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ORIGINAL ARTICLE

Bisphosphonate use after clinical fracture and risk of new fracture

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Abstract

Summary Among older adults with a previous fracture, treatment for osteoporosis was initially associated with a higher risk of new fracture. However, the relative risk of new fracture decreased over time, a trend that is consistent with a beneficial effect, as treatment for osteoporosis is prescribed to reduce high fracture risks.

Introduction The purpose of this study was to examine whether bisphosphonate use is associated with a lower risk of new fracture after a clinical fracture in older adults.

Methods Data were available for 3,329,400 adults in Sweden who were aged ≥ 50 years between 2006 and 2011. During this period, 260,353 sustained a clinical fracture and were naïve to bisphosphonates at the time. Those who subsequently received a bisphosphonate were matched to up to three others on sex, year of birth, and type and year of initial fracture. The final cohort comprised 83,104 adults (26.3% bisphosphonate users).

Results During the period from initial fracture to initiation of bisphosphonate treatment, the incidence rate of any new clinical fracture was higher in those who later became bisphosphonate users than in those who remained nonusers (175.1 vs. 75.9 per 1000 person-years; hazard ratio 2.30, 95% confidence interval 2.19 to 2.41). Similarly, during the first 6 months of treatment, the incidence rate was higher in bisphosphonate users than in nonusers (128.8 vs. 90.2 per 1000 person-years; hazard ratio 1.41, 95% confidence interval 1.32 to 1.51). However, this difference decreased over time: by months 12 to 18, the incidence rate was similar in users and nonusers (59.3 vs. 55.3 per 1000 person-years; hazard ratio 1.03, 95% confidence interval 0.91 to 1.16).

Conclusions There was a decrease in the relative risk of new fracture during bisphosphonate treatment, a trend that is consistent with a beneficial treatment effect, as bisphosphonates are prescribed to reduce high fracture risks.

Keywords Elderly · Men · Nonvertebral · Older · Osteoporosis · Refracture

Introduction

Adults who sustain a fracture are at high risk of sustaining a new fracture. According to two meta-analyses, this risk is approximately twofold that seen in adults without a previous fracture [1, 2]. Although this association cannot be explained by any one cause [2, 3], the absolute risk of new fracture increases progressively with increasing age and decreasing bone mineral density [3–5]. Therefore, researchers have concluded that older adults who sustain a fracture at any skeletal site should be screened for osteoporosis [1, 4, 5].

Treatment with anti-osteoporotic drugs is not reserved for patients with osteoporosis, as defined by a T-score of − 2.5 or less. Practice guidelines also recommend treating adults who have sustained a low-trauma fracture and/or have high scores on the FRAX tool [6–13], which in turn includes previous low-trauma fractures in its estimation of future fracture risk [14]. Of note, however, high-trauma fractures are also associated with low bone mineral density and new fractures [15]. When anti-osteoporotic drugs are prescribed, bisphosphonates are the most common choice [16].

Bisphosphonates have been shown to prevent new fractures after a hip or vertebral fracture in clinical trials [17–20]. However, only two observational studies have

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shown that bisphosphonates are associated with a lower risk new fracture after fractures at various sites [21, 22]. Therefore, we used a nationwide cohort of older men and women to examine whether bisphosphonate use is associated with a lower risk of new fracture after a clinical fracture.

Methods

Data collection This study was based on data for every resident of Sweden who was 50 years of age or older on 31 December 2005. These data came from five registries. First, the National Patient Registry provided data on medical conditions diagnosed in inpatient care in Sweden since 1987 and outpatient specialist care since 2001 [23]. Second, the Prescribed Drug Registry supplied data on prescriptions filled at pharmacies in Sweden since July 2005 [24]. Third, the Cancer Registry provided data on cases of cancer diagnosed since 1958 [25]. Fourth, the Cause of Death Registry provided data on vital status. Fifth, the Longitudinal Integration Database for Health Insurance and Labour Market Studies supplied data on marital status and educational attainment. These data were linked and sent to us in de-identified form by Statistics Sweden. The study was approved by the Regional Ethical Review Board in Umeå and by the National Board of Health and Welfare.

