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Incident long-term warfarin use and risk of osteoporotic fractures: propensity-score matched cohort of elders with new onset atrial fibrillation

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Summary

Association between warfarin use and fracture risk is unclear. We examined the association between long-term warfarin use and fracture risk at the hip, spine, and wrist in elders. No significant association was found between long-term warfarin use and fracture risk, despite biological plausibility.

Introduction—Prior studies examining the association of warfarin use and osteoporotic fractures have been conflicting, potentially related to methodological limitations. Thus, we examined the

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association of long-term warfarin use with risk of hip, spine, and wrist fractures among older adults with atrial fibrillation, attempting to address prior methodologic challenges.

Methods—We included men and women ≥65 years of age with incident atrial fibrillation and without prior history of fractures from The Health Improvement Network followed between 2000 and 2010. Long-term warfarin use was defined in two ways: (1) warfarin use ≥1 year; (2) warfarin use ≥3 years. Propensity-score matched cohorts of warfarin users and nonusers were created to evaluate the association between long-term warfarin use and risk of hip, spine, and wrist fractures separately as well as combined, using Cox-proportional hazards regression models.

Results—Among >20,000 participants with incident atrial fibrillation, the hazard ratios (HR) for hip fracture with warfarin use ≥1 and ≥3 years, respectively, were 1.08 (95%CI 0.87, 1.35) and 1.13 (95 % CI 0.84, 1.50). Similarly, no significant associations were observed between long-term warfarin use and risk of spine or wrist fracture. When risk of any fracture was assessed with warfarin use, no association was found [HR for warfarin use ≥1 year 0.92 (95%CI 0.77, 1.10); HR for warfarin use ≥3 years 1.12 (95%CI 0.88, 1.43)].

Conclusions—Long-term warfarin use among elders with atrial fibrillation was not associated with increased risk of osteoporotic fractures and therefore does not appear to necessitate additional surveillance or prophylaxis.

Keywords

Fracture; Oral anti-coagulant; Osteoporosis; Warfarin

Introduction

Warfarin is clinically utilized as an anticoagulant due to its antagonism of vitamin K's essential co-factor role in conferring functionality to blood coagulation proteins through the process of gamma carboxylation [1]. Specifically, the uncarboxylated (nonfunctional) proteins are converted to their carboxylated (functional) forms by vitamin K's actions. Through this same process, vitamin K also confers functionality to skeletal bone Gla proteins, including osteocalcin, which plays an important role in bone mineralization [2–4]. Low vitamin K serum concentration and nutritional intake from food frequency questionnaires have been associated with low bone mineral density [5, 6] and increased risk of fractures in some studies [7, 8], which may be related to the functionality of skeletal bone Gla proteins such as osteocalcin. In the carboxylated form, osteocalcin binds calcium to the hydroxy-apatite (crystal) in bone matrix [1, 3, 9]. Indeed, higher levels of undercarboxylated osteocalcin and lower levels of carboxylated osteocalcin have been associated with fractures, particularly hip fractures, in older adults [10, 11]. Further, serum concentrations of undercarboxylated osteocalcin have been shown to decrease with vitamin K supplementation [12] and increase with warfarin [13].

Thus, as an inhibitor of vitamin-K-dependent gamma-carboxylation of Gla proteins [14], warfarin may lead to bone effects similar to that seen with low serum vitamin K levels or high undercarboxylated osteocalcin levels. Epidemiologic studies that have examined the association of warfarin with osteoporotic fractures to date have reported conflicting results [15–22]. One reason for conflicting results may be related to methodological issues,

including confounding by indication and other residual confounding that limit interpretability. For example, the condition for which warfarin is used may itself increase risk of fracture (confounding by indication), and those conditions may also be associated with other issues that could contribute to fracture risk (confounding). Further contributing to difficulty in discerning warfarin's effects on fractures is that warfarin's effects on bone mineralization are not likely to occur quickly, and this is typically a chronically used medication. Thus, one would ideally need to assess the effect of warfarin over a long period of time; however, many of the prior studies limited their assessment of warfarin's effects over the course of 1 or 2 years only [15, 19, 20], and most used a prevalent user design [15, 18–20, 23], which can bias the results [24].

