ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (7): 579-591
0114-5916/10/0007-0579/$49.95/0

Incidence of Venous Thromboembolism in Users of Strontium Ranelate

An Analysis of Data from a Prescription-Event Monitoring Study in England

Vicki Osborne,[1,2] *Deborah Layton*,[1,2] *Michael Perrio*,[1,2] *Lynda Wilton*[1,2] and *Saad A.W. Shakir*[1,2]

1 Drug Safety Research Unit, Bursledon Hall, Southampton, UK
2 University of Portsmouth, Portsmouth, UK

Abstract

Background: Strontium ranelate is indicated for the treatment of postmenopausal osteoporosis. An association between strontium ranelate and venous thromboembolism (VTE) was identified in an analysis of phase III clinical trials.

Objective: To estimate the incidence of VTE in patients within the strontium ranelate (Protelos®) Prescription-Event Monitoring (PEM) study cohort during the first 12 months after starting treatment.

Methods: Patients in this analysis were identified from dispensed prescriptions that had been issued by general practitioners (GPs) in England for strontium ranelate between October 2004 and January 2008. For each individual patient, a Green Form questionnaire was sent to their GP 12 months after the date of the first prescription issued for strontium ranelate, requesting information about the patient including start and stop dates of treatment (if stopped), age, sex, indication, any history of VTE events, reasons for stopping and whether the patient had any events since starting the drug. VTE was defined as reports of deep vein thrombosis (DVT) or pulmonary embolism (PE). The crude incidence of VTE was calculated for events that occurred during the first 12 months after starting treatment (plus 30 days after stopping), with 95% Poisson exact CIs for the whole cohort, and subsets defined by age and past history of VTE.

Results: The final analysis cohort consisted of 10 782 patients. Where specified, mean age was 73.3 years (SD 11.45) [n = 10 696]; 9833 (91.3%) were female and 934 (8.7%) were male. Where the history of VTE was specified, 233 patients (2.6%) had a history of VTE prior to starting. In the first 12-month period, there were 48 incident reports of VTE (DVT or PE) during treatment (or within 30 days of stopping) in the cohort, with 7696.89 years of exposure, giving a crude incidence rate of VTE of 6.24 cases (95% CI 4.60, 8.27) per 1000 patient-years exposed.

Conclusions: This analysis has provided an estimate of the incidence of VTE in patients treated with strontium ranelate in the general practice setting. The rate is similar to estimates in populations of similar age and corresponds to the incidence found in patients from phase III clinical studies and observational cohort studies of strontium ranelate on this topic. The crude annual incidence rate of VTE in the PEM cohort is higher than the background annual incidence rate found in the UK population, but is similar to estimates in populations of similar age and populations receiving treatment for postmenopausal osteoporosis. Also, we acknowledge the potential for underestimating the incidence in this population. Nevertheless, this analysis contributes to the ongoing postmarketing safety assessment of this product.

Background

Strontium ranelate (Protelos®) is licensed in the UK for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fracture.[1] Strontium ranelate has a dual mode of action and works by increasing bone formation and reducing bone resorption. An analysis of phase III clinical trials identified that there was an increase in the reporting of terms related to embolus and thrombosis in patients treated with strontium ranelate compared with placebo.[2] The Summary of Product Characteristics (SPC) records the annual incidence of venous thromboembolism (VTE) in phase III studies over 5 years as approximately 0.7%, with a relative risk of 1.4 (95% CI 1.0, 2.0) in patients treated with strontium ranelate compared with placebo.[1] A study investigating haemostatic safety of strontium ranelate found no increase in markers of prothrombotic activity in patients treated with strontium ranelate; however, this was a study of very short duration and on a small population.[3] Another study using a self-controlled case series approach in the General Practice Research Database (GPRD), estimated the age-adjusted rate ratio of VTE events in patients treated with strontium ranelate to be 1.1 (95% CI 0.2, 5.0); however, no information on the incidence of VTE in this population was provided.[4] Recently, another study has estimated the incidence of VTE in a population of strontium ranelate users to be 7.0 per 1000 patient-years, with an adjusted hazard ratio of 1.1 (95% CI 0.6, 2.0) for treated versus untreated osteoporotic women.[5]

