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ORIGINAL ARTICLE

# Risk of venous thromboembolism among users of different anti-osteoporosis drugs: a population-based cohort analysis including over 200,000 participants from Spain and the UK

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**Abstract**

*Summary* The venous thromboembolism risk among anti-osteoporotics is unknown. In this primary care study, the risk with other bisphosphonates [1.05 (0.94–1.18) and 0.96 (0.78–1.18)], strontium [0.90 (0.61–1.34) and 1.19 (0.82–1.74)], in the UK and Spain respectively, and denosumab [1.77 (0.25–12.66)] and teriparatide [1.27 (0.59–2.71)] in Spain, did not differ versus alendronate.

*Introduction* Most of the known adverse drug reactions described for anti-osteoporosis medication (AOM) have been described in studies comparing AOM users to non-users. We aimed to compare the risk of venous thromboembolism (VTE) among incident users of different AOM compared to alendronate (first line therapy).

*Methods* Two cohort studies were performed using data from the UK (CPRD) and Spain (BIFAP) primary care records separately. All patients aged ≥ 50 years with at least 1 year of data available and a new prescription or dispensation of AOM (date for therapy initiation) during 2000–2014 (CPRD) or 2001–2013 (BIFAP) were included. Users of raloxifene/bazedoxifene were excluded from both databases. Five exposure cohorts were identified according to first treatment: (1) alendronate, (2) other bisphosphonates, (3) strontium ranelate, (4) denosumab, and (5) teriparatide. Participants were followed from the day after therapy initiation to the earliest of a treated VTE (cases), end of AOM treatment (defined by a refill gap of 180 days), switching to an alternative AOM, drop-out, death, or end of study period. Incidence rates of VTE were estimated by cohort. Adjusted hazard ratios (HR 95%CI) were estimated according to drug used.

*Results* Overall, 2035/159,209 (1.28%) in CPRD and 401/83,334 (0.48%) in BIFAP had VTE. Compared to alendronate,

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adjusted HR of VTE were 1.05 (0.94–1.18) and 0.96 (0.78–1.18) for other bisphosphonates, and 0.90 (0.61–1.34) and 1.19 (0.82–1.74) for strontium in CPRD and BIFAP, respectively; 1.77 (0.25–12.66) for denosumab and 1.27 (0.59–2.71) for teriparatide in BIFAP.
*Conclusions* VTE risk during AO therapy did not differ by AOM drug use. Our data does not support an increased risk of VTE associated with strontium ranelate use in the community.

**Keywords** Anti-osteoporosis medication · Electronic health records · Pharmacoepidemiology · Primary care · Venous thromboembolism

## Introduction

Strontium ranelate was approved in Europe in 2004, for the treatment of postmenopausal osteoporosis to reduce vertebral and hip fractures [1], and in 2012 for men at increased risk of fractures [2]. Following a retrospective evaluation of clinical trials an increased risk of venous thromboembolism (VTE) was observed in strontium ranelate arms compared to placebo [3]. Thus, new contraindications for patients with a history of VTE or immobilization were added to strontium-containing medicines in 2012 [4], and additional risk minimization measures were imposed due to a suspected increase in cardiovascular risk in 2014, including contraindications for patients with history of ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or uncontrolled hypertension was established [5–8].

Despite increasing evidence on the potentially thrombotic effects of strontium ranelate and selective estrogens receptor modulators (raloxifene and bazedoxifene), no data is to our knowledge available on the potential risk of VTE among users of other anti-osteoporosis medication (AOM). Increased risks of VTE (as for most of the known adverse drug reactions described for AOM) have been described in studies comparing AOM users to AOM-naïve patients. To what extent VTE risk is different among actual users of different AOM in a clinical practice setting is hence yet unknown.

We, therefore, aimed to compare the risk of VTE among incident users of different AOM available in primary care settings in the UK and Spain (including alendronate, other oral bisphosphonates, strontium ranelate, denosumab, and teriparatide) using alendronate (first line therapy) as a reference group.

## Methods

### Source of data

We obtained data from primary care outpatient records for the UK Clinical Practice Research Datalink (CPRD) and Spanish "Base de datos para la investigación Farmacoepidemiológica en Atención Primaria" (BIFAP).

*CPRD*

In the UK, the majority of CPRD [9] is linked to secondary care inpatient diagnoses and procedures, as coded in the Hospital Episodes Statistics (HES) [10]. CPRD comprises computerized records of all clinical and referral events in both primary and secondary care, in addition to comprehensive demographic information. Data include medication prescriptions by general practitioners (GPs) using the British National Formulary [11], clinical events recorded using READ codes [12, 13], referrals, and hospital admissions with their major outcomes in a sample of > seven million patients, chosen to be the representative of the wider UK population. HES is the national statistical data warehouse of the care provided by NHS hospitals, and it stores data on diagnoses and procedures carried out during hospital admission for the whole of England.

*BIFAP*

In Spain, the BIFAP database [14] is a longitudinal population-based database of anonymized electronic medical records of primary care practitioners and pediatricians (PCP) from nine different regions in Spain. BIFAP is fully financed by the Spanish Agency on Medicines and Medical Devices (AEMPS), belonging to the Department of Health. The database includes information of 2324 physicians (84% general practitioners and 15% pediatricians), on patient demographics, clinical events (coded through ICPC medical terms dictionary, free text notes, specialist referrals, and laboratory test results of around four million patients (19 million patient-years) covering around 8.6% of the Spanish population at the time this study was performed. Prescriptions are automatically recorded in BIFAP at consultation.

The study protocol was approved by the UK Independent Scientific Advisory Committee ISAC (REF 14_110R) and BIFAP Scientific Committee (Number 02_2015).

### Study design

Two cohort studies were performed using data from CPRD and BIFAP separately.

### Study population

All patients aged ≥ 50 years with a new prescription or dispensation of AOM (date for therapy initiation) during each database study period, i.e., 2000–2014 (CPRD) or 2001–2013 (BIFAP), and at least 1 year of available recorded data before therapy initiation were included. Patients with a

prescription or dispensation of AOM recorded during the year before that therapy initiation were excluded (considered as prevalent users). Users of raloxifene and bazedoxifene were also excluded as these were formally contraindicated for patients with a history of VTE and warned for patients at VTE risk from marketing authorization [15].

### Treatment episodes and exposure definition

The study population was divided in five exposure cohorts according to AOM of first treatment episode: (1) alendronate (Anatomical Therapeutic Chemical (ATC) classification, M05BA04 and M05BB03), (2) other oral bisphosphonates (etidronate [M05BA01], ibandronate [M05BA06], risedronate [M05BA07], clodronate [M05BA02], and tiludronate [M05BA05]; these last two were only available in Spain), (3) strontium ranelate (M05BX03), (4) denosumab (M05BX04), and (5) teriparatide (H05AA02).