With the aging of the population, the need for warfarin, primarily for atrial fibrillation, is rising [25]. Thus, it is prudent to clarify the adverse effects of long-term use of this drug using methods to minimize confounding by indication, other potential confounding, and selection bias that may be contributing to the lack of clarity on warfarin's effect on fracture risk. To accomplish this, we focused on older adults with new onset atrial fibrillation, which enables minimization of confounding by indication, a major threat to validity of some prior studies. Specifically, we conducted a propensity-score matched cohort study to evaluate the association of incident long-term warfarin use with common osteoporotic fractures at hip, spine, and wrist, among elderly men and women with incident atrial fibrillation.

Materials and methods

Study sample and eligibility criteria—The Health Improvement Network (THIN) is a UK primary care electronic database that has anonymized health data on 7.3 million patients who were systematically followed in 477 primary care practices from as early as 1986. The information available in THIN is collected by primary care physicians as part of their routine patient care, which is then de-identified and integrated into a central database, making the data available for research. THIN contains patient information such as demographic factors, consultation rates, referrals, hospitalizations, laboratory test results, and prescriptions ordered by primary care physicians, including the doses, strength, and formulation of medication. While diagnoses and test procedures are recorded with Read Codes, prescriptions written by primary care physicians are recorded automatically in the database as Drug Codes, with the use of a coded drug dictionary (Multilex). Quality is checked regularly, and the information from this database has been found to be representative of the UK population as a whole [26].

Participants from THIN followed during 2000–2010, who were 65 years or older with *incident* (new-onset) atrial fibrillation, no prior warfarin use, had no prior fracture history, and were enrolled within THIN for at least 2 years prior were deemed eligible for this study. Limiting our sample to those with new onset atrial fibrillation minimizes confounding by indication and enables assessment of new users of warfarin to avoid biases related to studying prevalent users. The sample selection as well as inclusion and exclusion criteria are depicted in Fig. 1.

Study design

Exposure definition—Incident warfarin use was identified using Drug Codes for prescriptions of warfarin, by multiple sequential prescriptions to ensure continuous use, allowing a gap of 6 months within prescriptions. Long-term warfarin use (exposure) was defined in two ways: (1) warfarin use for 1 year and (2) warfarin use for 3 years.

Propensity-score matched cohort—Sex-specific 1-year calendar blocks were created between 2000 and 2010. Propensity scores for long-term warfarin use (i.e., 1 and 3 years of use, separately) were calculated using logistic regression, with long-term warfarin use (i.e., 3 and 1 year use) as the dependent variable and age, sex, body mass index (BMI), high fall risk (history of multiple falls, or referral for falls evaluation), deep venous thrombosis (DVT), pulmonary embolism (PE), heart failure, neuropsychiatric impairment, hyperthyroidism, estrogen use, beta blockers, corticosteroids, diuretics (thiazide and/or loop), bisphosphonates, statins, smoking, and alcoholism (acute or chronic alcohol intoxication, complications related to alcohol use such as cerebellar ataxia/degeneration and referrals for alcoholism screening) as independent variables. Separate propensity-score matched cohorts were created for each definition of long-term warfarin use (i.e., 1 and 3 years). Specifically, long-term warfarin users were matched 1:1 warfarin nonusers within the 1-year block based on propensity scores using the “greedy matching” method [27]. “Greedy matching” refers to the matched pairs being fixed once the pairs are established and is commonly used for creating propensity-score matched cohorts. We utilized propensity score matching to mitigate effects of confounding, including confounding by indication (by DVT, PE, and heart failure), especially in the presence of a large number of covariates [28].

Outcome definition—The following fractures were identified using Read Codes: (1) hip fractures: proximal femur, trochanteric, and neck fractures, open or closed; (2) spine: clinical vertebral fractures at thoracic and lumbar spine, open or closed, without neurologic symptom; and (3) wrist: distal forearm (radius and ulna) and carpal bone fractures, but not metacarpal fractures because fractures of metacarpal and phalanges are typically not related to osteoporosis. The outcomes of interest were incident (new) fractures at hip, spine, or wrist, assessed separately as well as combined. Pathological and traumatic fractures were excluded. “Read Codes” for identifying hip fractures in THIN have been validated in prior studies [29].

Statistical analysis

Follow-up for long-term warfarin users started after 1 or 3 years of warfarin use, depending on the exposure definition for the particular analysis (i.e., after the exposure definition was met). The follow-up time for nonusers started on a randomly assigned date (computer-generated) within the 1-year block within which they had been matched to long-term warfarin users. Follow-up continued until occurrence of outcome, death, dropout, or end of study period (5/31/10), whichever occurred first.