Inclusion criteria and matching

Adults were included in the analysis if they sustained a clinical fracture from 2006 to 2011; they were excluded if they were not naïve to bisphosphonates at the time of fracture, which was defined as not having filled a prescription for a bisphosphonate before the initial fracture or 6 months prior to the study (that is, from July to December 2005) [26]. The bisphosphonates considered were alendronate, risedronate, and zoledronic acid (Anatomical Therapeutic Chemical codes M05BA04, M05BA07, and M05BA08).

We defined bisphosphonate use as having filled a prescription for a bisphosphonate on or after the day of the initial fracture. Each bisphosphonate user was matched to a nonuser on year of birth, sex, and type and year of initial fracture. For each bisphosphonate user, baseline was defined as the date of the first filled prescription. The interval between the initial fracture and the first prescription was used to define baseline in matched nonusers; for example, if a user received bisphosphonates 30 days after his or her initial fracture, then baseline in a matched nonuser would be 30 days after this patient's initial fracture, as well. The nonuser was placed back in the pool of unmatched nonusers if the baseline date came before the date of death or after the end date of the study (31 December 2011). The whole procedure was done three times, leaving each user matched to up to three nonusers.

Outcomes and confounders

Using International Classification of Diseases, 10th Revision, (ICD-10) codes, we examined the outcomes of any new clinical fracture, hip fracture (S720, S721), and renal failure (N17-N19). Any clinical fracture included fractures at the following sites: neck (S12), ribs/sternum/thoracic spine (S22), lumbar spine/pelvis (S32), shoulder/upper arm (S42), forearm (S52), femur (S72), lower leg/ankle (S82), and foot (S92). These diagnoses were required to be main diagnoses, meaning that the fracture was the main reason for the inpatient or outpatient service. To avoid misclassifying readmissions and follow-up examinations as new fractures, a diagnosis was excluded if it was made within 90 days of an identical diagnosis.

We considered the following diagnoses to be potential confounders (ICD-10): stroke (I63, I64), dementia (F00, F01, F03), diabetes (E10, E11), depression (F32, F33), renal failure (N17-N19), myocardial infarction (I21), rheumatoid arthritis (M06, M08), chronic obstructive pulmonary disease (J44), any new clinical fracture between initial fracture and baseline, and any type of cancer available in the Cancer Registry [25].

Bone mineral density

In a subpopulation of eligible patients, we compared the bone mineral density of bisphosphonate users and nonusers. These data were obtained data for patients who underwent testing with dual-energy X-ray absorptiometry at the University Hospital of Umeå from 1999 to 2014. In addition to the inclusion criteria of the main analysis, we required that that the test had been performed after the initial fracture but before any bisphosphonate prescription. T-scores were obtained using the reference group of non-Hispanic white females in the third National Health and Nutrition Examination Survey [27].

Statistical analysis

We followed subjects separately for each outcome until outcome occurrence, death, or 31 December 2011 (whichever came first). The median follow-up duration was similar for all outcomes, so we report only that for any clinical fracture. Patients were excluded from the analysis of renal failure if they had been diagnosed with this at baseline.

As we did not expect bisphosphonates to have instantaneous effects, we analyzed outcomes in 6-month intervals from baseline to month 24. Incidence rates were computed for each interval. Hazard ratios were obtained using Cox regression models, stratified by matched set. We tested for trends (equivalent to testing the proportional hazards assumption) using score tests for correlation between scaled

Schoenfeld residuals and time. Since patients could have sustained a new fracture between their initial fracture and baseline, we also analyzed new fractures in this period using incidence rates and hazard ratios. Unadjusted and confounder-adjusted hazard ratios were similar, so adjusted hazard ratios are provided in Supplemental Table 1. T-scores were compared using two-sided *t* tests.