Treatment episodes were periods of continuous use, i.e., with no gaps of over 180 days between repeat prescriptions. Such episodes were defined as a series of subsequent prescription durations for each AOM (into each cohort), independent of ATC/BNF code switching and change of dose within each cohort (Figure 1). Treatment episodes were constructed according to the method 1 by Gardarsdottir et al. [16] and similarly for the reference and the comparison exposure cohorts.

Defined daily dose (DDD) assigned by the WHO were assumed by default of the AOM studied. Duration of a prescription was based on the calculated prescribed DDD. The theoretical end date of each prescription equaled the prescription/dispensing date plus the duration of drug use calculated through DDD prescribed. In case a subsequent prescription with the same drug was collected before the theoretical end date of a previous prescription, the number of overlapping days/DDD was disregarded assuming that overlapping days compensate gaps between prescriptions.

If the subsequent prescription within the same treatment episode included another drug type into same cohort, the patient was considered to have switched therapy and the remaining tablet days from the prior prescription was disregarded.

A new treatment episode was considered when an interval of more than 180 days was present between the theoretical end date of a prescription and the prescription date of the subsequent prescription for the same patient. Only first treatment episode was assessed in this study, as well as the 180 days afterwards. Sensitivity analysis using 90 and 30 days of intervals were also performed.

### Case ascertainment

Participants from exposure cohorts were followed from the day after therapy initiation to the earliest of the following: a record of VTE diagnosis with at least one prescription of heparin or oral anticoagulant recorded during the 60 days after VTE (case definition), 180 days after the end of the first AOM treatment episode (end of the supply of the last prescription before a gap of > 180 days), switching to an alternative cohort exposure, lost to follow up, death, or end of study period. Table S1 from Annex I shows READ and ICPC codes for VTE diagnosis identification in the contributing databases.

### Potential confounders

Risk factors for VTE based on NICE guidelines [17] and other factors related to the AOM were collected as present or not, anytime before therapy initiation (unless otherwise mentioned afterwards), as potential confounders of the studied association. Confounders included age, sex, history of VTE, venous insufficiency or phlebitis, recent fractures (recorded during 2 months before therapy initiation), hormone replacement therapy (HRT; prescribed during the year before therapy initiation), Charlson index (when available, i.e. CPRD), cancer, and peripheral arterial disease (in BIFAP, since Charlson index was not available for ICPC classification). BMI ($kg/m^2$) and current smoking (yes/no) were collected as recorded during the year of therapy initiation. Information about the use of other AOM (i.e., parathyroid hormone, calcitonin, and elcatonin), calcium-vitamin D supplements, glucocorticoids, heparins, and oral anticoagulant drugs were also collected for description.

### Statistical methods

Incidence rate (IR 95% CI) of treated VTE per 1000 person-years under first AOM were estimated by exposure cohort and age.

Hazard ratios (HR) and 95% confidence intervals (95% CI) for treated VTE were computed for each exposure cohort compared to alendronate (reference group) using Cox regression after adjustment for potential confounders listed in Tables 2 and 3 footnotes. Potential effect modification and p for interaction (*p*-int) by calendar period (pre-2011 vs. 2011 onwards), sex and age categories (50–59, 60–69, 70–79, and ≥ 80 years) were evaluated. When *p*-int was below 0.2, HR were calculated for each strata.

Multiple imputation was performed to account for missing BMI and smoking data. Imputed BMI and smoking values were assigned after conditioning to variables included in the multivariable Cox model (i.e., type of cohort exposure, outcome, the Nelson-Aalen estimate of the survival model, and all the confounders listed above), and the identified predictors of both missingness and values of BMI and current smoking, respectively [18]. Fifteen datasets were imputed and combined using Rubin's rules.

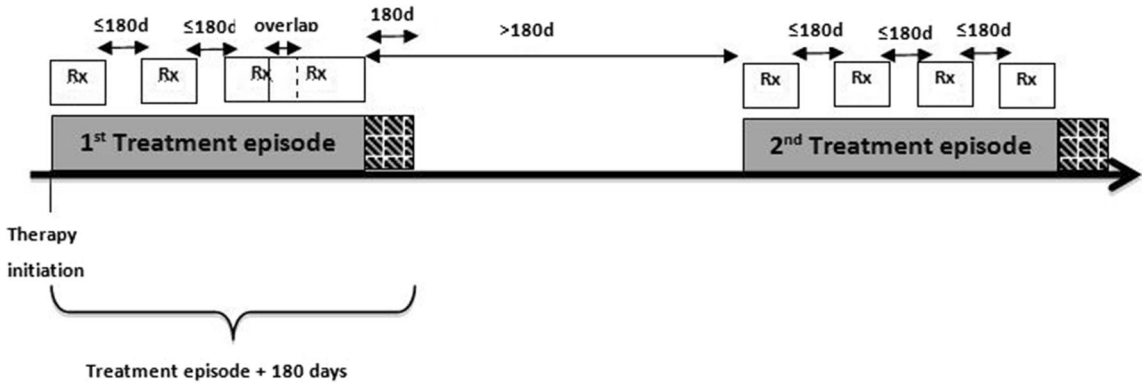



**Fig. 1** Treatment episodes construction. Rx, prescription duration; 180d, 180 days

### Patient involvement

No patient/s or public representatives have been involved as part of this work.

## Results

The study populations were made of 159,209 and 83,334 new users of AOM in the UK (CPRD) and Spanish (BIFAP) primary care settings. The majority were women 80 and 90%, while alendronate constituted 79.8 and 43.4% of the study population in CPRD and BIFAP, respectively. Baseline characteristics according to exposure cohort are reported in Table 1.

In CPRD, patients on other bisphosphonates did not show differences in baseline characteristics compared to alendronate users, while users of strontium ranelate were older (56.7 vs. 31.7% were ≥ 80 years) and had a higher prevalence of recent fractures (16.2 vs. 6.2%) and calcium-D supplementation (35.6 vs. 24.6%), but a lower proportion of glucocorticoids use (26.9 vs. 40.8%). History of VTE was more commonly present in the denosumab cohort (10.3 vs. 5.2% in alendronate cohort). As there were only seven patients prescribed teriparatide in CPRD comparisons are poor. In BIFAP, users of strontium ranelate had higher prevalence of venous insufficiency or phlebitis (22.1 vs. 19.2%), recent fractures (10.3 vs. 7.8%), and heparin use (15.4 vs. 11.9%) than alendronate users. Users of denosumab or teriparatide were older than alendronate users (27.0 and 27.8% vs. 15.6% aged ≥ 80 years), and had a higher prevalence of other AOM (13.3 and 14.8% vs. 7.5%), calcium-D (65.9 and 42.10% vs. 34.0%), glucocorticoids (32.1 and 28.3% vs. 18.0%), heparin (18.1 and 26.7% vs. 11.9%), and oral anticoagulant drugs (5.1 and 10.5% vs. 4.9%). History of VTE was higher in teriparatide users (3.1%) than in alendronate users (1.4%). The distribution of time and stop reasons to follow up during the first treatment episode by AOM in CPRD and BIFAP is shown in Table S2 of Annex I. The IR and risk of VTE associated to each AOM versus alendronate, overall and by age in CPRD and BIFAP, are shown in Table 2.

