Risk of venous thromboembolism amongst 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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Mini-abstract

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.

Abstract

Purpose/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) amongst 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, 2,035/159,209 (1.28%) in CPRD, and 401/83,334 (0.48%) in BIFAP had VTE. Compared to alendronate, 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; and 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.

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 ischaemic 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 amongst 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 amongst actual users of different AOM in a clinical practice setting is hence yet unknown.

We therefore aimed to compare the risk of VTE amongst 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 >7 million patients, chosen to be 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 paediatricians (PCP) from 9 different regions in Spain (9). 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% paediatricians), on patient demographics, clinical events (coded through ICPC medical terms dictionary, free text notes, specialist referrals and laboratory test results of around 4 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 two last 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 prescriptions 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 180 days or more 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 1 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. 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 1,000 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.

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% versus 5.2% in alendronate cohort). As there were only 7 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 ≥80y), 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 alendronate users (1.4%).

The time to follow-up and incidence rates of VTE by AOM cohort and database 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 1,000 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 HRs 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 vs. 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 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 69.8y vs. 68.4y 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 3 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.

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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 versus 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 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 trials 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 minimise 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 SR in the studied populations. At a glance, the crude prevalence of VTE risk factors was not 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 populations 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 SR or alendronate users than non-osteoporotic patients in an observational study in CPRD (23). However, that risk did not differ by type of drug among patients under anti-osteoporosis therapy (23), nor was it higher during exposure versus non-exposure periods in patients with VTE that were ever exposed to SR (24). 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 (22).

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 SR, 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 SR decreased as the interval was reduced from 180 days 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.

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 SR 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).

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Unfortunately, no external source is available to validate incidence of VTE in SR 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 re-fill 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 DVT or PE 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.

Competing interest statement

Acknowledgements:

Figure 1. Treatment episodes construction.

Figure 1 footnote: Rx: prescription duration; 180d: 180 days

Figure 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.

Figure 2 footnote: 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)

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

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Mini-abstract

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.

Abstract

Purpose/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) amongst 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, 2,035/159,209 (1.28%) in CPRD, and 401/83,334 (0.48%) in BIFAP had VTE. Compared to alendronate, 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; and 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.

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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 ischaemic 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 amongst 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 amongst actual users of different AOM in a clinical practice setting is hence yet unknown.

We therefore aimed to compare the risk of VTE amongst 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 >7 million patients, chosen to be 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 paediatricians (PCP) from 9 different regions in Spain (9). 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% paediatricians), on patient demographics, clinical events (coded through ICPC medical terms dictionary, free text notes, specialist referrals and laboratory test results of around 4 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 two last 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 prescriptions 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 180 days or more 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 1 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. 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 1,000 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.

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% versus 5.2% in alendronate cohort). As there were only 7 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 ≥80y), 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 alendronate users (1.4%).

The time to follow-up and incidence rates of VTE by AOM cohort and database 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 1,000 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 HRs 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 vs. 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 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 69.8y vs. 68.4y 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 3 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 versus 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 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 trials 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 minimise 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 SR in the studied populations. At a glance, the crude prevalence of VTE risk factors was not 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 populations 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 SR or alendronate users than non-osteoporotic patients in an observational study in CPRD (23). However, that risk did not differ by type of drug among patients under anti-osteoporosis therapy (23), nor was it higher during exposure versus non-exposure periods in patients with VTE that were ever exposed to SR (24). 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 (22).

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 SR, 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 SR decreased as the interval was reduced from 180 days 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.

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 SR 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).