We performed three sensitivity analyses. First, we analyzed injurious falls (ICD-10 W00, W01, W19) without fractures, as bisphosphonate use should not affect the risk of falling. Second, we used a strict definition of new fracture that excluded a fracture diagnosis if it was identical to a previous diagnosis to the third position (for example, S250 was excluded if there was a previous diagnosis of S521). Third, we did not follow bisphosphonate users beyond their final prescription, so that only the active treatment period was captured. Statistical analyses were performed in Stata IC version 14. *P* values < 0.05 were considered to indicate statistical significance.

Results

Study cohort

Data were available for 3,329,400 individuals aged 50 years and older. During the study period, 280,295 sustained a clinical fracture and 260,353 were naïve to bisphosphonates at the time. Among these bisphosphonate-naïve patients, 8.5% subsequently received a bisphosphonate ($n = 22{,}242$). No matches were found for 377 bisphosphonate users. The final study cohort included 83,104 matched patients (21,865 bisphosphonate users, 26.3%). Baseline characteristics are provided in Table 1.

The initial fractures occurred at the following sites: 0.0% foot or neck ($n = 26$); 7.1% pelvis, thorax, lumbar spine, or thoracic spine ($n = 5921$); 10.5% lower leg or ankle ($n = 8696$); 16.1% shoulder or upper arm ($n = 13{,}406$); 29.2% femur ($n = 24{,}273$), and 37.0% forearm ($n = 30{,}782$).

The mean age was 72 years and 27.5% of patients were over 80 years of age. Eleven percent were men. The median time between initial fracture and bisphosphonate treatment (baseline) was 6.7 months (Table 1). The most common bisphosphonate was alendronate ($n = 19{,}394$, 88.7%), whereas risedronate was more common than zoledronic acid ($n = 1977$ vs. $n = 494$, 9.0 vs. 2.3%). Only 5.7% ($n = 1247$) of bisphosphonate users switched drugs during the study period. The median interval between the initial and final bisphosphonate prescriptions was 21.6 months for the oral drugs alendronate and risedronate (interquartile range 7.7 to 40.3 months); it was 11.1 months for the intravenous drug zoledronic acid (interquartile range 0 to 15.1 months).

Table 1 Baseline characteristics

Variable	Bisphosphonate nonusers ($n = 61{,}239$, 73.7%)	Bisphosphonate users ($n = 21{,}865$, 26.3%)
Mean (SD) age, years	72 (10)	72 (9)
No. (%) ≥ 80 years	16,839 (27.5)	5991 (27.4)
No. (%) men	6568 (10.7)	2316 (10.6)
Median (IQR) months between initial fracture and baseline	6.7 (3.2–17.4)	6.7 (3.2–16.9)
No. (%) with diagnosis		
Rheumatoid arthritis	1124 (1.8)	966 (4.4)
Chronic obstructive pulmonary disease	2575 (4.2)	1390 (6.4)
Cancer	12,170 (19.9)	4682 (21.4)
Depression	3572 (5.8)	1129 (5.2)
Diabetes	6524 (10.7)	1832 (8.4)
Stroke	4552 (7.4)	1288 (5.9)
Dementia	3925 (6.4)	449 (2.05)
Myocardial infarction	3513 (5.7)	1130 (5.1)
Renal failure	976 (1.6)	275 (1.3)
No. (%) retired early[a]	7033 (11.5)	2726 (12.5)
No. (%) with educational attainment[ab]		
Primary school	27,326 (45.2)	8945 (41.3)
Secondary school, 1–2 years	18,237 (30.2)	6705 (31.0)
Secondary school, 3 years	3485 (5.8)	1435 (6.6)
Post-secondary	11,440 (18.9)	4557 (21.1)
No. (%) marital status[a]		
Married	29,331 (47.9)	10,973 (50.2)
Never married	6162 (10.1)	1971 (9.0)
Divorced	10,744 (17.5)	3757 (17.2)
Widowed	14,986 (24.5)	23.6 (23.6)
Other	3 (0.0)	0 (0.0)

SD standard deviation, *IQR* interquartile range

[a] As of 31 December 2005

[b] 974 (1.2%) missing values

The median follow-up was 1.8 years. A smaller percentage of bisphosphonate users than nonusers died ($n = 2070$ vs. 7716; 9.5 vs. 12.6%).