Crude incidence rates (CI) were calculated for hip, spine, and wrist fractures separately as well as combined (i.e., “any” such fractures) by dividing number of cases of respective fractures by person-years accrued, separately for long-term warfarin users and nonusers.

Cumulative incidence curves for hip, spine, and wrist fractures were plotted against follow-up time, by long-term warfarin use utilizing the Kaplan-Meier method. We then examined the risk of hip, spine, and wrist fractures separately as well as combined (i.e., “any” of the three types of fractures), with long-term warfarin use (< 1 and ≥ 3 years, respectively, in separate analyses) using Cox proportional hazards regression to calculate hazard ratios (HR), with and without adjusting for the covariates that were used to create propensity-score matched cohorts. We separately tested whether the relation of warfarin use ≥ 1 year to hip fracture was modified by sex or presence of heart failure, by evaluating for interaction. Similarly, in sensitivity analyses, we examined the relation of short-term warfarin use (<1 year of use) to hip, spine, and wrist fracture risk, respectively, using propensity score matching to create cohorts of short-term warfarin users and nonusers.

All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). A two-sided $P < 0.05$ was considered statistically significant.

Results

Warfarin users and nonusers were well-matched by propensity scores with respect to the distribution of covariates, as presented in Table 1 for the cohort of ≥ 1 year of warfarin use in relation to hip fractures. Demographic information and covariate distribution were similar for the cohorts of ≥ 1-year of warfarin use in relation to spine and wrist fracture cohorts (Supplementary Tables 1 and 2) and for each of the cohorts examining the effects of warfarin use of ≥ 3 years (data not shown).

Among 20,346 subjects (48 % women, mean age of 77 ± 6.3 years, mean BMI of 27 ± 5.1 kg/m²) in the analysis of warfarin use ≥ 1 year and the risk of incident hip fracture, there were 321 incident hip fractures in total for this cohort. The crude cumulative incidence of hip fracture among warfarin users and nonusers was 5.29 and 4.91 per 1,000 person-years, respectively. For warfarin use ≥ 3 years, the cumulative incidence of hip fracture among users and nonusers was 6.20 and 5.51 per 1,000 person-years, respectively. There were 20,550 and 20,158 subjects in the cohorts examining the risk of fracture related to warfarin use ≥ 1 year at the spine ($n=55$ total incident spine fractures) and wrist ($n=147$ total incident wrist fractures), respectively. The cumulative incidence in warfarin users and nonusers were 0.95 and 0.77 for spine fracture, respectively, and 2.24 and 2.48, respectively, for wrist fracture. When fractures at the hip, spine, and wrist were combined, the cumulative incidence of “any” fracture in the warfarin use ≥ 1-year cohort was 7.86 and 8.48 per 1,000 person-years among warfarin users and nonusers, respectively, and in the warfarin use ≥ 3-year cohort was 9.06 and 7.95 per 1,000 person-years among users and nonusers, respectively.

Cumulative incidence curves for hip fractures related to warfarin use of ≥ 1 and ≥ 3 years, respectively, versus nonuse, shown in Figs. 2 and 3, demonstrated lack of difference in cumulative incidence of hip fracture with or without use of warfarin. Similar curves were observed for wrist and spine fractures (Supplemental Figures 1, 2, 3, and 4).

There was no significant association of warfarin use of 1 year (HR 1.08, 95 % CI 0.87, 1.35) or 3 years (HR 1.13, 95 % CI 0.84, 1.5) with hip fracture (Table 2). Similarly, no association of warfarin use was found with spine fracture (HR for 1 year of use: 1.23, 95 % CI 0.72, 2.09; HR for 3 years of use: 0.98, 95%CI 0.47, 2.05) or wrist fracture (HR for 1 year of use: 0.91, 95 % CI 0.66, 1.26; HR for 3 years of use: 1.01, 95 % CI 0.64, 1.59) (Table 2). Results were similar for “any” fractures combined (HR for 1 year of use: 0.92, 95 % CI 0.77, 1.10; HR for 3 years of use: 1.12, 95% CI 0.88, 1.43).

