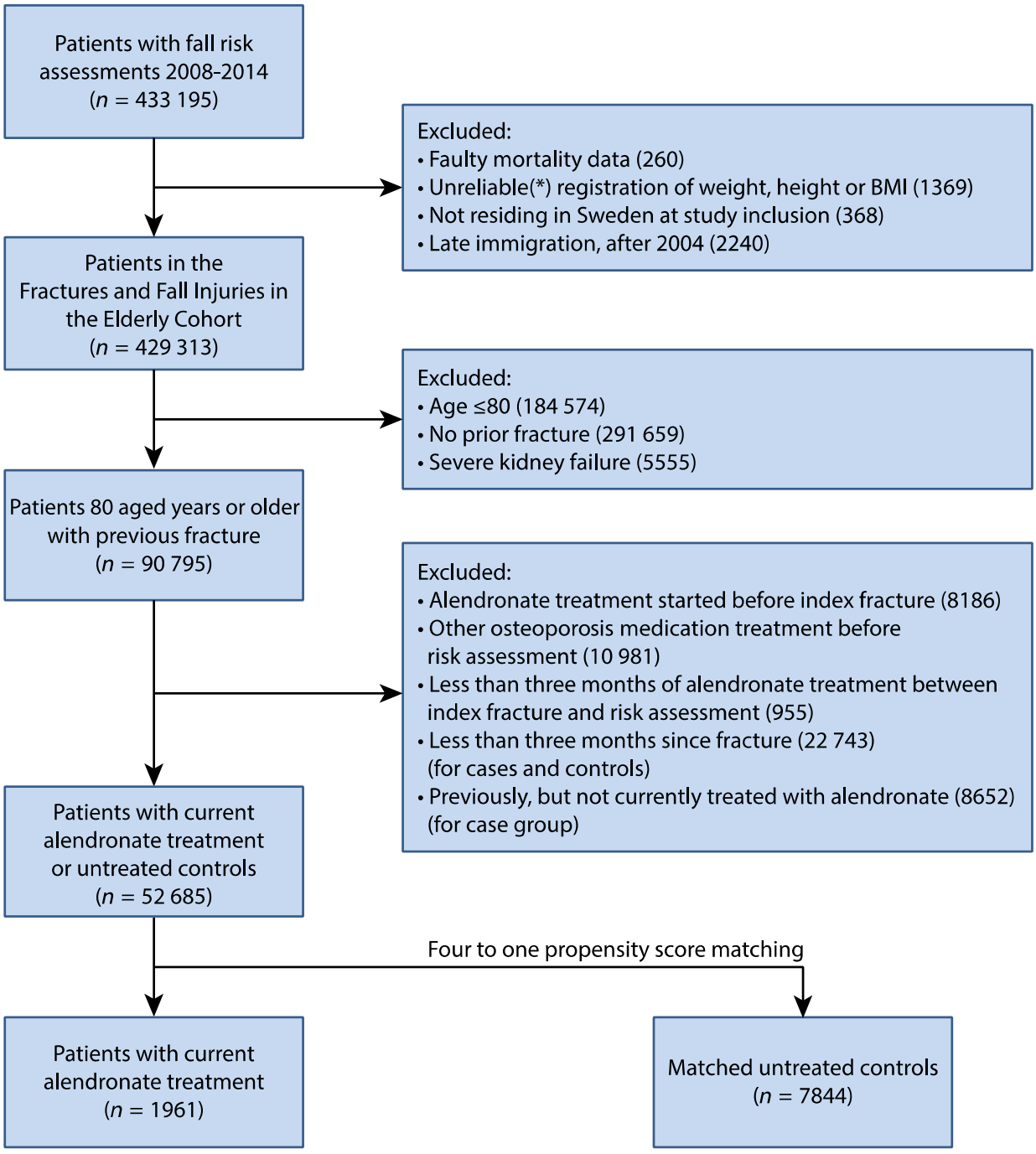

Fig. 1 *Study population. (*) Accepted values after exclusion of top and bottom 1‰ of weight, height and BMI. Weight: 30-176 kg; Height: 114-197 cm; BMI: 12.23–73.05 kg m^{-2}.*

divided by the treatment time resulting in a value between 0 and 1. Concomitant medication was accounted for if a retrieved prescription was expected to be used within 90 days before baseline and if there were at least two retrieved prescriptions registered.