Fractures

During the period from initial fracture to initiation of bisphosphonate treatment, the rate of any new clinical fracture was higher in those who later became bisphosphonate users than in those who remained nonusers (175.1 vs. 75.9 per 1000 person-years; hazard ratio 2.30, 95% confidence interval 2.19 to 2.41) (Table 2; Fig. 1). Similarly, during the first 6 months of treatment, the rate of any new clinical fracture was higher in bisphosphonate users

Table 2 Incidence rates[a] (nos. of cases) of fractures and renal failure

Outcome	Prior to treatment	Months after initiation of treatment				
		0–5	6–11	12–17	18–23	24-
Any clinical fracture						
BP users	175.1 (3541)	128.8 (1276)	87.8 (722)	59.3 (403)	55.5 (310)	51.9 (819)
Nonusers	75.9 (4439)	90.2 (2552)	69.0 (1638)	55.3 (1084)	53.1 (848)	49.0 (2170)
Hip fracture						
BP users	38.2 (863)	26.7 (272)	20.8 (183)	16.1 (120)	13.4 (84)	14.1 (263)
Nonusers	16.4 (1027)	18.4 (531)	19.9 (497)	16.1 (339)	17.9 (312)	14.6 (743)
Renal failure						
BP users	–	4.6 (47)	4.8 (42)	3.2 (24)	4.7 (30)	4.9 (94)
Nonusers	–	4.3 (123)	4.1 (102)	4.6 (98)	4.2 (74)	4.8 (249)

[a] Per 1000 person-years

BP bisphosphonate

than in nonusers (128.8 vs. 90.2 per 1000 person-years; hazard ratio 1.41, 95% confidence interval 1.32 to 1.51). However, this difference decreased over time: by months 12 to 18, the rate of any new clinical fracture was similar in users and nonusers (59.3 vs. 55.3 per 1000 person-years; hazard ratio 1.03, 95% confidence interval 0.91 to 1.16).

During the period from initial fracture to initiation of bisphosphonate treatment, the rate of hip fracture was also higher in those who later became bisphosphonate users than in those who remained nonusers (38.2 vs. 16.4 per 1000 person-years; hazard ratio 2.32, 95% confidence interval 2.12 to 2.55). In addition, during the first 6 months of treatment, the rate was higher in bisphosphonate users than in nonusers (26.7 vs. 18.4 per 1000 person-years; hazard ratio 1.41, 95% confidence interval 1.22 to 1.64). This difference decreased over time, and it was similar in users and nonusers by months 6 to 12 (20.8 vs. 19.9 per 1000 person-years; hazard ratio 1.02, 95% confidence interval 0.85 to 1.21).

Subgroup analyses showed similar results in adults over and under 80 years of age and in men and women (Table 3; Fig. 2), although the time trends were not significant in men (Fig. 2). In another subgroup analysis, similar results were observed in patients whose initial fracture was or was not