Adjustment for the covariates on which the warfarin users and nonusers were matched (i.e., used in computing propensity scores) did not affect the results (Table 2). Similarly additionally adjusting for use of raloxifene and strontium ranelate did not alter the results (data not shown). No significant interaction by sex ($p=0.55$) or heart failure (warfarin use 1 year, $p=0.08$; warfarin use 3 years, $p=0.65$) was found for the relation of long-term warfarin use to hip fracture.

In the sensitivity analysis, short-term warfarin use (i.e., <1 year) was not associated with risk of hip fracture (HR 0.97, 95 % CI 0.69, 1.36), spine fracture (HR 0.89, 95 % CI 0.41, 1.94), or wrist fracture (HR 0.8, 95 % CI 0.48, 1.31).

Discussion

In this large population-based cohort, we did not find any significant association between incident long-term warfarin use and risk of hip, spine, or wrist fractures, suggesting that warfarin use itself may not necessitate increased surveillance or prophylactic therapy for osteoporosis in elders on long-term therapy.

Previous studies of warfarin use and fracture risk have had conflicting results. While a few studies demonstrated an increased risk of fractures, others have found no association [15–17, 19, 20, 22]. In one of the earliest studies reporting a positive association, Caraballo et al. found a greater than twofold higher age- and sex-adjusted standardized incidence of both spinal and rib fractures compared with incidence rates in the general population, among 572 mostly White women aged 35–95 years in Olmsted county, MN, USA, with incident venous thrombosis (DVT and PE) [16]. Further, additional analyses were performed with warfarin use <3 months as reference; the risk of vertebral and rib fracture still remained greater than twofold among subjects taking warfarin for >12 months. Since all subjects included in this study had VTE and received anticoagulation, the general population may not be a valid comparison group in this study. Furthermore, the wide age range included raises the possibility of residual confounding. Another positive study included men and women 68 years, from the National Atrial Fibrillation Registry in the USA, in which prevalent warfarin use preceding the index hospitalization for atrial fibrillation was assessed using regular INR monitoring and medical record of warfarin use [19]. Fractures at the hip, wrist, spine, and rib were assessed at the index hospitalization and at follow-up visits. Overall, warfarin use 1 year was associated with 25 % increased risk of any fracture, but on examination of specific fracture sites, associations were only found with spinal and rib fractures. In analyses stratified by sex, an association was noted only in men [19]. Concerns of potential bias remain in this study despite inclusion of all subjects with atrial fibrillation since warfarin use

preceded index hospitalization for atrial fibrillation (i.e., prevalent use of warfarin). In addition, residual confounding affects these effect estimates due to lack of adjustment for important confounders such as BMI and smoking. Finally, in a large case-control study using Danish National Health Service registry data, Rejnmark et al. found a small increased risk (OR 1.10; 95 % CI, 1.03–1.18) of any fractures with current (i.e., prevalent) use of low-dose oral anticoagulant (warfarin and phenprocoumon) compared with nonusers [23]. The authors acknowledge that the reason for the increased fracture risk might be related to the underlying clinical indication for oral anticoagulant use (such as atrial fibrillation, DVT, or PE), which implies that the underlying condition might have made them more prone to fractures rather than the pharmacological effect of the anticoagulants [23].