Overall, 2035 (CPRD) and 401 (BIFAP) VTE cases were detected during the index (first) treatment episode. Crude IR of VTE were 4.84 (95%CI, 4.61–5.08) and 2.36 (95%CI, 2.04–2.72) per 1000 person-years at risk (PYAR) for alendronate; 5.08 (95%CI, 4.59–5.63) and 2.21 (95%CI, 1.91–2.56) for other biphosphonates; 5.06 (95%CI, 3.42–7.48) and 2.89 (95%CI, 2.04–4.09) for strontium ranelate; and 24.06 (3.39–170.8) and 5.16 (95%CI, 0.73–36.60) for denosumab in CPRD and BIFAP participants, respectively. IR of VTE among teriparatide users was 4.67 (95%CI, 2.22–9.79) in BIFAP. IR of VTE increased with age in all AOM cohorts.

The HR of VTE associated to each AOM is shown in Table 2 (results stratified by database). Compared to alendronate (reference group), adjusted HR were 1.05 (0.94–1.18) and 0.96 (0.78–1.18) for other biphosphonates, 0.90 (0.61–1.34) and 1.19 (0.82–1.74) for strontium ranelate, and 3.47 (0.49–24.7) and 1.77 (0.25–12.66) for denosumab in CPRD and BIFAP, respectively, and 1.27 (0.59–2.71) for teriparatide in BIFAP. After adjusting by heparin and oral anticoagulant drugs none of the HR changed significantly versus main model for any of the drugs studied in BIFAP or CPRD.

Figure 2 shows the HR observed in main analysis and sensitivity analysis using 90 and 30 days of gaps. In CPRD, the risk associated with strontium ranelate was slightly higher in the main analysis (HR, 0.90; 95%CI, 0.61–1.34) than in the sensitivity analyses (HR, 0.83 (0.53–1.31) and 0.86 (0.48–1.52), for 90 and 30 days intervals, respectively). The opposite was true for denosumab (HR, 3.91 (0.55–27.81) and 5.03 (0.71–35.81) for 90 and 30 days intervals, respectively. Risk associated with other bisphosphonates did not change with the different intervals, being 1.05 (0.92–1.18) for 90 days interval and 1.06 (0.90–1.24) for 30 days interval. In BIFAP, the risk of VTE associated to all exposure cohort versus alendronate was diluted with the increase in the interval, i.e., for other bisphosphonates HR was 1.04 (0.77–1.41) for 30 days