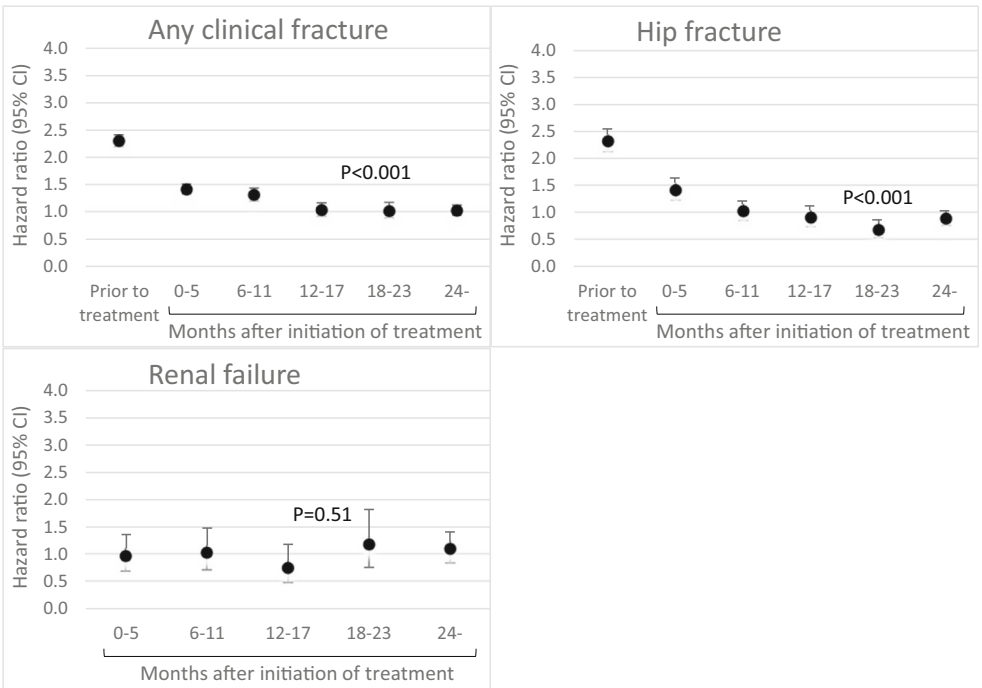

Fig. 1 Hazard ratios (95% confidence intervals [CIs]) for fractures and renal failure before and after the initiation of bisphosphonate treatment (nonusers as reference group). The *p* values test for trends in the period after the initiation of treatment

Table 3 Incidence rates[a] (nos. of cases) of fractures according to age and sex

Outcome	Prior to treatment	Months after initiation of treatment				
		0–5	6–11	12–17	18–23	24-
Any clinical fracture						
Women						
BP users	173.0 (3131)	126.6 (1126)	85.8 (637)	60.0 (369)	54.7 (278)	51.3 (744)
Nonusers	75.3 (3929)	90.3 (2285)	68.0 (1450)	55.1 (974)	52.9 (764)	49.7 (2008)
Men						
BP users	192.3 (410)	148.3 (150)	106.5 (85)	53.5 (34)	64.0 (32)	58.8 (75)
Nonusers	80.7 (510)	89.5 (267)	77.5 (188)	56.8 (110)	55.0 (84)	41.2 (162)
50–79 years						
BP users	167.2 (2413)	121.6 (882)	82.1 (500)	48.0 (245)	49.9 (213)	43.4 (543)
Nonusers	67.0 (2822)	80.0 (1659)	58.9 (1045)	44.9 (669)	43.6 (539)	39.4 (1411)
≥ 80 years						
BP users	194.7 (1128)	148.5 (394)	104.0 (222)	93.5 (158)	73.6 (97)	84.2 (276)
Nonusers	98.6 (1617)	118.2 (893)	98.8 (593)	88.3 (415)	85.7 (309)	89.1 (759)
Hip fracture						
Women						
BP users	35.8 (723)	25.1 (229)	20.2 (160)	15.4 (104)	12.6 (72)	13.7 (236)
Nonusers	16.0 (894)	17.9 (460)	19.1 (427)	15.8 (300)	17.6 (278)	14.7 (678)
Men						
BP users	58.4 (140)	41.3 (43)	26.8 (23)	22.8 (16)	21.4 (12)	17.8 (27)
Nonusers	19.7 (133)	23.4 (71)	27.6 (70)	18.9 (39)	20.4 (34)	14.5 (65)
50–79 years						
BP users	30.9 (498)	19.6 (146)	16.0 (104)	11.3 (63)	9.5 (45)	10.6 (155)
Nonusers	10.3 (460)	11.3 (239)	14.1 (262)	10.3 (164)	11.9 (160)	9.1 (369)
≥ 80 years						
BP users	56.4 (365)	46.2 (126)	34.6 (79)	30.5 (57)	26.1 (39)	27.0 (108)
Nonusers	32.0 (567)	37.9 (292)	37.1 (235)	34.4 (175)	37.9 (152)	37.3 (374)