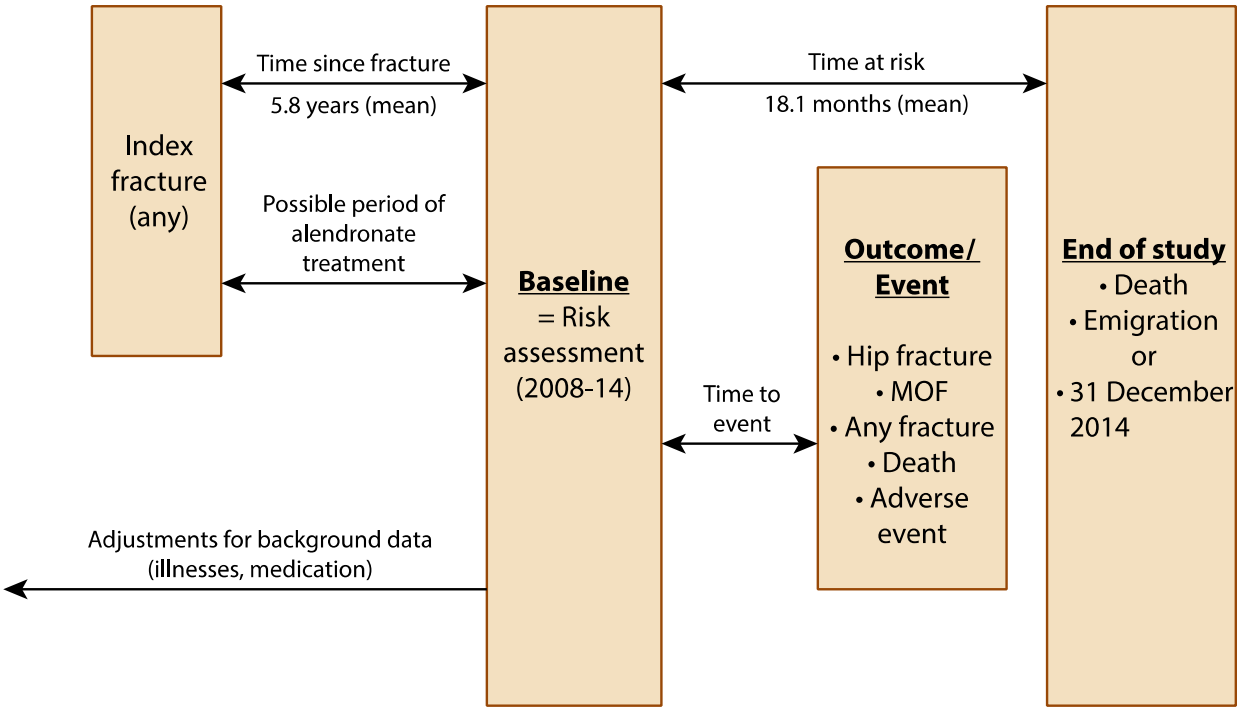

Fig. 2 *Method overview.*

Definition of fracture

Fracture information was collected from the National Patient Register. All nonmalignant fracture diagnoses in ICD-10 regardless of type of trauma were included, apart from head fractures (Table S1). If a fracture diagnosis on the same skeletal site (ICD-10 two digits) was repeated within five months, it was discarded as it most likely was a revisit and not a new fracture.

Ascertainment of hip fracture

The main outcome, hip fracture, was defined as a fractured femoral head, neck, trochanter or subtrochanteric part of femur, in combination with a code for surgical procedure (Table S2). Identification of hip fracture using this procedure has high accuracy [16]. Time to hip fracture was calculated from the time of the risk assessment to the actual hip fracture, and censored for death (from the Cause of Death Register), emigration (from Statistics Sweden) and end of study period (31 December 2014).

Ascertainment of other outcomes

Other outcomes included major osteoporotic fractures, any fracture (Tables S1 and S2), as well as death. Dyspepsia, acid reflux and esophagitis were combined from the National Patient Register to analyse mild upper gastrointestinal (UGI) symptoms as a possible adverse outcome during follow-up after risk assessment. Also, peptic ulcer, drug-induced osteonecrosis and femoral shaft fractures were analysed (Table S3). Time to mild UGI symptoms and peptic ulcer, respectively, were also censored for death, emigration and end of study period. Information regarding cause of death was retrieved from the National Causes of Death Register.

Assessment of morbidity and covariates

All data regarding prior illnesses before risk assessment were collected from the National Patient Register (2001–2014 for outpatient visits and 1987–2014 for admitted patients). The register collects information from hospitals but not from primary care clinics. Clinical risk factors for

fracture, including rheumatoid arthritis, alcohol-related diseases, previous glucocorticoid treatment (≥5 mg per day for more than 3 months) as well as diseases related to secondary osteoporosis (insulin-dependent diabetes, hyperthyroidism, hypogonadism, malnutrition, osteogenesis imperfecta or chronic liver disease), were accounted for. Prevalent calcium and vitamin D treatment was defined as a treatment length exceeding 3 months occurring during the last 2 years prior to the risk assessment. Charlson comorbidity index was used to summarize and quantify comorbidity [17]. Covariate definitions are presented in Tables S2, S4–S9. Characterization of mobility status, general condition, food and liquid intake at the time of risk assessment was performed using questions from the validated RAPS or Norton scales [18]. Weight and height were measured at the time of the risk assessment and collected from Senior Alert.