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Unfortunately, no external source is available to validate incidence of VTE in SR 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 re-fill 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 DVT or PE 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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7 Figure 1. Treatment episodes construction.
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17 Figure 1 footnote: Rx: prescription duration; 180d: 180 days
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5 Figure 2. Risk of VTE associated to each AOM versus alendronate (Hazard Ratio) using 90 and 30 days as
6 a gap (Sensitivity analysis), in CPRD and BIFAP.
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15 Figure 2 footnote: CPRD: Clinical Practice Research Datalink; BIFAP: Base de datos para la investigación
16 Farmacoepidemiológica en Atención Primaria; O. Bisphosphonates: Other oral Bisphosphonates; HR: Hazard ratio;
17 CI: 95% Confidence Interval; 180d/90d/30d: days of interval between prescriptions durations in main (180 days)
18 and sensitivity analysis (90 and 30 days)
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Table 1

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

CPRD		Alendronate N=127121		Other biphosphonates N=29007		Strontium ranelate N=3045		Denosumab N=29		Teriparatide N=7	
		No.	%	No.	%	No.	%	No.	%	No.	%
Females		101302	79.7	23763	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)	
	50-59y	15249	12.0	3488	12.0	173	5.7	2	6.9	0	0.0
	60-69y	29537	23.2	6813	23.5	371	12.2	5	17.2	2	28.6
	70-70y	42037	33.1	9685	33.4	776	25.5	8	27.6	4	57.1
	>=80y	40298	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	2,389	78.5	1	3.5	7	100
	≥2011	23,321	18.4	1,008	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		19150	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	68107	53.6	15687	54.1	1476	48.5	12	41.4	4	57.1
	mild	22625	17.8	5853	20.2	520	17.1	4	13.8	0	0.0
	moderate	18355	14.4	3699	12.8	499	16.4	3	10.3	1	14.3
	severe	18034	14.2	3768	13.0	550	18.1	10	34.5	2	28.6
Other comedication											
Other anti-osteoporosis medication		320	0.3	413	1.4	12	0.4	0	0.0	0	0.0
Calcium-Vitamin-D		31224	24.6	8178	28.2	1084	35.6	20	69.0	6	85.7
Glucocorticoids		51830	40.8	12058	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

		Alendronate No.	%	Other biphosphonates No.	%	Strontium ranelate No.	%	Denosumab No.	%	Teriparatide No.	%
Oral anticoagulant drugs		10641	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	20701	16.3	4598	15.9	557	18.3	6	20.7	2	28.6
	25-29.9	16335	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	76524	60.2	18109	62.43	1858	61.0	11	37.9	3	42.9
Current smoker	No	56179	44.2	12610	43.5	1418	46.6	13	44.8	4	57.1
	Yes	11222	8.8	2407	8.3	217	7.1	1	3.5	0	0.0
	Missing	59720	47.1	13990	48.2	1410	46.3	15	51.7	3	42.9

BIFAP		Alendronate N=36182		Other biphosphonates N=37594		Strontium ranelate N=7978		Denosumab N=293		Teriparatide N=1287	
		No.	%	No.	%	No.	%	No.	%	No.	%
Females		32348	89.4	33732	89.7	7191	90.1	264	90.1	1037	80.6
Age at therapy initiation Mean (sd)		68.67; SD 10.13		68.19; SD 10.09		68.83; SD 10.58		70.90; SD 10.71		73.00; SD 9.78	
	50-59y	8200	22.7	9048	24.1	1878	23.5	51	17.4	151	11.7
	60-69y	10387	28.7	11069	29.5	2215	27.8	86	29.4	273	21.2
	70-70y	11948	33.0	11963	31.8	2452	30.7	77	26.3	505	39.2
	>=80y	5647	15.6	5514	14.7	1433	18.0	79	27.0	358	27.8
Calendar start year	<2011	33948	93.8	34730	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
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	12292	34.0	13719	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	21101	58.3	22217	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	24575	67.9	25720	68.4	5469	68.6	206	70.3	902	70.1

Table 2   Click here to download Table Table 2_r1.docx ⬇

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	127121	29007	3045	29	7
VTE treated	1644	365	25	1	0
50-59y	141	33	2	0	0
60-69y	342	73	3	0	0
70-70y	608	144	7	0	0
>=80y	553	115	13	1	0
Incidence rate per 1000 person-years	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)	-	-
>=80y	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	36182	37594	7978	293	1287
VTE treated	186	175	32	1	7
50-59y	7	17	1	0	0
60-69y	35	35	5	0	2
70-79y	89	82	13	1	3
>=80y	55	41	13	0	2
Incidence rate per 1,000 person-years	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)