[a] Per 1000 person-years

BP bisphosphonate

located at one of the following sites: femur, lumbar spine/pelvis, or ribs/sternum/thoracic spine (Supplemental Fig. 1).

Renal failure

The rate of renal failure was slightly higher in bisphosphonate users than in nonusers throughout most of the follow-up period (Table 2), but there was no time trend (Fig. 1). After adjustment for comorbidities, the rate of renal failure was slightly lower in users (Supplemental Table 1).

Bone mineral density

Data on bone mineral density were available for 350 patients who met the inclusion criteria ($n = 177$ bisphosphonate users, 50.6%). Mean bone mineral density was lower in patients who became bisphosphonate users than in those who remained nonusers (femoral neck T-score − 1.32 vs. − 0.74, $P < 0.001$).

Sensitivity analyses

The first sensitivity analysis showed no time trend in the hazard ratio for injurious fall without fracture (Supplemental Fig. 2). The second sensitivity analysis showed a decrease in fracture rates when a stricter definition of new fracture was used (Supplemental Table 2); however, there were similar decreases in hazard ratios over time, although these decreases became insignificant (Supplemental Fig. 3). The third sensitivity showed that results were similar when we did not follow bisphosphonate users beyond their final prescription (Supplemental Fig. 4).

Discussion

In this study of older adults who had sustained a clinical fracture, those who received a bisphosphonate were at higher risk of new fracture before receiving treatment than were nonusers.