VTE manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE), which are related but distinct elements of the same dynamic process.[6,7] DVT occurs after thrombus formation in the deep veins, and PE occurs if a thrombus is dislodged and blocks the pulmonary artery.[6,7] A recent study estimated the incidence of VTE in patients aged 20–79 years in UK general practice and found it to be the equivalent of 0.75 per 1000 person-years.[8] Other studies have estimated the incidence of VTE in the general population to be 0.7–1.1 per 1000 person-years.[9] Risk factors for the development of VTE include immobilization, surgery, trauma, cancer, overweight, prior VTE, and use of oral contraceptives, hormone replacement therapy and oral corticosteroids.[8,10-13]

Prescription-event monitoring (PEM) is a non-interventional observational cohort technique conducted by the Drug Safety Research Unit (DSRU) to monitor the safety of newly marketed drugs prescribed in general practice in England.[14] Cohorts often comprise over 10 000 patients, and provide details on the characteristics of patients prescribed the medication as well as clinical information, including events reported during treatment and reasons for stopping.[14]

The aims of this study were to provide an estimate of the incidence of VTE (DVT and PE) for the whole strontium ranelate PEM cohort, and to

determine any differences in incidence between subsets of patients defined by age, sex and past history of VTE.

Methods

A PEM study was conducted to monitor the safety of strontium ranelate (Protelos®) as used in general practice in England. The methods of PEM are reported elsewhere.[14] Patients were identified from dispensed prescriptions that had been issued by general practitioners (GPs) for strontium ranelate between October 2004 and January 2008. For each individual patient, a Green Form questionnaire was sent to their GP 12 months after the date of the first prescription issued for strontium ranelate requesting information, including start and stop dates of treatment (if stopped), age, sex, indication, any history of VTE events, suspected adverse drug reactions, reasons for stopping and whether the patient had any events.[1] In this analysis, cases of VTE were defined as patients that had DVT or PE recorded on the Green Form. Reports of DVT and PE were followed up for further information. Green Forms for events that may be indicative of, or potentially related to, DVT or PE (e.g. swollen ankles, cramp, leg pain/swelling) were also reviewed and followed-up as appropriate to identify whether DVT or PE were associated with these events.

Analysis

Summary statistics of the demographic characteristics of the subjects in the cohort and the subsets of patients who were cases were calculated. Differences between categorical variables were tested using Pearson's chi-squared (χ^2) test, and differences between continuous variables were tested using parametric two-sample t-tests, where appropriate. Associations between variables were examined using univariate (Mantel-Haenszel) analysis.

Time-to-Event Analysis

Eligible cases were those VTE events that occurred during treatment. Cases reported within 30 days of stopping if the patient stopped treatment were also included. If follow-up information revealed that the patient did not have DVT or PE, they were excluded as cases from the analysis, but contributed person-time. Events that had no further information from follow up were included in the final analysis, as one could not exclude the possibility that the event occurred.

In order to estimate the crude annual incidence of VTE during treatment with strontium ranelate in this population it was necessary to determine the treatment exposure period for each patient, which was calculated as the difference between the 30th day after stopping (or end of survey date for patients who had not stopped) and the start date. Where events occurred within 30 days after stopping, for those patients time at risk was censored at event date and not stop date. For missing stop dates, imputations were used that took into account the start date, reason for stopping, event dates, last prescription date, standard number of days' therapy for one prescription, latest prescription date (where more than one prescription was issued for each patient during study observation period), and median time on drug for all patients and patients who stop therapy. For patients with a VTE event, patient-years exposed was calculated up to the date of the event; for events with a missing event date, the median time to onset was used. This information was used to create the denominator of years' exposure to strontium for the whole cohort, and the crude annual incidence rate was calculated as the number of cases per 1000 patient-years exposed, with 95% Poisson exact CIs, within the first 12 months after starting treatment. If patients had both DVT and PE, only the incident event was used in the analysis of VTE events. Cumulative hazard estimates were also calculated in

1 An 'event' in PEM is defined as "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint that was considered of sufficient importance to enter in the patient's notes."

order to examine the time to event of VTE events during the treatment period. Data were stratified according to sex, age (≤69 years, 70–79 years, ≥80 years) and past history of VTE and stratum-specific incidence rates examined.