Statistical analyses

Nontreated patients were matched through a four to one propensity score matching according to age, sex, weight, height, rheumatoid arthritis, alcohol-related diseases, previous glucocorticoid treatment, the individual diseases included in both secondary osteoporosis definition (Table 1) and Charlson comorbidity index as well as time since index fracture, previous vertebral fracture, previous hip fracture, number of previous fractures, previous fall injury and osteoporosis diagnosis (M80-M81) [19, 20]. Differences between the matched controls and the treated patients were investigated using Fisher's exact test on categorical variables, chi-square test if multiple categories and with *t*-tests on continuous variables. To investigate the association between alendronate treatment and fracture risk, we used a Cox proportional hazards model starting at the date of the risk assessment, adjusted for age, sex, weight and height, and previous medication (glucocorticoids and calcium/vitamin D), secondary osteoporosis, rheumatoid arthritis, alcohol-related diseases, Charlson comorbidity index, time since fracture, previous vertebral fracture, previous hip fracture, previous hip replacement, number of previous fractures, previous fall injury and osteoporosis diagnosis (multivariable adjustment). In contrast to logistic regression, the Cox regression model uses the length of each individual's follow-up period (Fig. 2). The follow-up time to fracture was censored for death, emigration or end of study period. Cox proportional hazard analyses were repeated for all investigated alendronate treatment variables: binary alendronate treatment variable (yes/no), treatment length or medication possession ratio. To investigate whether the alendronate association changed with age, an interaction term between age and alendronate treatment was used in the Cox model. To analyse whether the association between alendronate and hip fracture was dependent on prevalence of previous fall injury, an interaction term between alendronate (yes/no) and prevalent fall injury was constructed and tested in the multivariable Cox model. When analysing the other outcomes (mild UGI symptoms, peptic ulcers or shaft fractures), adjustments were made for age, sex, weight, height Charlson comorbidity index and previous UGI symptoms, peptic ulcers or femoral shaft fracture, respectively. When analysing death as outcome, adjustment was made for age, sex, weight, height and Charlson comorbidity index. Statistical analyses were performed with the use of IBM® SPSS® software, version 22, and the propensity score matching was performed using R 3.3.2. To address the issue of potential persistence bias and the possible healthy adherer effect [21], we analysed the persistence of the commonly used drug acetylsalicylic acid and compared current alendronate users with their matched untreated controls. A *P*-value <0.05 was considered significant. The Cox assumption of proportional hazards was tested for all outcomes using a time-dependent Cox model with a linear interaction term between time and alendronate.

Results

The present study included a total of 9805 patients of which 1961 had current alendronate treatment at the time of the risk assessment and 7844 matched controls that never had had any osteoporosis medication (Table 1). The accumulated follow-up time or time at risk was 14 800 years, of which 3135 years in the treated group and 11 666 years in the untreated group. The mean time at risk was significantly longer in the treated group compared to the untreated (Table 2). All patients in the treated group were currently being treated and had a mean previous treatment time of 3.5 years, during which the mean medication possession ration was 91%. The primary inclusion sites were hospital wards (46%) or nursing homes (38%), with the remaining of the patients included at residential home care (8.6%), health centres (4.5%) and rehabilitation units (3.1%). In the total cohort, 89% of the patients were characterized to be in good or

Table 1 *Baseline characteristics*

Description	No alendronate	Alendronate	*P*-value
Number of patients	7844	1961	
Female sex – no. (%)	6871 (87.6)	1719 (87.7)	0.97
Age, years – mean (SD)	85.7 (4.4)	85.7 (3.9)	0.63
Weight, kg – mean (SD)	62.1 (13.9)	62.3 (13.0)	0.52
Height, cm – mean (SD)	160.8 (8.4)	160.8 (8.1)	0.85
Alcohol-related diseases – no. (%)	32 (0.4)	7 (0.4)	0.84
Rheumatoid arthritis – no. (%)	367 (4.7)	110 (5.6)	0.09
Previous 'intense' glucocorticoid – no. (%)	1909 (24.3)	515 (26.3)	0.08
Time since fracture, years – mean (SD)	5.7 (4.2)	5.9 (3.6)	0.20
Previous fall injury – no. (%)	5569 (71.0)	1366 (69.7)	0.24
Previous hip fracture – no. (%)	1806 (23.0)	436 (22.2)	0.47
Previous hip replacement – no. (%)	1271 (16.2)	331 (16.9)	0.47
Previous vertebral fracture – no. (%)	1949 (24.8)	506 (25.8)	0.38
Number of previous fractures – no. (%)			0.28*
1	5728 (73.0)	1423 (72.6)	
2	1426 (18.2)	395 (20.1)	
≥3	690 (8.8)	143 (7.3)	
Osteoporosis – no. (%)	2125 (27.1)	632 (32.2)	<0.001
Secondary osteoporosis – no. (%)	337 (4.3)	94 (4.8)	0.36
Insulin-dependent diabetes – no. (%)	215 (2.7)	55 (2.8)	0.88
Hyperthyroidism – no. (%)	165 (2.1)	46 (2.3)	0.49
Hypogonadism – no. (%)	0 (0)	0 (0)	–
Malnutrition – no. (%)	33 (0.4)	8 (0.4)	1.00
Osteogenesis imperfecta – no. (%)	0 (0)	0 (0)	–
Chronic liver disease – no. (%)	37 (0.5)	1 (0.1)	0.86
Charlson morbidity index			0.67*
0	2842 (36.2)	722 (36.8)	
1–2	2739 (34.9)	656 (33.5)	
≥3	2263 (28.9)	583 (29.7)	
Charlson morbidity components:			
Ischaemic heart diseases – no. (%)	1596 (20.3)	419 (21.4)	0.32
Congestive heart failure – no. (%)	1413 (18.0)	366 (18.7)	0.51
Cerebrovascular diseases – no. (%)	1530 (19.5)	376 (19.2)	0.75
Diseases of arterioles and capillaries – no. (%)	666 (8.5)	170 (8.7)	0.79
Diabetes – no. (%)	829 (10.6)	211 (10.8)	0.81
Dementia – no. (%)	840 (10.7)	202 (10.3)	0.62
Chronic pulmonary disease – no. (%)	935 (11.9)	245 (12.5)	0.49
Chronic liver disease – no. (%)	37 (0.5)	10 (0.5)	0.86
Renal failure, mild – no. (%)	256 (3.3)	64 (3.3)	1.00
Renal failure, moderate – no. (%)	33 (0.4)	11 (0.6)	0.45
Peptic ulcer disease – no. (%)	287 (3.7)	73 (3.7)	0.89
Hemiplegia – no. (%)	150 (1.9)	33 (1.7)	0.58