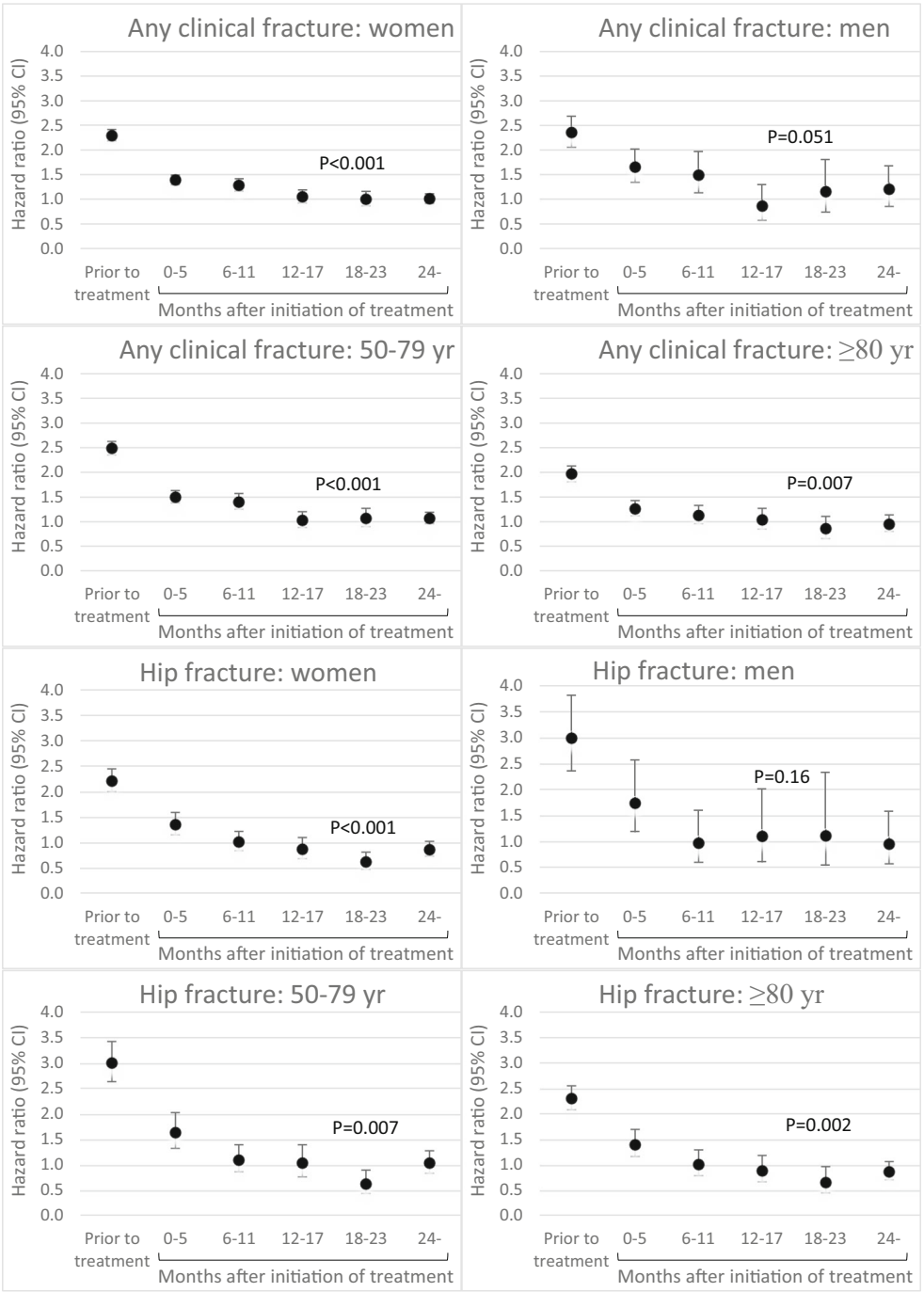

Fig. 2 Hazard ratios (95% confidence intervals [CIs]) for fractures before and after the initiation of bisphosphonate treatment (nonusers as reference group) according to age and sex. The *p* values test for trends in the period after the initiation of treatment

Although bisphosphonate users were also at higher risk initially during treatment, the relative risk decreased over time; by month 18, the risk of fracture was similar in users and nonusers. There was also a decrease in the relative risk of hip fracture over time. Similar trends were observed in adults over and under 80 years and in men and women, although these trends were not significant in men.

The higher risk of new fracture in bisphosphonate users before treatment suggests that physicians were prescribing bisphosphonates to high-risk patients, such a patients with a low bone mineral density. Such prescribing practices would cause confounding by indication, which in turn would explain the higher risk of new fracture in bisphosphonate users observed initially during treatment. This reasoning is supported by data we accessed for a subpopulation, which showed a lower mean bone mineral density in patients who received a bisphosphonate. In addition, it is supported by the reasoning of investigators of previous observational studies of bisphosphonates [28–30]. Confounding by indication is a common problem in observational studies [31], and it prevented us from estimating relative

risk reductions because baseline fracture risks were not balanced in bisphosphonate users and nonusers. However, we suggest that confounding by indication did not prevent our study from showing a potential treatment effect: the decrease in relative risk of fracture that occurred over time is consistent with a beneficial effect of bisphosphonates, as these drugs are prescribed to reduce high fracture risks.

The decrease in relative risk was observed in patients with various types of initial fractures. More than 70% of patients had an initial fracture that was not located at the hip or vertebrae, whereas clinical trials have shown only that bisphosphonate prevent new fractures after a hip or vertebral fracture [17–20]. Two of these trials showed that new fractures were prevented without restricting treatment to patients with osteoporosis or osteopenia [19, 20]. However, a post hoc analysis of another clinical trial showed that bisphosphonates were not effective in women without osteoporosis who had sustained a nonvertebral fracture since age 45, although this analysis was underpowered [32]. Since we lacked data on bone mineral density tests performed in the main cohort, we could not examine whether restricting treatment to patients with osteoporosis is necessary after a fracture. Therefore, the necessity of doing so after nonhip nonvertebral fractures is still unknown.