50-59y	0.42(0.20-0.88)	0.95(0.59-1.53)	0.42(0.06-3.00)	0(-)	0(-)
60-69y	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)
70-79y	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)
>=80y	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)

[a]Hazard ratio (HR) were adjusted as per protocol by age, sex, history of VTE, cancer, peripheral arterial disease, vein insufficiency or phlebitis, recent fractures (recorded during two 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. VTE: Venous thromboembolism including deep vein thrombosis and pulmonary embolism (Annex I). AOM: anti-osteoporosis medication.

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

Table 3

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	2,389	21	0.93	0.60	1.44	7,016	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.	-	-	2,234	7	Ref.	-	-
Other Bisphosphonates	1,008	11	1.09	0.59	2.00	2,864	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.	-	-	3,834	29	Ref.	-	-
Other Bisphosphonates	5,244	76	0.87	0.68	1.10	3,862	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	1,197	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	2,575	21	0.93	0.61	1.44	7,191	27	1.20	0.79	1.81
Teriparatide	6	0	-	-	-	1,037	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		
50-59y										
Alendronate	15,249	141	Ref.	-	-	8,200	7	Ref.	-	-
Other Bisphosphonates	3,488	33	1.12	0.76	1.63	9,048	17	1.97	0.81	4.78
Strontium Ranelate	173	2	2.21	0.55	9.00	1,878	1	0.84	0.10	6.89
Teriparatide	0	0	-	-	-	151	0	0.00	-	-
Denosumab	2	0	-	-	-	51	0	0.00	-	-
60-69y										
Alendronate	29,537	342	Ref.	-	-	10,387	35	Ref.	-	-
Other Bisphosphonates	6,813	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	2,215	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	-	-
70-79y										
Alendronate	42,037	608	Ref.	-	-	11,948	89	Ref.	-	-
Other Bisphosphonates	9,685	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	2,452	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
80-89y										
Alendronate	40,298	553	Ref.	-	-	5,647	55	Ref.	-	-
Other Bisphosphonates	9,021	115	0.96	0.79	1.80	5,514	41	0.78	0.52	1.17
Strontium Ranelate	1,725	13	0.78	0.45	1.35	1,433	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 two 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.