Table 1 (*Continued*)

Description	No alendronate	Alendronate	*P*-value
Tumour without metastasis (<5 years) – no. (%)	1683 (21.5)	425 (21.7)	0.83
Metastatic solid tumour – no. (%)	176 (2.2)	45 (2.3)	0.87
Lymphoma or leukaemia – no. (%)	138 (1.8)	32 (1.6)	0.77

*χ^2 test.

fairly good general condition, 74% ate three quarters of a portion or more and 85% drank 700 mL or more each day (Table S10). At baseline, 40.7% of the patients had full mobility, 34.8% had slightly limited mobility, 13.5% had very limited mobility, 0.8% were immobile, and 10.2% had missing data. Patients immigrating to Sweden 2004 or earlier amounted to 8.5% (836).

Apart from osteoporosis being more common amongst the treated patients, there were no significant differences in prevalent diseases or risk factors for fracture, between the treated and untreated patients (Table 1). There were no significant differences between groups in terms of general condition or food portion sizes, whilst reduced liquid intake was significantly more common in the untreated group (Table S10). At baseline, alendronate-treated patients more frequently used diuretics, statins, calcium channel blockers, angiotensin-converting enzyme inhibitors and opioids but less frequently used benzodiazepines than patients not treated with alendronate (Table S11). Calcium and vitamin D supplementation, normally prescribed together with alendronate, was used by 85% in the alendronate group and by 30% in the untreated group.

Hip fracture incidence in the alendronate-treated patients was significantly lower than in the untreated patients, in both percentage and per 100 000 person-years (Table 2a). In a crude Cox model, alendronate treatment was associated with a 38% reduced risk of hip fracture. The association was somewhat attenuated, but remained highly significant in a multivariable Cox models (Tables 2a and 3; Fig. 3). The three-year absolute risk reduction (ARR), based on the multivariable Cox models, was estimated to 3.9%, corresponding to number needed to treat (NNT) of 26. These associations were maintained for both men and women analysed separately (Table S11). The interaction term of age and alendronate was not associated with hip fracture risk in a multivariable Cox model ($P = 0.49$), indicating no age-dependent alendronate association. In the whole cohort, 6935 patients had suffered a previous fall injury. In the multivariable Cox model, alendronate was associated with hip fracture in these patients (hazard ratio (HR) 0.64 (0.47-0.87)), but the association was not significant in patients without a prevalent fall injury ($n = 2870$, HR 0.72 (0.45-1.18). There was no significant interaction between alendronate use (yes/no) and previous fall injury ($P = 0.85$ for the interaction term).

Repeating the multivariable-adjusted Cox model with alendronate treatment length as a predictor instead of alendronate yes/no revealed that treatment length was associated with a 9% reduced risk of hip fracture per year of treatment. Using the same Cox model with medication possession ratio (MPR) instead of alendronate treatment length, we found that alendronate MPR was associated with a 4% reduced risk of hip fracture per 10 per cent improvement of MPR (Table 2a).

Alendronate treatment was also associated with significant risk reductions in major osteoporotic and any fracture, in both crude and multivariable Cox models (Table 2a).

The multivariable-adjusted cox models used to study the associations between alendronate and hip fracture were essentially unaffected when also including adjustments for (i) general condition, portion size and liquid intake (HR for alendronate treatment 0.66 (0.51–0.86); (ii) inclusion site (HR 0.67 (0.52–0.87)); and (iii) mobility status HR 0.65 (0.49–0.85).

The mortality rate in the alendronate-treated group was significantly lower both in percentage and per 100 000 person-years (Table 2b). Using a multivariable Cox model, alendronate treatment was associated with a 12% reduced mortality risk (Table 2b). Analysis on causes of deaths revealed a nonsignificant trend that hip fracture-related deaths were reduced with alendronate, whilst there were no significant differences in deaths related to

Table 2 *(a) Fracture risk and alendronate treatment. (b) Other outcomes and alendronate treatment*