**Table 1** Baseline characteristics according to AOM exposure cohort in CPRD and BIFAP

| CPRD | | Alendronate $N = 127,121$ | | Other biphosphonates $N = 29,007$ | | Strontium ranelate $N = 3045$ | | Denosumab $N = 29$ | | Teriparatide $N = 7$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % | No. | % | No. | % |
| Females | | 101,302 | 79.7 | 23,763 | 81.9 | 2575 | 84.6 | 25 | 86.2 | 6 | 85.7 |
| Age at therapy initiation | Mean (sd) | 73.4 (10.6) | | 73.3 (10.5) | | 79.3 (10.3) | | 78.1 (10.5) | | 72.9 (8.3) | |
| | 50–59 years | 15,249 | 12.0 | 3488 | 12.0 | 173 | 5.7 | 2 | 6.9 | 0 | 0.0 |
| | 60–69 years | 29,537 | 23.2 | 6813 | 23.5 | 371 | 12.2 | 5 | 17.2 | 2 | 28.6 |
| | 70–70 years | 42,037 | 33.1 | 9685 | 33.4 | 776 | 25.5 | 8 | 27.6 | 4 | 57.1 |
| | ≥ 80 years | 40,298 | 31.7 | 9021 | 31.1 | 1725 | 56.7 | 14 | 48.3 | 1 | 14.3 |
| Calendar start year | < 2011 | 103,800 | 81.7 | 27,999 | 96.5 | 2389 | 78.5 | 1 | 3.5 | 7 | 100 |
| | ≥ 2011 | 23,321 | 18.4 | 1008 | 3.5 | 656 | 21.5 | 28 | 96.6 | 0 | 0 |
| VTE before therapy initiation | | 6634 | 5.2 | 1578 | 5.4 | 159 | 5.2 | 3 | 10.3 | 0 | 0.0 |
| Risk factors for VTE | | | | | | | | | | | |
| Venous insufficiency or phlebitis | | 19,150 | 15.1 | 4273 | 14.7 | 467 | 15.3 | 7 | 24.1 | 1 | 14.3 |
| HRT the year before therapy initiation | | 6036 | 4.8 | 1615 | 5.6 | 65 | 2.1 | 0 | 0.0 | 1 | 14.3 |
| Recent fractures | | 7850 | 6.2 | 1624 | 5.6 | 492 | 16.2 | 3 | 10.3 | 0 | 0.0 |
| Charlson index | None | 68,107 | 53.6 | 15,687 | 54.1 | 1476 | 48.5 | 12 | 41.4 | 4 | 57.1 |
| | Mild | 22,625 | 17.8 | 5853 | 20.2 | 520 | 17.1 | 4 | 13.8 | 0 | 0.0 |
| | Moderate | 18,355 | 14.4 | 3699 | 12.8 | 499 | 16.4 | 3 | 10.3 | 1 | 14.3 |
| | Severe | 18,034 | 14.2 | 3768 | 13.0 | 550 | 18.1 | 10 | 34.5 | 2 | 28.6 |
| Other co-medication | | | | | | | | | | | |
| Other anti-osteoporosis medication | | 320 | 0.3 | 413 | 1.4 | 12 | 0.4 | 0 | 0.0 | 0 | 0.0 |
| Calcium-vitamin D | | 31,224 | 24.6 | 8178 | 28.2 | 1084 | 35.6 | 20 | 69.0 | 6 | 85.7 |
| Glucocorticoids | | 51,830 | 40.8 | 12,058 | 41.6 | 818 | 26.9 | 13 | 44.8 | 2 | 28.6 |
| Heparin | | 1483 | 1.2 | 235 | 0.8 | 46 | 1.5 | 2 | 6.9 | 0 | 0.0 |
| Oral anticoagulant drugs | | 10,641 | 8.4 | 2439 | 8.4 | 256 | 8.4 | 6 | 20.7 | 0 | 0.0 |
| BMI ($Kg/m^2$) | < 18.5 | 3082 | 2.4 | 718 | 2.5 | 133 | 4.4 | 1 | 3.45 | 0 | 0.0 |
| | 18.5–24.9 | 20,701 | 16.3 | 4598 | 15.9 | 557 | 18.3 | 6 | 20.7 | 2 | 28.6 |
| | 25–29.9 | 16,335 | 12.9 | 3429 | 11.8 | 316 | 10.4 | 4 | 13.8 | 2 | 28.6 |
| | 30–34.9 | 7246 | 5.7 | 1473 | 5.1 | 144 | 4.7 | 5 | 17.2 | 0 | 0.0 |
| | 35–39.9 | 2272 | 1.8 | 481 | 1.7 | 27 | 0.9 | 2 | 6.9 | 0 | 0.0 |
| | ≥ 40 | 961 | 0.8 | 199 | 0.7 | 10 | 0.3 | 0 | 0.0 | 0 | 0.0 |
| | Missing | 76,524 | 60.2 | 18,109 | 62.43 | 1858 | 61.0 | 11 | 37.9 | 3 | 42.9 |
| Current smoker | No | 56,179 | 44.2 | 12,610 | 43.5 | 1418 | 46.6 | 13 | 44.8 | 4 | 57.1 |
| | Yes | 11,222 | 8.8 | 2407 | 8.3 | 217 | 7.1 | 1 | 3.5 | 0 | 0.0 |
| | Missing | 59,720 | 47.1 | 13,990 | 48.2 | 1410 | 46.3 | 15 | 51.7 | 3 | 42.9 |
| BIFAP | | Alendronate $N = 36,182$ | | Other biphosphonates $N = 37,594$ | | Strontium ranelate $N = 7978$ | | Denosumab $N = 293$ | | Teriparatide $N = 1287$ | |
| | | No. | % | No. | % | No. | % | No. | % | No. | % |
| Females | | 32,348 | 89.4 | 33,732 | 89.7 | 7191 | 90.1 | 264 | 90.1 | 1037 | 80.6 |
| Age at therapy initiation | Mean (sd) | 68.67; (10.13) | | 68.19; (10.09) | | 68.83; (10.58) | | 70.90; (10.71) | | 73.00; (9.78) | |
| | 50–59 years | 8200 | 22.7 | 9048 | 24.1 | 1878 | 23.5 | 51 | 17.4 | 151 | 11.7 |
| | 60–69 years | 10,387 | 28.7 | 11,069 | 29.5 | 2215 | 27.8 | 86 | 29.4 | 273 | 21.2 |
| | 70–70 years | 11,948 | 33.0 | 11,963 | 31.8 | 2452 | 30.7 | 77 | 26.3 | 505 | 39.2 |
| | ≥ 80 years | 5647 | 15.6 | 5514 | 14.7 | 1433 | 18.0 | 79 | 27.0 | 358 | 27.8 |
| Calendar start year | < 2011 | 33,948 | 93.8 | 34,730 | 92.4 | 7016 | 88.0 | 0 | – | 856 | 66.5 |
| | ≥ 2011 | 2234 | 6.2 | 2864 | 7.6 | 962 | 12.1 | 293 | 100.0 | 431 | 33.5 |
| VTE before therapy initiation | | 506 | 1.4 | 505 | 1.3 | 98 | 1.2 | 5 | 1.7 | 40 | 3.1 |

**Table 1** (continued)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Risk factors for VTE | | | | | | | | | | | |
| Cancer | | 3603 | 10.0 | 3871 | 10.3 | 831 | 10.4 | 50 | 17.1 | 150 | 11.7 |
| Peripheral arterial disease | | 416 | 1.2 | 442 | 1.2 | 102 | 1.3 | 4 | 1.4 | 40 | 3.1 |
| Venous insufficiency or phlebitis | | 6957 | 19.2 | 7579 | 20.2 | 1762 | 22.1 | 88 | 30.0 | 293 | 22.8 |
| HRT the year before therapy initiation | | 1098 | 3.0 | 1056 | 2.8 | 198 | 2.5 | 0 | 0.0 | 9 | 0.7 |
| Recent fractures | | 2821 | 7.8 | 2807 | 7.5 | 820 | 10.3 | 43 | 14.7 | 268 | 20.8 |
| Other co-medication | | | | | | | | | | | |
| Other anti-osteoporosis medication | | 2698 | 7.5 | 2733 | 7.3 | 610 | 7.7 | 39 | 13.3 | 191 | 14.8 |
| Calcium-vitamin D | | 12,292 | 34.0 | 13,719 | 36.5 | 2709 | 34.0 | 193 | 65.9 | 542 | 42.1 |
| Glucocorticoids | | 6496 | 17.8 | 7761 | 20.6 | 1485 | 18.6 | 94 | 32.1 | 364 | 28.3 |
| Heparin | | 4292 | 11.9 | 4664 | 12.4 | 1225 | 15.4 | 53 | 18.1 | 343 | 26.7 |
| Oral anticoagulant drugs | | 1783 | 4.9 | 1786 | 4.8 | 361 | 4.5 | 15 | 5.1 | 135 | 10.5 |
| BMI ($Kg/m^2$) | < 18.5 | 111 | 0.3 | 106 | 0.3 | 18 | 0.2 | 2 | 0.7 | 9 | 0.7 |
| | 18.5–24.9 | 3200 | 8.8 | 3122 | 8.3 | 629 | 7.9 | 31 | 10.6 | 109 | 8.5 |
| | 25–29.9 | 6094 | 16.8 | 6242 | 16.6 | 1267 | 15.9 | 40 | 13.7 | 201 | 15.6 |
| | 30–34.9 | 4000 | 11.1 | 4104 | 10.9 | 931 | 11.7 | 33 | 11.3 | 141 | 11.0 |
| | 35–39.9 | 1244 | 3.4 | 1347 | 3.6 | 305 | 3.8 | 4 | 1.4 | 46 | 3.6 |
| | ≥ 40 | 432 | 1.2 | 456 | 1.2 | 99 | 1.2 | 0 | 0.0 | 15 | 1.2 |
| | Missing | 21,101 | 58.3 | 22,217 | 59.1 | 4729 | 59.3 | 183 | 62.5 | 766 | 59.5 |
| Current smoker | No | 6937 | 19.2 | 7079 | 18.8 | 1514 | 19.0 | 52 | 17.8 | 242 | 18.8 |
| | Yes | 4670 | 12.9 | 4795 | 12.8 | 995 | 12.5 | 35 | 12.0 | 143 | 11.1 |
| | Missing | 24,575 | 67.9 | 25,720 | 68.4 | 5469 | 68.6 | 206 | 70.3 | 902 | 70.1 |

interval and 0.98 (0.78–1.24) for 90 days interval, for denosumab 2.02 (0.28–14.61) and 1.89 (0.26–13.6), for teriparatide 1.48 (0.59–3.68) and 1.32 (0.58–3.00), and for strontium ranelate 1.50 (0.90–2.51) and 1.44 (0.96–2.15) for 90 and 30 days intervals, respectively.