Figure 1   Click here to download Figure Fig 1.JPG

Figure 1

Figure 2

CPRD — -180d · x 90d · • 30d

		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

BIFAP — -180d · x 90d · • 30d

		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
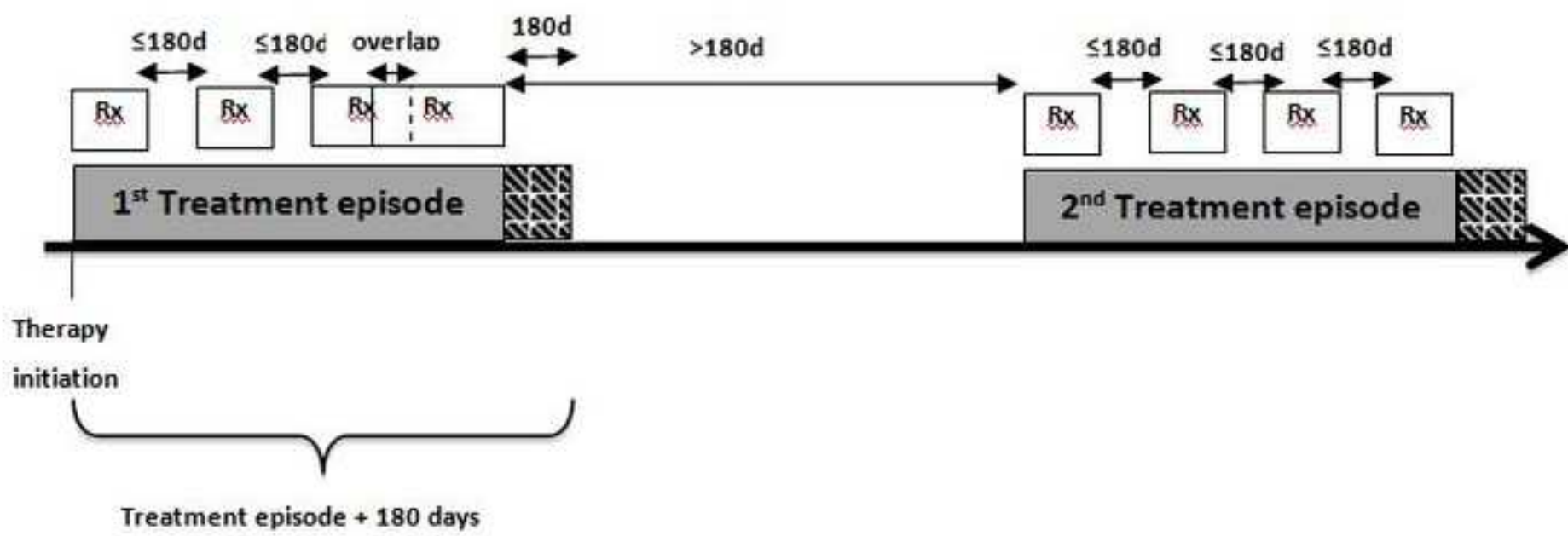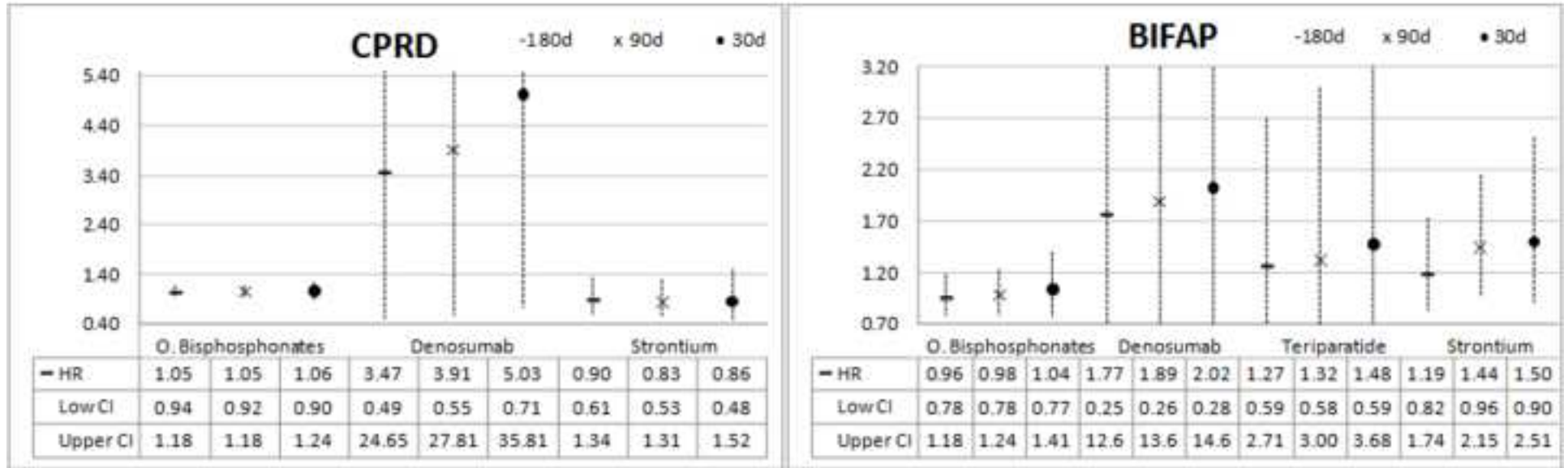
Annex I.

Table 1. Deep vein thrombosis or Pulmonary embolism READ term used in CPRD, and ICPC term and string text used in BIFAP.