Description	No alendronate	Alendronate	*P*-value
(a)			
Patients – no.	7844	1961	
Time at risk, days – mean (SD)	543 (418)	584 (436)	<0.001
Hip fracture			
No. (%)	484 (6.2)	81 (4.1)	<0.01
Per 100 000 person-years	4149	2584	<0.001
Time to fracture, days – mean (SD)	366 (326)	426 (317)	0.12
Alendronate treatment (yes/no) HR (95% CI)			
Crude		0.62 (0.49–0.79)	<0.001
Adjusted for age, sex, weight, height		0.62 (0.49–0.79)	<0.001
Multivariable adjustment[a]		0.66 (0.51–0.86)	<0.01
3 years ARR – multivariable adjustment[a]		3.9%	
3 years NNT – multivariable adjustment[a]		26	
Alendronate treatment time (years)			
HR per year (95% CI) – multivariable adjustment[a]		0.91 (0.85–0.97)	<0.01
Alendronate medication possession ratio (MPR)			
HR per 10% MRP (95% CI) – multivariable adjustment[a]		0.96 (0.93–0.98)	<0.01
Major osteoporotic fractures			
No. (%)	641 (8.2)	117 (6.0)	<0.01
Per 100 000 person-years	5495	3733	<0.001
Time to fracture, days – mean (SD)	353 (318)	389 (333)	0.27
Alendronate treatment (yes/no) HR (95% CI)			
Crude		0.68 (0.56–0.83)	<0.001
Adjusted for age, sex, weight, height		0.68 (0.56–0.83)	<0.001
Multivariable adjustment[a]		0.70 (0.56–0.87)	<0.01
3 years ARR – multivariable adjustment[a]		4.3%	
3 years NNT – multivariable adjustment[a]		23	
Alendronate treatment time (years)			
HR per year (95% CI) – multivariable adjustment[a]		0.93 (0.88–0.98)	<0.01
Alendronate medication possession ratio (MPR)			
HR per 10% MRP (95% CI) – multivariable adjustment[a]		0.96 (0.94–0.99)	<0.01
Any fracture			
No. (%)	1020 (13.0)	214 (10.9)	0.01
Per 100 000 person-years	8743	6827	<0.01
Time to fracture, days – mean (SD)	339 (313)	386 (338)	0.05
Alendronate treatment (yes/no) HR (95% CI)			
Crude		0.78 (0.67–0.90)	<0.01
Adjusted for age, sex, weight, height		0.78 (0.67–0.90)	<0.01
Multivariable adjustment[a]		0.77 (0.66–0.91)	<0.01
3 years ARR – multivariable adjustment[a]		5.0%	
3 years NNT – multivariable adjustment[a]		20	

Table 2 (*Continued*)

Description	No alendronate	Alendronate	*P*-value
Alendronate treatment time (years)			
HR per year (95% CI) – multivariable adjustment[a]		0.97 (0.93–1.00)	0.07
Alendronate medication possession ratio (MPR)			
HR per 10% MRP (95% CI) – multivariable adjustment[a]		0.97 (0.96–0.99)	<0.01
(b)			
Deaths			
No. (%)	3422 (43.6)	792 (40.4)	0.01
Per 100 000 person-years	29 333	25 267	<0.001
Time to death, days – mean (SD)	396 (355)	416 (362)	0.16
Alendronate treatment (yes/no) HR (95% CI)			
Crude		0.87 (0.80–0.94)	<0.001
Adjusted for age, sex, weight, height		0.89 (0.82–0.96)	<0.01
Adjusted for age, sex, weight, height and Charlson comorbidity index		0.88 (0.82–0.95)	<0.01
3 years ARR – adjusted for age, sex, weight, height and Charlson comorbidity index		5.2%	
3 years NNT – adjusted for age, sex, weight, height and Charlson comorbidity index		19	
Mild upper gastrointestinal symptoms (UGI)			
No. (%)	110 (1.4)	45 (2.3)	<0.01
Per 100 000 person-years	943	1436	0.02
Time to UGI, days – mean (SD)	297 (297)	333 (293)	0.49
Alendronate treatment (yes/no) HR (95% CI)			
Crude		1.57 (1.11–2.21)	0.01
Adjusted for age, sex, weight, height		1.57 (1.11–2.22)	0.01
Adjusted for age, sex, weight, height, Charlson comorbidity index and previous UGI		1.58 (1.12–2.24)	0.01
3 years ARR – adjusted for age, sex, weight, height, Charlson comorbidity index and previous UGI		1.1%	
3 years NNH – adjusted for age, sex, weight, height, Charlson comorbidity index and previous UGI		91	
Peptic ulcers			
No. (%)	82 (1)	23 (1.2)	0.62
Per 100 000 person-years	703	734	0.86
Time to peptic ulcers, days – mean (SD)	242 (277)	401 (365)	0.03
Alendronate treatment (yes/no) HR (95% CI)			
Crude		1.08 (0.68–1.71)	0.76
Adjusted for age, sex, weight, height		1.08 (0.68–1.71)	0.76
Adjusted for age, sex, weight, height, Charlson comorbidity index and previous peptic ulcer		1.06 (0.67–1.69)	0.80

Table 2 (*Continued*)

Description	No alendronate	Alendronate	*P*-value
Femoral shaft fractures			
No. (%)	24 (0.3)	9 (0.5)	0.30
Per 100 000 person-years	206	287	0.40
Time to fracture, days – mean (SD)	474 (396)	484 (394)	0.95
Alendronate treatment (yes/no) HR (95% CI)			
Crude		1.39 (0.65–2.99)	0.40
Adjusted for age, sex, weight, height		1.44 (0.67–3.10)	0.35
Multivariable adjustment[a]		1.36 (0.57–3.23)	0.48

[a]Multivariable adjustment = age, sex, weight and height, and previous medication (glucocorticoids and calcium/vitamin D), secondary osteoporosis, rheumatoid arthritis, alcohol-related diseases, Charlson comorbidity index, time since fracture, previous vertebral fracture, previous hip fracture, previous hip replacement, number of previous fractures, previous fall injury and osteoporosis diagnosis.