In CPRD and BIFAP, overall patients treated with any AOM from 2011 onwards seem to be slightly older compared to those initiating AOM before 2011 (74.5 vs. 73.3 in CPRD and 69.8 vs. 68.4 years in BIFAP), and more frequently had a history of recent fractures (10.1 vs. 5.5% in CPRD and 11.8 vs.7.8% in BIFAP), previous use of calcium-vitamin D (27.1 vs. 25.1% in CPRD and 37.8 vs. 35.1% in BIFAP), glucocorticoids (42.4 vs. 40.3% in CPRD and 31.3 vs. 18.4% in BIFAP), heparin (3.0 vs. 0.8% in CPRD and 18.8 vs. 12.2% in BIFAP) and oral anticoagulant drugs (10.1 vs. 8.1% in CPRD and 7.6 vs. 4.7% in BIFAP) and less use of HRT (1.4 vs. 5.5% in CPRD and 0.6 vs. 3.0% in BIFAP). Additionally, in BIFAP, patients treated with any AOM from 2011 onwards seem to more frequently have a history of VTE (2.2 vs. 1.3% specially bisphosphonates), cancer (14.7 vs. 9.8%), peripheral arterial disease (1.9 vs. 1.1%), and vein insufficiency or phlebitis (24.3 vs. 19.6%). These overall data are not reported in tables.

Baseline characteristics of patients initiating the therapy before 2011 and from 2011 onwards by exposure cohort are reported in Table S3 of Annex I. In particular for strontium ranelate, the crude prevalence of recent fractures was much higher among patients initiating therapy from 2011 onwards than before 2011 (23.3 vs. 14.2% in CPRD and 18.8 vs. 9.1% in BIFAP, respectively), as was the previous use of anticoagulant drugs (3.4 vs. 1.0% used heparin and 8.8 vs. 8.2% used oral anticoagulants in CPRD; and 23.5 vs. 14.2% used heparin and 7.5 vs. 4.1% used oral anticoagulants from 2011 onwards and before 2011, respectively). The VTE history seemed similar among patients initiating therapy from 2011 onwards than before 2011 (4.6 vs. 5.4% in CPRD and 1.6 vs. 1.2% in BIFAP, respectively).

Table 3 shows the HR by calendar periods (stratified as before 2011 and from 2011 onwards), sex and age for CPRD and BIFAP.

Borderline effect modification was suggested among calendar periods in BIFAP ($p$-int = 0.08), while no effect modification in CPRD ($p$-int = 0.99). Regarding sex strata, borderline effect modification was suggested in CPRD ($p$-int = 0.19), while no effect modification in BIFAP ($p$-int = 0.83). Regarding age categories, no effect modification was suggested in BIFAP ($p$-int = 0.21), or in CPRD ($p$-int = 0.51). Therefore, similar to overall analysis, non-statistically significant differences in risk (compared with alendronate) were found in calendar periods, either sex or age strata.

## Discussion

In the current study, VTE risk during first AOM treatment period did not differ by type of AOM prescribed in the UK or Spain primary care settings. In particular, our data does not support an increased risk of VTE associated with strontium ranelate vs. alendronate. No association was observed, irrespective of calendar period, sex or length of different risk windows for VTE evaluation as used in sensitivity analyses.

Strontium ranelate was approved in Europe in 2004 for treatment of postmenopausal osteoporosis to reduce vertebral and hip fractures [1], and in 2012 for men at increased risk of

**Table 2** Incidence rate and risk of VTE associated to each AOM versus alendronate (hazard ratio) overall and by age in CPRD and BIFAP

| | Alendronate | Other biphosphonates | Strontium ranelate | Denosumab | Teriparatide |
|---|---|---|---|---|---|
| CPRD | | | | | |
| Number of patients at risk | 127,121 | 29,007 | 3045 | 29 | 7 |
| VTE treated | 1644 | 365 | 25 | 1 | 0 |
| 50–59 years | 141 | 33 | 2 | 0 | 0 |
| 60–69 years | 342 | 73 | 3 | 0 | 0 |
| 70–70 years | 608 | 144 | 7 | 0 | 0 |
| ≥ 80 years | 553 | 115 | 13 | 1 | 0 |
| Incidence rate per 1000 person-years (95%CI) | 4.84 (4.61–5.08) | 5.08 (4.59–5.63) | 5.06 (3.42–7.48) | 24.06 (3.39–170.8) | – |
| 50-59y | 3.15 (2.67–3.72) | 3.60 (2.56–5.06) | 6.59 (1.64–26.4) | – | – |
| 60-69y | 3.87 (3.48–4.30) | 3.87 (3.07–4.87) | 4.06 (1.30–12.6) | – | – |
| 70-70y | 5.07 (4.69–5.49) | 5.75 (4.88–6.77) | 5.12 (2.44–10.73) | – | – |
| ≥ 80 years | 6.39 (5.88–6.94) | 6.13 (5.11–7.37) | 5.13 (2.98–8.83) | 59.9 (8.16–411.12) | – |
| Crude HR (95%CI) | Ref. | 1.03 (0.92–1.15) | 0.94 (0.63–1.39) | 4.20 (0.59–29.8) | – |
| Adjusted HR (95%CI)[a] | Ref. | 1.05 (0.94–1.18) | 0.90 (0.61–1.34) | 3.47 (0.49–24.7) | – |
| Adjusted HR (95%CI)[b] | Ref. | 1.06 (0.94–1.18) | 0.90 (0.61–1.34) | 3.09 (0.43–22.0) | – |
| BIFAP | | | | | |
| Number of patients at risk | 36,182 | 37,594 | 7978 | 293 | 1287 |
| VTE treated | 186 | 175 | 32 | 1 | 7 |
| 50–59 years | 7 | 17 | 1 | 0 | 0 |
| 60–69 years | 35 | 35 | 5 | 0 | 2 |
| 70–79 years | 89 | 82 | 13 | 1 | 3 |
| ≥ 80 years | 55 | 41 | 13 | 0 | 2 |
| Incidence rate per 1000 person-years (95%CI) | 2.36 (2.04–2.72) | 2.21 (1.91–2.56) | 2.89 (2.04–4.09) | 5.16 (0.73–36.60) | 4.67 (2.22–9.79) |
| 50–59 years | 0.42 (0.20–0.88) | 0.95 (0.59–1.53) | 0.42 (0.06–3.00) | 0 (−) | 0 (−) |
| 60–69 years | 1.44 (1.04–2.01) | 1.42 (1.02–1.98) | 1.52 (0.63–3.65) | 0 (−) | 6.20 (1.55–24.80) |
| 70–79 years | 3.25 (2.64–4.01) | 3.07 (2.48–3.82) | 3.56 (2.07–6.13) | 19.69 (2.77–139.77) | 5.00 (1.61–15.50) |
| ≥ 80 years | 5.21 (4.00–6.79) | 4.09 (3.01–5.55) | 7.40 (4.30–12.74) | 0 (−) | 4.91 (1.23–19.65) |
| Crude HR (95%CI) | Ref. | 0.94 (0.76–1.16) | 1.22 (0.84–1.79) | 2.08 (0.29–14.86) | 1.99 (0.93–4.26) |
| Adjusted HR (95%CI)[a] | Ref. | 0.96 (0.78–1.18) | 1.19 (0.82–1.74) | 1.77 (0.25–12.66) | 1.27 (0.59–2.71) |
| Adjusted HR (95%CI)[b] | Ref. | 0.96 (0.78–1.18) | 1.17 (0.80–1.71) | 1.68 (0.23–12.05) | 1.19 (0.56–2.56) |