READ Term description	READ codes
Pulmonary embolism	G401.00
Pulmonary embolus	G401.12
Post operative pulmonary embolus	G401000
Recurrent pulmonary embolism *	G401100
Deep vein phlebitis and thrombophlebitis of the leg	G801.00
Deep vein thrombosis	G801.11
Deep vein thrombosis, leg	G801.12
DVT - Deep vein thrombosis	G801.13
Thrombophlebitis of the femoral vein	G801600
Deep vein thrombophlebitis of the leg unspecified	G801B00
Deep vein thrombosis of leg related to air travel	G801C00
Deep vein thrombosis of lower limb	G801D00
Deep vein thrombosis of leg related to intravenous drug use	G801E00
Recurrent deep vein thrombosis	G801G00
Deep vein phlebitis and thrombophlebitis of the leg NOS	G801z00
Post operative deep vein thrombosis	SP12200
[V] Personal history deep vein thrombosis *	ZV12800
[V] Personal history DVT- deep vein thrombosis *	ZV12811
[V] Personal history of pulmonary embolism *	ZV12900
Thromboembolic pulmonary hypertension *	G41y100
ICPC-BIFAP Term description	**ICPC-BIFAP codes**
EMBOLISMO (ARTERIAL) PULMONAR	K93.1
INFARTO PULMONAR (EMBOLISM.)	K93.2
TROMBOSIS PULMONAR (EMBOLIA)	K93.3
TROMBOEMBOLISMO PULMONAR	K93.4
TVP (TROMB. VENOSA PROFUNDA)	K94.6
TROMBOSIS VENOSA PROFUNDA EEII	K94.15
String text recorded in BIFAP Diagnosis files	**Search pattern**
TEP	OWA
T.E.P	LIKE
EMBOL PULMON	MW1
TROMBOEMBO PULM	MW1
TROMB PULMON	MW1
INFART PULMON	MW1
TVP	OWA
TROMB VEN PROF	MW3

Table 2. Distribution of time from therapy initiation to VTE and stop reasons to follow-up during the first treatment episode by AOM in CPRD and BIFAP.

	Alendronate	Other Bisphosphonates	Strontium Ranelate	Denosumab	Teriparatide
CPRD					
Number of patients at risk	127121	29007	3045	29	7
Median time of follow-up (range)	1.74y (1d-14.30y)	1.68y (1d-16.22y)	0.92y (1d-9.06y)	1.39y (65d-3.59y)	1.51y (208d-1.82y)
Stop reason:					
VTE treated	1644	365	25	1	0
VTE untreated	757	170	12	0	0
Switching	9,147	8,704	448	1	0
Discontinuation (180d without refill)	54,462	10,668	1,437	9	7
End of study	32,722	2,858	355	15	0
Dead	18,414	4,188	514	3	0
Lost to follow-up	9,975	2,054	254	0	0
BIFAP					
Number of patients at risk	36182	37594	7978	293	1287
Median time of follow-up (range)	1.29y (1d-12.04y)	1.31y(1d-11.42)	0.82y(1d-8.45y)	0.61y(1d-2.16y)	1.02y(1d-3.99y)
Stop reason:					
VTE treated	186	175	32	1	7
VTE untreated	53	51	8	0	0
Switching	3876	3172	1068	4	238
Discontinuation (180d without refill)	19,924	19,951	4,914	32	611
End of study	2,075	2,875	247	217	168
Dead	1,094	1,051	175	5	36
Lost to follow-up	8,974	34	1,534	10319	227

Table 3. Baseline characteristics and number of VTE cases according to AOM exposure cohort* in CPRD and BIFAP before 2011, and from 2011 onwards.