Table 3 *Number of hip fracture events and censored cases during study period*

Year	0–1	1–2	2–3	3–4	4–5	5–6	6–7
No alendronate							
Number of patients at risk at the beginning of period	7844	4368	2273	880	178	26	2
Number of hip fractures	292	114	65	11	2	0	0
Censored[a]	3184	1981	1328	691	150	24	2
Alendronate							
Number of patients at risk at the beginning of period	1961	1191	639	267	65	13	2
Number of hip fractures	43	23	12	3	0	0	0
Censored[a]	727	529	360	199	52	11	2

[a]Due to death, emigration or end of study (Dec 31st, 2014).

cancer, stroke or acute myocardial infarction between treated and untreated patients (Table S12).

The incidence of mild UGI symptoms (dyspepsia, reflux or esophagitis) was significantly higher amongst the alendronate-treated compared to the untreated group (Table 2b). In a multivariable Cox model, alendronate treatment was associated with 58% increased risk of mild UGI symptoms. Using the interaction term in the adjusted Cox model revealed no significant age-dependent alendronate association with risk of UGI ($P = 0.81$). The three-year absolute risk increase was 1.1% corresponding to a number needed to harm (NNH) of 91.

Treatment was not associated with an increased risk of incident peptic ulcers in a multivariable Cox model (Table 2b).

Drug-induced osteonecrosis was rare with only one case in the treated group. Atypical femur fractures (AFFs) cannot be specifically identified using register data, but the frequency of femoral shaft fractures (including AFFs) was investigated. The incidence of femoral shaft fractures was low and not significantly higher amongst treated patients (Table 2b).

Medication persistence to acetylsalicylic acid did not differ between current alendronate users and nonalendronate users (Figure S1, $P = 0.91$).

The Cox assumption of proportional hazards was fulfilled for all outcomes (Table S14).

Discussion

In the present study of patients aged 80 years and older, we found robust and consistent associations between alendronate use, regardless of treatment definition, and reduced risk of hip fractures.

These results are consistent with a previous randomized trial, reporting a maintained RRR of a composite end-point of hip, spine and wrist

fracture, with increasing age, although patients were less than 80 years at inclusion [22]. There are no available studies with adequate sample size and power investigating the effect of alendronate on hip fracture risk in patients older than 80 years [10]. Risedronate has shown a remarkable 83% risk reduction in vertebral fracture in an old population (n = 1392, aged 80–98, mean (SD) 83.0 (3.0)), but the risk of nonvertebral fractures was not significantly lower; however, unlike in our study, not all participants had a prior fracture [23].

Screening women aged 65 years and older followed by treatment with alendronate resulted in cost savings and QALY increases if the yearly alendronate cost is USD 200 or less [24]. The current cost of alendronate is less than a third and our study population is older indicating a highly favourable cost-benefit perspective for alendronate treatment amongst the oldest-old.

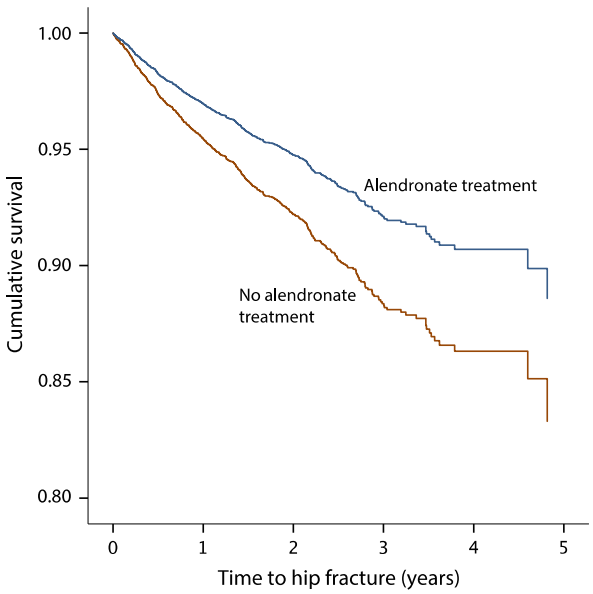

Fig. 3 *Hip fracture risk with and without alendronate amongst the oldest-old. Cox regression model, multivariable adjustment*. *multivariable adjustment = age, sex, weight and height, and previous medication (glucocorticoids and calcium/vitamin D), secondary osteoporosis, rheumatoid arthritis, alcohol-related diseases, Charlson comorbidity index, time since fracture, previous vertebral fracture, previous hip fracture, previous hip replacement, number of previous fractures, previous fall injury and osteoporosis diagnosis.*

Treating older and often frail patients could increase the rate of known adverse events such as UGI symptoms and possibly be harmful. We observed indeed an increased risk of mild UGI symptoms, but the NNH for current users was 91, as compared to the NNT of 26 for hip fracture, which in all could be considered as a favourable risk-benefit ratio. As no significant increased risk of peptic ulcers, femoral shaft fracture or mortality was found, and the cases of drug-induced osteonecrosis were too few to analyse, our data indicate that alendronate treatment is safe, also in very old patients. Despite the relatively large sample size, the short follow-up time may have limited the ability to detect rare adverse events such as atypical femur fractures, linked to long treatment durations. However, a recent nested case control study showed an acceptable balance of risk and benefit even with long alendronate treatment [25]. We found that treatment was associated with a 12% reduction in mortality, which is in line with a meta-analysis of RCTs demonstrating a 10% risk reduction in mortality with antiresorptive treatment [26]. Deaths in relation to hip fracture were less common, although not significantly, in alendronate users (Table S13).