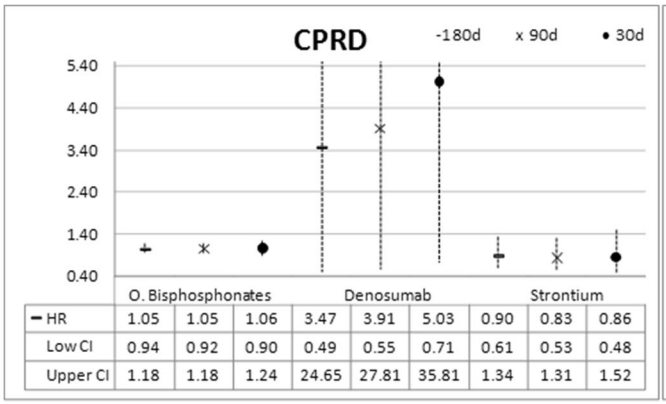
*VTE* venous thromboembolism including deep vein thrombosis and pulmonary embolism (Annex I). *AOM* anti-osteoporosis medication

[a] Hazard ratios (HR) were adjusted as per protocol by age, sex, history of VTE, cancer, peripheral arterial disease, vein insufficiency or phlebitis, recent fractures (recorded during 2 months before therapy initiation as a proxy for patients who are bed-bound), and hormone replacement therapy prescribed during the year before therapy initiation, BMI and current smoking as recorded during the year of therapy initiation

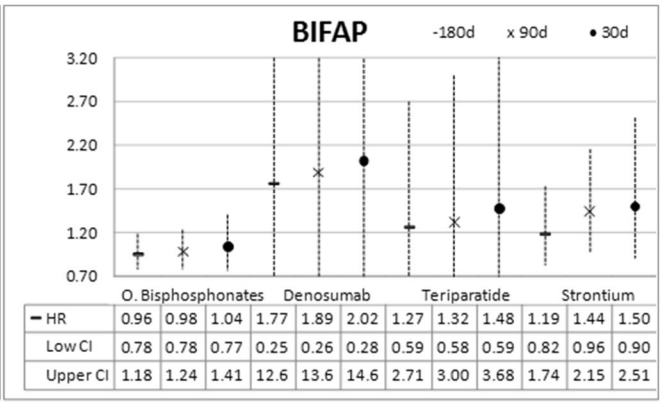
[b] HR were adjusted by heparins and oral anticoagulant drugs anytime before AOM therapy initiation additionally to HR[a] adjustment

fractures [2]. The risk of VTE was identified in clinical trials, and warnings were included in the product information. In 2011, a manuscript reported that 28% of the 93 VTE spontaneously reported with strontium ranelate in France had VTE risk factors (mainly VTE history and immobilization) [19]. Thus, a formal review by the CHMP was released in October 2011 [20]. After retrospective evaluation of clinical trial results (3803 strontium versus 3769 placebo), a non-significant 37% increased risk of VTE versus placebo was observed (95%CI, 0.99–1.89), being higher (87% increased risk; 95%CI, 1.06–3.31) among patients aged 80 years [3]. The evaluation of the epidemiological studies and post-marketing surveillance showed that a history of VTE or immobilization were important risk factors for VTE, so in order to minimize the risk of VTE in these patients the existing warnings were upgraded to a contraindication for strontium-containing medicines in 2012 [4].

We did not formally assess whether the release of that safety review and further contraindication affected the profile of patient treated with strontium ranelate in the studied populations. At a glance, the crude prevalence of VTE risk factors was not




| | O. Bisphosphonates | | | Denosumab | | | Strontium | | |
|---|---|---|---|---|---|---|---|---|---|
| HR | 1.05 | 1.05 | 1.06 | 3.47 | 3.91 | 5.03 | 0.90 | 0.83 | 0.86 |
| Low CI | 0.94 | 0.92 | 0.90 | 0.49 | 0.55 | 0.71 | 0.61 | 0.53 | 0.48 |
| Upper CI | 1.18 | 1.18 | 1.24 | 24.65 | 27.81 | 35.81 | 1.34 | 1.31 | 1.52 |




| | O. Bisphosphonates | | | Denosumab | | | Teriparatide | | | Strontium | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HR | 0.96 | 0.98 | 1.04 | 1.77 | 1.89 | 2.02 | 1.27 | 1.32 | 1.48 | 1.19 | 1.44 | 1.50 |
| Low CI | 0.78 | 0.78 | 0.77 | 0.25 | 0.26 | 0.28 | 0.59 | 0.58 | 0.59 | 0.82 | 0.96 | 0.90 |
| Upper CI | 1.18 | 1.24 | 1.41 | 12.6 | 13.6 | 14.6 | 2.71 | 3.00 | 3.68 | 1.74 | 2.15 | 2.51 |