CPRD	Before 2011¥								From 2011 onwards									
	Alendronate N=103800		Other bisphosphonates N=27999		Strontium ranelate N=2389		Teriparatide N=7		Alendronate N=23321		Other bisphosphonates N=1008		Strontium ranelate N=656		Denosumab N=28		Teriparatide N=0	
	No.	%	No.	%	No.	%	No.	%										
Females	83493	80.4	22995	82.1	2046	85.6	6	85.7	17809	76.4	768	76.2	529	80.6	24	85.7	-	-
Age at therapy initiation Mean (St.Dev.)	73.2 (10.5)		73.3 (10.5)		78.9 (10.3)		72.9 (8.3)		74.3 (10.7)		73.7 (10.8)		80.7 (10.2)		77.8 (10.6)		-	
Age at therapy initiation																		
50-59y	12795	12.3	3371	12.0	148	6.2	0	0.0	2454	10.5	117	11.6	25	3.8	2	7.1	-	-
60-69y	24226	23.3	6562	23.4	289	12.1	2	28.6	5311	22.8	251	24.9	82	12.5	5	17.9	-	-
70-70y	34778	33.5	9387	33.5	629	26.3	4	57.1	7259	31.1	298	29.6	147	22.4	8	28.6	-	-
>=80y	32001	30.8	8679	31.0	1323	55.4	1	14.3	8297	35.6	342	33.9	402	61.3	13	46.4	-	-
VTE before therapy initiation	5263	5.1	1515	5.4	129	5.4	0	0.0	1371	5.9	63	6.2	30	4.6	3	10.7	-	-
Risk factors for VTE																	-	-
Vein insufficiency or phlebitis	15427	14.9	4102	14.7	367	15.4	1	14.3	3723	16.0	171	17.0	100	15.2	7	25.0	-	-
HRT the year before therapy initiation	5699	5.5	1600	5.7	56	2.3	1	14.3	337	1.4	15	1.5	9	1.4	0	0	-	-
Recent fractures	5584	5.4	1516	5.4	339	14.2	0	0.0	2266	9.7	108	10.7	153	23.3	3	10.7	-	-
Charlson index none	56264	54.2	15193	54.3	1148	48.1	4	57.1	11843	50.8	494	49.0	328	50.0	11	39.3	-	-
mild	18896	18.2	5702	20.4	418	17.5	0	0.0	3729	16.0	151	15.0	102	15.5	4	14.3	-	-
moderate	14393	13.9	3520	12.6	394	16.5	1	14.3	3962	17.0	179	17.8	105	16.0	3	10.7	-	-
severe	14247	13.7	3584	12.8	429	18.0	2	28.6	3787	16.2	184	18.3	121	18.4	10	35.7	-	-
Other co-medication																	-	-
Other anti-osteoporosis medication	303	0.3	412	1.5	9	0.4	0	0.0	17	0.1	1	0.1	3	0.5	0	0	-	-
Calcium-Vitamin-D	25036	24.1	7837	28.0	861	36.0	6	85.7	6188	26.5	341	33.8	223	34.0	20	71.4	-	-
Glucocorticoids	41843	40.3	11618	41.5	662	27.7	2	28.6	9987	42.8	436	43.3	156	23.8	13	46.4	-	-

	Alendronate No.	%	Other bisphosphonates No.	%	Strontium ranelate No.	%	Teriparatide No.	%	Alendronate No.	%	Other bisphosphonates No.	%	Strontium ranelate No.	%	Denosumab No.	%	Teriparatide No.	%
Heparin	820	0.8	184	0.7	24	1.0	0	0.0	663	2.8	51	5.1	22	3.4	2	7.1	-	-
Oral anticoagulant drugs	8296	8.0	2312	8.3	198	8.3	0	0.0	2345	10.1	127	12.6	58	8.8	6	21.4	-	-
BMI (Kg/m^2) <18.5	2449	2.4	689	2.5	109	4.6	0	0.0	633	2.7	29	2.9	24	3.7	1	3.6	-	-
18.5-24.9	16340	15.7	4415	15.8	440	18.4	2	28.6	4361	18.7	183	18.2	117	17.8	5	17.9	-	-
25-29.9	12769	12.3	3275	11.7	251	10.5	2	28.6	3566	15.3	154	15.3	65	9.9	4	14.3	-	-
30-34.9	5604	5.4	1401	5.0	113	4.7	0	0.0	1642	7.0	72	7.1	31	4.7	5	17.9	-	-
35-39.9	1737	1.7	445	1.6	23	1.0	0	0.0	535	2.3	36	3.6	4	0.6	2	7.1	-	-
>=40	745	0.7	186	0.7	8	0.3	0	0.0	216	0.9	13	1.3	2	0.3	0	0.0	-	-
Missing	64156	61.8	17588	62.8	1445	60.5	3	42.9	12368	53.0	521	51.7	413	63.0	11	39.3	-	-
Current smoker No	45177	43.5	12127	43.3	1140	47.7	4	57.1	11002	47.2	483	47.9	278	42.4	12	42.9	-	-
Yes	8876	8.6	2302	8.2	178	7.5	0	0.0	2346	10.1	105	10.4	39	5.9	1	3.6	-	-
Missing	49747	47.9	13570	48.5	1071	44.8	3	42.9	9973	42.8	420	41.7	339	51.7	15	53.6	-	-
VTE treated cases	1420	1.4	354	1.3	21	0.9	0	0.0	224	1.0	11	1.1	4	0.6	1	3.6	-	-