To minimize the uncertainty of selection bias, we used propensity score matching and obtained well-balanced groups of treated and untreated patients. Furthermore, we adjusted for Charlson morbidity index, and other potential confounders in multivariable Cox models, which did not substantially affect the observed associations. The lack of significant differences in acetylsalicylic acid medication persistence between alendronate-treated versus untreated patients indicates there was no healthy adherer effect. Furthermore, investigating concomitant medication in alendronate-treated and untreated patients did not indicate that alendronate users were healthier than nonusers. Despite these performed measures to control for possible bias, we cannot rule out that other selection factors for choosing which patients to treat could exist, and as a result, the observed associations could have been affected by other differences in patient characteristics not controlled for in this study.

The relatively high fallout from censored cases is a consequence of the cohort being old (all patients were 80 years or older – in order to study alendronate in the oldest-old) with high mortality and the relatively short follow-up time (mean 18 months), whilst some cases have up to 7 years

of follow-up. As alendronate has a very long half-time in the skeleton, (~10 years) not adjusting for incident alendronate during a short follow-up time is not likely to have a major impact on the observed observation, especially as most patients in the study had a short follow-up time.

In Sweden, supplementation treatment with calcium and vitamin D is recommended for all patients with active osteoporosis medication, including alendronate. Therefore, it was not possible to study the effect of alendronate alone, as this therapy should not be taken without calcium and vitamin D. Patients taking only alendronate and not calcium and vitamin D would neither be many, nor representative. Instead, we adjusted for calcium and vitamin D intake in the Cox models to study the independent association between alendronate and fracture risk. This adjustment did not have any substantial effect of the observed observations.

It has been argued that pharmacological treatment to prevent hip fracture is ineffective and that other measures such as physical activity, cessation of smoking and optimizing the diet should be prioritized instead [27]. Although no adequately powered randomized trial has been able to show that any of these measures can prevent hip fractures, there is available evidence supporting interventions to prevent falls [28]. Nonpharmacological measures including fall prevention are therefore currently recommended in addition to pharmacological treatment in clinical guidelines for treating osteoporosis [29, 30]. In the present study, we observed an association between alendronate treatment and reduced risk of hip fracture in the subset of patients (n = 6935) who had experienced a previous fall injury. Although this association was similar in patients without a fall injury, the association did not reach statistical significance, which could be due to the relatively small number of patients in that group (n = 2870). Lack of a significant interaction between alendronate treatment and prevalent fall injury regarding the association with hip fracture indicates a similar role of alendronate irrespective of fall history.

A limitation of the present study is the lack of data regarding bone densitometry and fracture trauma type. However, there is evidence that trauma type does not discriminate osteoporotic from nonosteoporotic fractures [31]. It should be acknowledged that treatments with zoledronic acid have become more widely used during recent years in Sweden [32], and are rarely registered in the Drug Dispensation Register as it is provided by hospital osteoporosis clinics. Therefore, it is likely that some of the patients in our control group could have received this treatment, which would then have reduced the fracture risk in the control group, resulting in attenuated associations between alendronate and hip fracture risk seen in our population. Furthermore, the proportion of patients with an osteoporosis diagnosis was larger in the alendronate treatment group than in the control group. Acknowledging these sources of bias, the observed relative risk reduction in our cohort of 34% for hip fractures (compared to the 40% reduction reported in RCTs) may be slightly underestimated [9]. Our results emanate from a primarily Caucasian population and may not be generalizable to other populations.

In conclusion, alendronate treatment was associated with reduced hip fracture risk in the oldest-old. These results suggest that alendronate treatment in the oldest-old is effective and safe, and should be considered in older patients in order to reduce the high fracture rates in this age group.

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Contributors

All authors contributed to the design of the study, interpreted the results and reviewed the manuscript. DL assembled the database. HJ provided statistical support. KA and ML performed the statistical analysis, wrote the first draft of the manuscript and are guarantors.

Compliance with ethical standards

The study was approved by the regional ethical review board in Gothenburg.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.

pdf and declare: no support from any organization for the submitted work.

Transparency

The lead authors affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing

No additional data available.

Conflict of interest statement

KA has received lecture fees from Lilly and Meda. MW has received lecture fees from Amgen. HJ and DL state they have no conflict of interests. ML has received lecture fees from Amgen, Lilly, Meda, UCB, Renapharma and consulting fees from Radius Health and Consilient Health.