**Fig. 2** Risk of VTE associated to each AOM versus alendronate (hazard ratio) using 90 and 30 days as a gap (sensitivity analysis), in CPRD and BIFAP. CPRD: Clinical Practice Research Datalink; BIFAP: Base de datos para la investigación Farmacoepidemiológica en Atención Primaria; O. Bisphosphonates: Other oral Bisphosphonates; HR, hazard ratio; CI, 95% confidence interval; 180d/90d/30d. days of interval between prescriptions durations in main (180 days) and sensitivity analysis (90 and 30 days)

lower among patients who initiated strontium ranelate therapy from 2011 onwards versus before 2011. In particular, the recent fractures (proxy for immobilization) and use of anticoagulant drugs was much higher among patients initiating therapy from 2011 onwards than before 2011, while the VTE history seemed similar in both periods. The same was observed among patients treated with bisphosphonates from 2011 onwards. This, together with the older age and less use of HRT from 2011 onwards, may suggest a higher baseline risk of VTE among overall patients treated with AOM in the latter years of the study. These data must be interpreted with caution since low population sizes from 2011 was analyzed. Formal studies using big population sizes after contraindication in 2012 and restrictions in 2014 confirmed a decrease of VTE risk factors after the minimization measures disseminated to reduce the cardiovascular risk in 2014 among patients treated with strontium ranelate [21].

Nonetheless, in the current study the risk of VTE associated with strontium ranelate was not different from alendronate, both before or from 2011 onwards.

The increased risk of VTE previously reported has been described in comparison to AOM-naïve patients, in which the risk of VTE is higher among strontium ranelate or alendronate users than non-osteoporotic patients in an observational study in CPRD [22]. However, that risk did not differ by type of drug among patients under anti-osteoporosis therapy [22], nor was it higher during exposure versus non-exposure periods in patients with VTE that were ever exposed to strontium ranelate [23]. These studies are in agreement with our finding of no statistically significant differences among the various types of AOM investigated. Recently, no difference in the risk of VTE between strontium ranelate and alendronate has been observed among patients without contraindications in a multi-database study [24].

In the current observational study, we tried to avoid confounding by indication by comparing patients with the same indication, i.e., osteoporosis or prescription of an AOM. In order to control by other potential confounders, baseline morbidity and medication were measured and revealed a pattern of older patients among the strontium than alendronate cohort, with more prevalence of calcium-D in CPRD and recent fractures (in both databases). Small differences of adjusted versus crude risk estimates were observed, but it cannot be ruled out that unmeasured confounders, such as severity of osteoporosis, might still be playing a role in the risk estimation.

Regarding biological plausibility, no clear pharmacological mechanism which could link strontium ranelate to thromboembolism has been evidenced. In clinical trials, an increase in factor VIII level and a concomitant decrease in activated partial thromboplastin time were observed, which tend to a more thrombotic state. Nevertheless, the clinical relevance of these changes is not clear, especially for older patients [4].

Since no pharmacological mechanism for triggering VTE was known for strontium ranelate, we arbitrarily selected a long risk window of 180 days, in addition to performing sensitivity analyses using two shorter different time intervals (i.e., 30 and 90 days) in order to understand the duration of potential thrombosis effect of each drug type and explore the potential mechanism. No risk associated with any AOM versus alendronate was observed in sensitivity analyses although results were heterogeneous in CPRD and BIFAP. The risk of VTE with strontium ranelate decreased as the interval was reduced from 180 to 30 days in CPRD, and the opposite was true in BIFAP where the risk for all AOM was stronger with the reduction of interval (suggesting a short-term effect).

It may happen that the comparison of type of drugs would have required the use of different risk windows according to the expected pharmacological mechanism (and potentially different duration of thrombosis effect). However, no VTE pharmacological mechanism was known for the studied drugs, so similar intervals were utilized for all exposures studied.

**Table 3** Risk of VTE associated to each AOM versus alendronate (hazard ratio) in sex strata and calendar periods (before 2011 and from 2011 onwards), in CPRD and BIFAP

| | CPRD | | | | | BIFAP | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patients at risk | No. VTE cases | HR[a] | 95%CI | | Patients at risk | No. VTE cases | HR[a] | 95%CI | |
| Before 2011 | | | | | | | | | | |
| Alendronate | 103,800 | 1420 | Ref. | – | – | 33,948 | 179 | Ref. | – | – |
| Other bisphosphonates | 27,999 | 354 | 1.06 | 0.94 | 1.19 | 34,730 | 162 | 0.93 | 0.75 | 1.15 |
| Strontium ranelate | 2389 | 21 | 0.93 | 0.60 | 1.44 | 7016 | 26 | 1.09 | 0.72 | 1.64 |
| Teriparatide | 7 | 0 | – | – | – | 856 | 6 | 1.64 | 0.72 | 3.72 |
| Denosumab | 1 | 0 | – | – | – | 0 | 0 | NA | NA | NA |
| From 2011 onwards | | | | | | | | | | |
| Alendronate | 23,321 | 224 | Ref. | – | – | 2234 | 7 | Ref. | – | – |
| Other bisphosphonates | 1008 | 11 | 1.09 | 0.59 | 2.00 | 2864 | 13 | 1.56 | 0.62 | 3.94 |
| Strontium ranelate | 656 | 4 | 0.74 | 0.27 | 1.99 | 962 | 6 | 1.98 | 0.65 | 6.01 |
| Teriparatide | 0 | 0 | – | – | – | 431 | 1 | 0.54 | 0.07 | 4.43 |
| Denosumab | 28 | 1 | 3.49 | 0.49 | 24.96 | 293 | 1 | 1.44 | 0.17 | 11.81 |
| *p* for period interaction | | | $p = 0.99$ | | | | | $p = 0.08$ | | |
| Men | | | | | | | | | | |
| Alendronate | 25,819 | 447 | Ref. | – | – | 3834 | 29 | Ref. | – | – |
| Other bisphosphonates | 5244 | 76 | 0.87 | 0.68 | 1.10 | 3862 | 36 | 1.25 | 0.77 | 2.05 |
| Strontium ranelate | 470 | 4 | 0.74 | 0.28 | 1.98 | 787 | 5 | 1.19 | 0.46 | 3.08 |
| Teriparatide | 1 | 0 | – | – | – | 250 | 2 | 1.29 | 0.30 | 5.51 |
| Denosumab | 4 | 0 | – | – | – | 29 | 1 | 9.13 | 1.21 | 68.95 |
| Women | | | | | | | | | | |
| Alendronate | 101,302 | 1197 | Ref. | – | – | 32,348 | 157 | Ref. | – | – |
| Other bisphosphonates | 23,763 | 289 | 1.11 | 0.97 | 1.26 | 33,732 | 139 | 0.90 | 0.71 | 1.13 |
| Strontium ranelate | 2575 | 21 | 0.93 | 0.61 | 1.44 | 7191 | 27 | 1.20 | 0.79 | 1.81 |
| Teriparatide | 6 | 0 | – | – | – | 1037 | 5 | 1.27 | 0.52 | 3.11 |
| Denosumab | 25 | 1 | 3.94 | 0.55 | 28.03 | 264 | 0 | 0.00 | – | – |
| *p* for sex interaction | | | $p = 0.19$ | | | | | $p = 0.83$ | | |
| 50–59 years | | | | | | | | | | |
| Alendronate | 15,249 | 141 | Ref. | – | – | 8200 | 7 | Ref. | – | – |
| Other bisphosphonates | 3488 | 33 | 1.12 | 0.76 | 1.63 | 9048 | 17 | 1.97 | 0.81 | 4.78 |
| Strontium ranelate | 173 | 2 | 2.21 | 0.55 | 9.00 | 1878 | 1 | 0.84 | 0.10 | 6.89 |
| Teriparatide | 0 | 0 | – | – | – | 151 | 0 | 0.00 | – | – |
| Denosumab | 2 | 0 | – | – | – | 51 | 0 | 0.00 | – | – |
| 60–69 years | | | | | | | | | | |
| Alendronate | 29,537 | 342 | Ref. | – | – | 10,387 | 35 | Ref. | – | – |