On the other hand, several studies have failed to find an association of warfarin use and fracture risk. In a population-based cohort study of 6,000 ambulatory, mostly white women 65 years of age and older, self-reported prevalent warfarin use irrespective of indication was not associated with fracture risk, despite adjustment of several potential confounders [15]. Similarly, a case-control study using administrative data of older men and women (mean age 83 years) reported no significant association between prevalent oral anticoagulant use (use ≥90 days vs. no use or use <90 days in the 5–7 years preceding the index date) with risk of nonvertebral osteoporotic fractures (OR: 1.2, 95 % CI: 0.9–1.6) [18]. Although the results were not statistically significant, the magnitude of effect was similar to that found in the study by Gage et al. [19]. Residual confounding by unadjusted pertinent confounders such as BMI, smoking status, and history of falls might explain the slightly greater (albeit nonsignificant) odds of fracture among warfarin users. It is also not clear as to whether those receiving warfarin were sicker and more prone to increased fracture risk, again pointing to an issue of potential confounding by indication. Another study using administrative data from Ontario, Canada also did not find an increased risk of fracture with warfarin use when compared with proton pump inhibitor (PPI) use (OR 0.94, 95 % CI 0.81–1.09) [17], suggesting no association between warfarin use and fracture risk. However, there have recently been reports of increased fracture risk with use of PPI [30–32], potentially suggesting that the null findings reported in this study may actually indicate a similar slightly increased risk of fracture rather than no effect. Current (prevalent) warfarin use assessed at a single time-point was not significantly associated with risk of nonvertebral fractures in a study among community-dwelling ambulatory men ≥65 years from the Osteoporotic Fractures in Men Study (adjusted HR for hip fracture 1.15, 95 % CI, 0.51–2.61, and adjusted HR for wrist fractures 1.55, 95 % CI 0.46–5.26). In this study, warfarin users were older, had greater fall risk, and had more comorbidities, i.e., warfarin users were frailer than nonusers. While these factors were adjusted for in the regression model, there is potential for residual confounding since this study did not account for indication for warfarin therapy, which may be the underlying reason for heightened risk for fracture. Yet, another study that compared incident hip fractures in a cohort of stroke patients among warfarin users with nonrheumatic atrial fibrillation (NRAF) and nonusers (without a history of NRAF) did not find any increased risk of incident hip fractures over 5 years [22]. However, since stroke itself is associated with increased risk of fracture [33, 34], a small increment in fracture risk due to warfarin use might not be detected in this study.

Thus, the body of evidence regarding warfarin use and risk of fractures suggests either small or no increased risk. However, concerns about confounding by indication, prevalent user design, and other residual confounding remain in these studies, limiting their interpretability. These issues are challenging to address in observational studies. Our use of a propensity-score matched cohort of warfarin users and nonusers among older adults with incident atrial fibrillation (and therefore incident warfarin use, thereby avoiding analysis of prevalent users) is an attempt to decrease these sources of bias. Without accounting for the reason (indication) for warfarin therapy, the fracture risk in the short term may be related to the underlying diagnosis, such as syncope related to atrial fibrillation that is not yet controlled. On the other hand, long-term effects may be more reasonably related to warfarin's effects on bone Gla protein functionality. Specifically, vitamin K has an important role in bone mineralization through its carboxylating effects on osteocalcin [1–4]. Since warfarin blocks this process [14], warfarin may have a potential deleterious effect on bone mineralization, which over time could be expected to have an effect on risk of fracture. Our results, however, do not support this hypothesis.

Limitations of our study should be acknowledged. While we attempted to address confounding by indication and other confounding by propensity score matching, there still remains the possibility of residual confounding due to the observational nature of this study. Although the propensity score matching reduced the likelihood of substantial confounding, this method restricts the sample size for this study, potentially limiting our power to precisely estimate the effects. This may account for small number of fractures in this study. In particular, the number of spine fractures was low in this study. However, our sample sizes were as large as or even larger than prior efforts to address this question. Further, the effect estimates were close to 1, suggesting that the true effect is likely null. Another potential source of bias stems from information on fractures being based on Read Codes (diagnosis codes entered by general practitioners), which could lead to outcome misclassification. However, there has been recent validation of hip fractures in THIN [29]. Nonetheless, ascertainment of incident spine fractures is difficult because spine fractures can be asymptomatic, and thus, identification of primarily asymptomatic spine fractures is dependent upon X-ray acquisition, creating a bias (detection bias). Unfortunately, given the observational nature of this study, we were unable to account for detection bias, a similar problem faced by other observational studies of spine fractures.

Strengths of our study include our efforts to address confounding. We limited our study sample to those patients with *incident* atrial fibrillation, thereby limiting not only confounding by indication, which was a major limitation of prior studies, but also confounding by duration of disease. This also enabled us to use an incident user design, since all subjects were new users of warfarin after their incident atrial fibrillation diagnosis [24]. In addition, using propensity score matching methodology helped to further mitigate the confounding by indication. This large population-based cohort followed prospectively avoids the potential for selection bias and is generalizable to men and women. Despite a comprehensive effort to mitigate confounding and other bias present in some of the prior work and common to observational studies, we did not find an association between long-term warfarin use and risk of fracture. Our results suggest that either truly there is no (or a

clinically insignificant small) association of warfarin use with fracture risk or there remains unmeasured confounding that cannot be accounted for in this observational study. Putting our results in the context of the existing literature, it appears that warfarin use, even over longer periods, is unlikely to significantly increase the risk of osteoporotic fractures in older adults with atrial fibrillation.