References

1 Ortman JM, Velkoff VA, Hogan H. *An Aging Nation – The Older Population in the United States*. Current Population Reports, P25-1140. Washington, DC: U.S. Census Bureau, 2014.
2 Sambrook P, Cooper C. Osteoporosis. *Lancet* 2006; **367:** 2010–8.
3 Johnell O, Kanis JA, Jonsson B, Oden A, Johansson H, De Laet C. The burden of hospitalised fractures in Sweden. *Osteoporos Int* 2005; **16:** 222–8.
4 Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 2007; **22:** 465–75.
5 Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; **359:** 1761–7.
6 Dyer SM, Crotty M, Fairhall N *et al.* A critical review of the long-term disability outcomes following hip fracture. *BMC Geriatr* 2016; **16:** 158.
7 Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 1999; **353:** 878–82.
8 Sattui SE, Saag KG. Fracture mortality: associations with epidemiology and osteoporosis treatment. *Nat Rev Endocrinol* 2014; **10:** 592–602.
9 Wells GA, Cranney A, Peterson J *et al.* Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 2008; (1): Cd001155.
10 Boonen S, Dejaeger E, Vanderschueren D *et al.* Osteoporosis and osteoporotic fracture occurrence and prevention in the elderly: a geriatric perspective. *Best Pract Res Clin Endocrinol Metab* 2008; **22:** 765–85.
11 McClung MR, Geusens P, Miller PD *et al.* Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001; **344:** 333–40.
12 *The Swedish National Board of Health and Welfare's Drug Dispensation Register*, 2014.
13 Wallander M, Axelsson KF, Nilsson AG, Lundh D, Lorentzon M. Type 2 diabetes and risk of hip fractures and non-skeletal fall injuries in the elderly – a study from the fractures and fall injuries in the elderly cohort (FRAILCO). *J Bone Miner Res* 2017; **32:** 449–60.
14 Edvinsson J, Rahm M, Trinks A, Hoglund PJ. Senior alert: a quality registry to support a standardized, structured, and systematic preventive care process for older adults. *Qual Manag Health Care* 2015; **24:** 96–101.
15 Statistics Sweden's Population Statistics. 2014.
16 Vu T Davie G, Barson D, Day L, Finch CF. Accuracy of evidence-based criteria for identifying an incident hip fracture in the absence of the date of injury: a retrospective database study. *BMJ Open* 2013; **3:** e003222
17 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40:** 373–83.
18 Kallman U, Lindgren M. Predictive validity of 4 risk assessment scales for prediction of pressure ulcer development in a hospital setting. *Adv Skin Wound Care* 2014; **27:** 70–6.
19 Randolph JJ, Falbe K, Manuel AK, Balloun JL. A step-by-step guide to propensity score matching in R. *Pract Assess Res Eval* 2014; **19:** 1–6.
20 Harris H, Horst SJ. A brief guide to decisions at each step of the propensity score matching process. *Pract Assess Res Eval* 2016; **21:** 1–10.
21 Curtis JR, Yun H, Lange JL *et al.* Does medication adherence itself confer fracture protection? An investigation of the healthy adherer effect in observational data. *Arthritis Care Res (Hoboken)* 2012; **64:** 1855–63.
22 Hochberg MC, Thompson DE, Black DM *et al.* Effect of alendronate on the age-specific incidence of symptomatic osteoporotic fractures. *J Bone Miner Res* 2005; **20:** 971–6.
23 Boonen S, McClung MR, Eastell R, El-Hajj Fuleihan G, Barton IP, Delmas P. Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: implications for the use of antiresorptive agents in the old and oldest old. *J Am Geriatr Soc* 2004; **52:** 1832–9.
24 Nayak S, Roberts MS, Greenspan SL. Impact of generic alendronate cost on the cost-effectiveness of osteoporosis screening and treatment. *PLoS ONE* 2012; **7:** e32879.
25 Abrahamsen B, Eiken P, Prieto-Alhambra D, Eastell R. Risk of hip, subtrochanteric, and femoral shaft fractures among mid and long term users of alendronate: nationwide cohort and nested case-control study. *BMJ* 2016; **353:** i3365.
26 Bolland MJ, Grey AB, Gamble GD, Reid IR. Effect of osteoporosis treatment on mortality: a meta-analysis. *J Clin Endocrinol Metab* 2010; **95:** 1174–81.
27 Jarvinen TL, Michaelsson K, Jokihaara J *et al.* Overdiagnosis of bone fragility in the quest to prevent hip fracture. *BMJ* 2015; **350:** h2088.

28 Gillespie LD, Robertson MC, Gillespie WJ *et al.* Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 2012; (9): Cd007146.
29 Cosman F, de Beur SJ, LeBoff MS *et al.* Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 2014; **25:** 2359–81.
30 Compston J, Cooper A, Cooper C *et al.* UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos* 2017; **12:** 43.
31 Mackey DC, Lui L, Cawthon PM *et al.* HIgh-trauma fractures and low bone mineral density in older women and men. *JAMA* 2007; **298:** 2381–8.
32 Axelsson KF, Jacobsson R, Lund D, Lorentzon M *et al.* Effectiveness of a minimal resource fracture liaison service. *Osteoporos Int* 2016; **27:** 3165–75.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Persistence analysis of acetylsalicylic acid.

Table S1. Definition of any fracture (prior or incident)

Table S2. Definition of hip fracture, major osteoporotic fracture, vertebral fracture, fall injury and hip replacement

Table S3. Definition of adverse events

Table S4. Definition of rheumatoid arthritis

Table S5. Definition of alcohol related diseases

Table S6. Definition of previous prednisolone treatment

Table S7. Definition of diseases related to secondary osteoporosis

Table S8. Definition of previous calcium and vitamin D treatment

Table S9. Definition of Charlson Morbidity Index

Table S10. General health, nutrition and liquid intake

Table S11. Medications at baseline

Table S12. Hip fracture risk and alendronate treatment analyzed according to gender

Table S13. Cause of death analysis with and without alendronate treatment

Table S14. Analysis to investigate if the Cox assumption of proportional hazard is fulfilled■