The present study included men and adults over 80 years of age, two groups that have often been excluded from clinical trials of bisphosphonates [33, 34]. The investigators of two trials suggested that adults over 80 years benefit less from treatment than do younger adults because older adults frequently fall, thus potentially offsetting the beneficial skeletal effects of bisphosphonates [34, 35]. In contrast, we found similar associations in patients over and under 80 years. This similarity is consistent with the results of a post hoc analysis of a clinical trial that did not indicate decreasing effectiveness with increasing age [36]; it is also consistent with two previous observational studies that showed a lower risk of new fracture in patients over 80 years who adhered to bisphosphonate treatment after a fracture [21, 22].

Our study showed decreases in the relative risks of any clinical fracture and hip fracture that were similar in men and women. These similarities are consistent with the finding of a previous observational study that showed a lower risk of hip fracture in alendronate-treated patients over 80 years who had previously sustained a fracture [22]. In the present study, the decreases in relative risks were insignificant in men, despite a higher incidence of fractures in male than in female bisphosphonate users. This higher incidence suggests that decreases in relative risks in men were not insignificant because men benefitted less from treatment but because men constituted only 11% of the study cohort.

The absolute risk of fracture also decreased over time in nonusers of bisphosphonates, probably because the risk of new fracture is greatest soon after a previous fracture [4, 37]. The relative risk of new fracture was substantially lower in the first 6 months of treatment than in the period between initial fracture and the start of treatment. Although treatment effects have previously been observed within 6 months [38], this rapid decrease was probably at least in part due an increased likelihood of receiving bisphosphonates among patients who sustained a second fracture.

Bisphosphonate users were not at higher risk of renal failure than were nonusers. This finding is consistent with previous research [39]. Nevertheless, severe renal impairment is a contraindication for bisphosphonate treatment [39], so our results may not be generalizable to patients with this condition.

The main limitations of this study were as follows. First, the observed decreases in hazard ratios may have been caused by fractures occurring earlier in higher-risk than in lower-risk bisphosphonate users, a bias known as depletion of susceptibles [40]. Second, clinical vertebral fractures were probably underreported because most of these are managed in the primary-care setting in Sweden [41]. Therefore, our results apply primarily to nonvertebral fractures. Third, the use of zoledronic acid was probably also underreported because medications administered during inpatient care were unavailable. Since underreporting would lead to a misclassification of some bisphosphonate users as nonusers, relative risks may be too small. Fourth, the incidence of new fracture may have been overestimated, as this incidence decreased substantially when only diagnoses for fractures at new skeletal sites were classified as new fractures. This strict definition, in turn, probably lead to an underestimation the incidence of new fractures, but it yielded similar decreases in relative risks. Nonetheless, these decreases became statistically insignificant, probably due to a lower statistical power. Finally, preventive care might also explain the decreases in relative risks, although this possibility is not supported by the lack of association between bisphosphonate use and injurious falls without fractures. The main strength of this study was its nationwide coverage of bisphosphonate users, meaning that the study cohort was representative of the diversity of patients seen in clinical practice.

In sum, we suggest that the decreases in relative risk of fracture that occurred are consistent with a beneficial effect of bisphosphonates, as these drugs are prescribed to reduce high fracture risks. If these decreases were indeed treatment effects, then they would suggest that bisphosphonates not only prevent new fractures after a hip or vertebral fracture but also after other clinical fractures. Future studies may want to examine the extent to which it is necessary to restrict treatment after a fracture to patients with osteoporosis.

Compliance with ethical standards

Conflicts of interest None.

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