In summary, despite biological plausibility, long-term warfarin therapy does not appear to increase the risk of osteoporotic fractures. Elders who are on long-term warfarin therapy may not need additional surveillance or prophylactic therapy for osteoporosis above and beyond age- and comorbidity-appropriate screening and management as for the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Schematic representation of subject selection, inclusion, and exclusion criteria

Warfarin users					
(N):	10,173	6182	3196	1399	484
Non-users					
(N):	10,173	5828	2930	1290	479

Fig. 2. Cumulative incidence curves for hip fracture by warfarin use 1 year

Fig. 3. Cumulative incidence curves for hip fracture by warfarin use 3 years

Table 1
Participant characteristics from hip fracture analysis of warfarin use 1 year among
older adults with atrial fibrillation

Characteristics	Warfarin users (N=10,173)	Warfarin nonusers (N=10,173)
Age, mean (SD) (years)	77.7 (6.1)	77.6 (6.7)
Sex (% women)	48.0	48.0
BMI, mean (SD) (kg/m ²)	27.2 (5.0)	27.2 (5.2)
DVT (%)	2.3	2.2
PE (%)	1.5	1.2
Heart failure (%)	21.0	20.5
High fall risk (%)	3.2	3.1
Hyperthyroidism (%)	2.7	2.5
Neuro-psychiatric impairment (%)	1.7	1.2
Current smokers (%)	7.7	7.5
Alcoholics (%)	0.2	0.2
Beta-blockers (%)	56.0	56.0
Bisphosphonates (%)	6.9	6.8
Diuretics (%)	65.5	65.0
Estrogen (%)	3.0	3.0
Glucocorticoids (%)	17.1	17.2
Statins (%)	47.9	48.1
Follow-up time, mean (SD) (days)	1,155 (868.6)	1,105 (869.9)
Propensity score (mean)	0.2	0.2
Deaths (%)	20.9	23.9

DVT deep venous thrombosis, *PE* pulmonary embolism

Table 2
Association of long-term warfarin use and risk of hip, spine, and wrist fractures in propensity-score (PS) matched cohorts of older adults with atrial fibrillation

Warfarin use	Cases	Crude incidence rate (per 1000 person-years)	PS-matched hazard ratio (95 % CI)	Adjusted hazard ratio ^a (95 % CI)
Hip fracture				
1 year of use				
No (nonuse)	151	4.91	1.0 (referent)	1.0 (referent)
Yes	170	5.29	1.08 (0.87,1.35)	1.05 (0.84,1.31)
3 years of use				
No (nonuse)	87	5.51	1.0 (referent)	1.0 (referent)
Yes	101	6.20	1.13 (0.84,1.5)	1.15 (0.86,1.53)
Spine fracture				
1 year of use=				
No (nonuse)	24	0.77	1.0 (referent)	1.0 (referent)
Yes	31	0.95	1.23 (0.72,2.09)	1.19 (0.70,2.03)
3 years of use				
No (nonuse)	14	0.86	1.0 (referent)	1.0 (referent)
Yes	14	0.84	0.98 (0.47,2.05)	0.95 (0.45,2.02)
Wrist fracture				
1 year of use				
No (nonuse)	75	2.48	1.0 (referent)	1.0 (referent)
Yes	72	2.24	0.91 (0.66,1.26)	0.88 (0.64,1.22)
3 years of use				
No (nonuse)	37	2.31	1.0 (referent)	1.0 (referent)
Yes	38	2.35	1.01 (0.64,1.59)	1.02 (0.64,1.60)
Hip, spine, and wrist fracture				
1 year of use				
No (nonuse)	252	8.48	1.0 (referent)	1.0 (referent)
Yes	244	7.86	0.92 (0.77,1.10)	0.90 (0.75,1.07)
3 years of use				
No (nonuse)	123	7.95	1.0 (referent)	1.0 (referent)
Yes	143	9.06	1.12 (0.88,1.43)	1.09 (0.85,1.38)

^a Additionally adjusted for the covariates used to calculate propensity score [age, sex, body mass index (BMI), history of multiple falls, deep venous thrombosis, pulmonary embolism, heart failure, neuropsychiatric impairment, hyperthyroidism, estrogen use, beta blockers, corticosteroids, diuretics, bisphosphonates, statins, smoking, and alcoholism]