	Before 2011								From 2011 onwards									
BIFAP	Alendronate N=33948		Other bisphosphonates N=34730		Strontium ranelate N=7016		Teriparatide N=856		Alendronate N=2234		Other bisphosphonates N=2864		Strontium ranelate N=962		Denosumab N=293		Teriparatide N=431	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Females	30486	89.8	31287	90.1	6375	90.9	719	84.0	1862	83.3	2445	85.4	816	84.8	264	90.1	318	73.8
Age at therapy initiation Mean (St.Dev.)	68.6 (10.1)		68.1(10.0)		68.6(10.4)		73.3(9.5)		70.1(10.6)		69.0(10.7)		70.3(11.8)		70.9(10.7)		72.5(10.3)	
Age at therapy initiation																		
50-59y	7763	22.9	8400	24.2	1655	23.6	88	10.3	437	19.6	648	22.6	223	23.2	51	17.4	63	14.6
60-69y	9753	28.7	10223	29.4	1973	28.1	177	20.7	634	28.4	846	29.5	242	25.2	86	29.4	96	22.3
70-70y	11266	33.2	11145	32.1	2209	31.5	354	41.4	682	30.5	818	28.6	243	25.3	77	26.3	151	35.0
>=80y	5166	15.2	4962	14.3	1179	16.8	237	27.7	481	21.5	552	19.3	254	26.4	79	27.0	121	28.1
VTE before therapy initiation	453	1.3	449	1.3	83	1.2	22	2.6	53	2.4	56	2.0	15	1.6	5	1.7	18	4.2
Risk factors for VTE																		
Cancer	3302	9.7	3404	9.8	708	10.1	92	10.7	301	13.5	467	16.3	123	12.8	50	17.1	58	13.5