**Table 3** (continued)

| | CPRD | | | | | BIFAP | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patients at risk | No. VTE cases | HR[a] | 95%CI | | Patients at risk | No. VTE cases | HR[a] | 95%CI | |
| Other bisphosphonates | 6813 | 73 | 1.00 | 0.77 | 1.28 | 11,069 | 35 | 0.93 | 0.58 | 1.49 |
| Strontium ranelate | 371 | 3 | 1.14 | 0.37 | 3.57 | 2215 | 5 | 1.11 | 0.43 | 2.86 |
| Teriparatide | 2 | 0 | – | – | – | 273 | 2 | 3.06 | 0.72 | 12.96 |
| Denosumab | 5 | 0 | – | – | – | 86 | 0 | 0.00 | – | – |
| 70–79 years | | | | | | | | | | |
| Alendronate | 42,037 | 608 | Ref. | – | – | 11,948 | 89 | Ref. | – | – |
| Other bisphosphonates | 9685 | 144 | 1.13 | 0.94 | 1.36 | 11,963 | 82 | 0.96 | 0.71 | 1.30 |
| Strontium ranelate | 776 | 7 | 0.91 | 0.43 | 1.91 | 2452 | 13 | 1.10 | 0.61 | 1.98 |
| Teriparatide | 4 | 0 | – | – | – | 505 | 3 | 1.35 | 0.42 | 4.31 |
| Denosumab | 8 | 0 | – | – | – | 77 | 1 | 5.31 | 0.73 | 38.60 |
| 80–89 years | | | | | | | | | | |
| Alendronate | 40,298 | 553 | Ref. | – | – | 5647 | 55 | Ref. | – | – |
| Other bisphosphonates | 9021 | 115 | 0.96 | 0.79 | 1.80 | 5514 | 41 | 0.78 | 0.52 | 1.17 |
| Strontium ranelate | 1725 | 13 | 0.78 | 0.45 | 1.35 | 1433 | 13 | 1.35 | 0.73 | 2.48 |
| Teriparatide | 1 | 0 | – | – | – | 358 | 2 | 0.82 | 0.20 | 3.38 |
| Denosumab | 14 | 1 | 6.44 | 0.90 | 46.1 | 79 | 0 | 0.00 | – | – |
| *p* for age interaction | | | $p = 0.51$ | | | | | $p = 0.21$ | | |

[a] HR were adjusted as per protocol by age, sex, history of VTE, cancer, peripheral arterial disease, vein insufficiency or phlebitis, recent fractures (recorded during 2 months before therapy initiation as a proxy for patients who are bed-bound), and hormone replacement therapy prescribed during the year before therapy initiation, BMI and current smoking as recorded during the year of therapy initiation

The strengths of the current study include the large number of patients within exposure cohorts for bisphosphonates and strontium ranelate and the diversity of patients studied, in particular, elderly and more unwell patients which are not represented in a RCT setting. Our study is representative of the primary care treatment routine. The external validity or data was also showed by the similar incidence of VTE observed in CPRD (5.6 per 1000 patient-years) with the one published for patients dispensed with strontium ranelate during the first 12 months after starting treatment in the UK (6.24 per 1000 patient-years; mean age was 73.3 years [SD 11.45]) [25]. Unfortunately, no external source is available to validate incidence of VTE in strontium ranelate users in Spain. But comparing BIFAP with UK data, the lower incidence in BIFAP (2.8 per 1000 patient-years) may be the expected after considering the five time lower prevalence of history of VTE in BIFAP versus CPRD.

Other strengths include the comparison among patients prescribed with any AOM (hence avoiding confounding by indication), the new estimation of VTE risk in Spanish population treated with AOM, and the similar methodological protocol allowing for comparison of results from two databases and countries.

Some limitations may be mentioned. Confounding by severity of osteoporosis could not be ruled out. Also, we did not validate compliance to AOM treatment against physician or patient. One-year cessation of AOM treatment has been reported between 51 and 61% in the literature [26–28]. However, we only studied the first period of continuous refill prescriptions and a similar method to build treatment periods for all the compared exposures, expecting to minimize the potential impact of differential compliance (and other potential source of misclassification derived from the assumption taken to build the treatment episodes) according to type of AOM compared.

Furthermore, we did not validate the recorded diagnosis of VTE nor its date. However, we selected patients with anticoagulant treatment recorded on VTE recorded date or 60 days after in order to increase the predictive value of the episodes and their dates. Also, a high positive predictive value of deep vein thrombosis or pulmonary embolism records in CPRD (84–94%) was estimated previously in an information validation against hospital investigations, a death certificate, or physician [29, 30]. Also, in a post-hoc manual review of the clinical profiles of the 401 patients with a recorded treated VTE in BIFAP, we observed that 2.2% of them ($N = 9$) had a discharge or referral letter refuting the VTE episode. After excluding those non-cases, the final interpretation of the study did not change, i.e., no significant increased risk was associated with any AOM versus alendronate. The indication of treatment was not evaluated.

In conclusion, after assessment of the clinical information recorded during the first continuous treatment episode of other oral bisphosphonates, strontium ranelate, teriparatide, or denosumab (ranging a median duration of 7 months to 1.74 years) of around 240,000 patients attending their primary care physician in Spain and the UK, the risk of VTE did not differ versus alendronate. This result was irrespective of sex, calendar period, or length of risk windows used.

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**Compliance with ethical standards**

**Competing interest** EMM, SH, SK, AAG, AD, and ALG, declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

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The interpretation and conclusions contained in this study are those of the author/s alone.

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