Peripheral arterial disease	372	1.1	392	1.1	80	1.1	29	3.4	44	2.0	50	1.7	22	2.3	4	1.4	11	2.6
Vein insufficiency or phlebitis	6420	18.9	6924	19.9	1506	21.5	181	21.1	537	24.0	655	22.9	256	26.6	88	30.0	112	26.0
HRT the year before therapy initiation	1086	3.2	1036	3.0	192	2.7	7	0.8	12	0.5	20	0.7	6	0.6	0	0.0	2	0.5
Recent fractures	2577	7.6	2574	7.4	639	9.1	168	19.6	244	10.9	233	8.1	181	18.8	43	14.7	100	23.2
Other co-medication																		
Other anti-osteoporosis medication	2562	7.5	2592	7.5	544	7.8	140	16.4	136	6.1	141	4.9	66	6.9	39	13.3	51	11.8
Calcium-Vitamin-D	11521	33.9	12614	36.3	2380	33.9	378	44.2	771	34.5	1105	38.6	329	34.2	193	65.9	164	38.1
Glucocorticoids	5794	17.1	6830	19.7	1240	17.7	212	24.8	702	31.4	931	32.5	245	25.5	94	32.1	152	35.3
Heparin	3902	11.5	4193	12.1	999	14.2	211	24.6	390	17.5	471	16.4	226	23.5	53	18.1	132	30.6
Oral anticoagulant drugs	1610	4.7	1587	4.6	289	4.1	82	9.6	173	7.7	199	6.9	72	7.5	15	5.1	53	12.3
BMI (Kg/m^2) <18.5	98	0.3	96	0.3	14	0.2	5	0.6	13	0.6	10	0.3	4	0.4	2	0.7	4	0.9
18.5-24.9	2,989	8.8	2,853	8.2	539	7.7	75	8.8	211	9.4	269	9.4	90	9.4	31	10.6	34	7.9
25-29.9	5,748	16.9	5,821	16.8	1,136	16.2	141	16.5	346	15.5	421	14.7	131	13.6	40	13.7	60	13.9
30-34.9	3,777	11.1	3,877	11.2	860	12.3	104	12.1	223	10.0	227	7.9	71	7.4	33	11.3	37	8.6
35-39.9	1,176	3.5	1,278	3.7	272	3.9	30	3.5	68	3.0	69	2.4	33	3.4	4	1.4	16	3.7
>=40	411	1.2	438	1.3	91	1.3	11	1.3	21	0.9	18	0.6	8	0.8	0	0.0	4	0.9
9999	19,749	58.2	20,367	58.6	4,104	58.5	490	57.2	1,352	60.5	1,850	64.6	625	65.0	183	62.5	276	64.0
Current smoker No	6,578	19.4	6,663	19.2	1,368	19.5	173	20.2	359	16.1	416	14.5	146	15.2	52	17.7	69	16.0
Yes	4,377	12.9	4,458	12.8	898	12.8	95	11.1	293	13.1	337	11.8	97	10.1	35	11.9	48	11.1
Missing	22,993	67.7	23,609	68.0	4,750	67.7	588	68.7	1,582	70.8	2,111	73.7	719	74.7	206	70.3	314	72.9
VTE treated cases	179	0.5	162	0.5	26	0.4	6	0.7	7	0.3	13	0.5	6	0.6	1	0.3	1	0.2

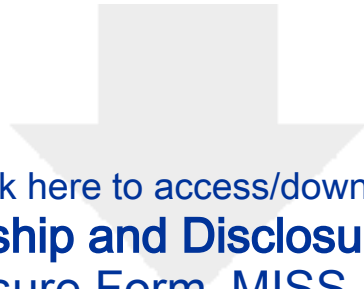*Only one denosumab user was available in CPRD and no one in BIFAP before 2011 so data are not included in this table.

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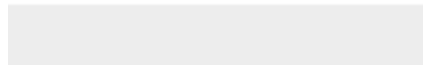
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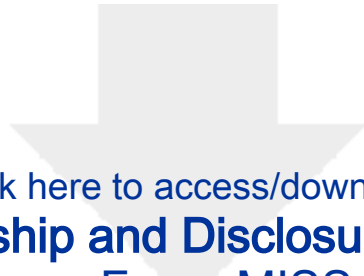
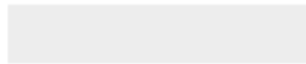Disclosure_form_MISS_EMM_AL_AA_DPA_AD_TVS_SK_AJ.pdf

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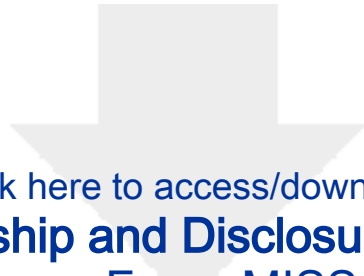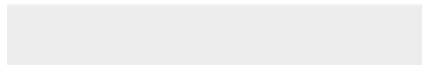**Authorship and Disclosure Form**
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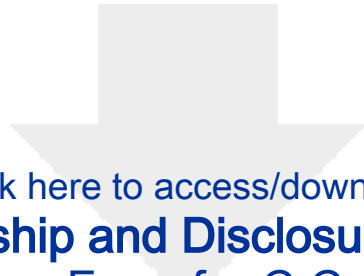**Authorship and Disclosure Form**
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