A Microsoft SQL query was used to retrieve data from the DSRU PEM database, followed by analysis using STATA 10 (StataCorp, College Station, TX, USA).

Causality Assessment and Sensitivity Analysis

For cases where follow-up information was returned by the GP, causality assessments were performed by two research staff, of which at least one was medically qualified. An assessment of probable, possible, unlikely or unassessable association to strontium ranelate was provided for each case. This assessment took account of whether the event was the reason for stopping therapy, concurrent medication, concurrent disorders, resolution of symptoms after withdrawal of strontium ranelate (with or without specific treatment of such symptoms), recurrence or absence of symptoms after re-exposure to the medicine, previous history of similar problems, or another specified cause.[15]

A sensitivity analysis was performed by restricting the analysis to include those cases assessed as probable, possible and unassessable, in order to examine the impact of such restriction on the crude annual incidence rate. Unassessable cases were incomplete cases that had insufficient information to determine if the event was related to strontium ranelate, although the event was reported to have occurred whilst taking the drug. Unlikely cases were excluded from this analysis as they were considered not to be associated with strontium ranelate use. Statistical analysis was performed using STATA 10.

Ethics

This PEM study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the CIOMS in collaboration with the WHO (2002).[16] The method of study also complies with the Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians.[17] In addition, PEM is mentioned in the 'Frequently Asked Questions' section of the General Medical Council booklet 'Confidentiality: Protecting and Providing Information' as "a professional organization that monitors the safety of medicines to which doctors should provide relevant information from patients' records wherever possible."[18]

Results

PEM Study Cohort Summary Data

Green Form questionnaires were sent to GPs for 23 832 patients and 12 642 forms were returned, giving a response rate of 53.0%. There were 1687 questionnaires classified as void (13.3% of returned questionnaires). The strontium ranelate PEM cohort consisted of 10 865 patients. For 83 patients, the information about dose indicated that they may not have been using strontium ranelate and therefore they have not been included in this current analysis. As a result, 10 782 patients were included. Patient characteristics are summarized in table I. The median duration of treatment for the whole cohort for the total analysis period was 399 days (interquartile range [IQR] 118–510).

Annual Incidence Rate of Venous Thromboembolism (VTE) in the Patient Cohort

Within the whole PEM study period, the number of reports of DVT received on the Green Form questionnaires was 44, while there were 24 reports of PE. Overall, there were 68 VTE events reported in 67 patients (59 females and 8 males), although one patient had both a DVT and PE event so this will only count as one VTE event in the analysis. No additional cases of VTE were identified from following up events that may have been indicative of DVT or PE (e.g. swollen ankles, cramp, leg pain/swelling). For eight patients receiving follow-up, the GP had indicated that tests had ruled out a diagnosis of DVT or PE, and these events were not included in the analysis (table II). There was no significant difference in

Table I. Summary characteristics of total cohort, venous thromboembolism (VTE) cases and non-cases within the first 12-month analysis period

Characteristics	VTE cases (n = 48)	Non-cases (n = 10 734)	p-Value	Total cohort (n = 10 782)
Age at start of treatment (y)				
≤69 [n (% of age specified)]	7 (14.89)	3569 (33.51)	χ^2; df(2); p = 0.012	3576 (33.43)
70–79 [n (% of age specified)]	17 (36.17)	3642 (34.20)		3659 (34.21)
≥80 [n (% of age specified)]	23 (48.94)	3438 (32.28)		3461 (32.36)
Mean age (SD)	78.36 (8.34)	73.24 (11.46)	t-test; p = 0.0011	73.26 (11.45)
Not known (% of stratum total)	1 (2.08)	85 (0.79)		86 (0.80)
Sex [n (%)]				
Males	7 (14.58)	927 (8.65)	χ^2; df(1); p = 0.145	934 (8.67)
Females	41 (85.42)	9792 (91.35)		9833 (91.33)
Not known (% of stratum total)	0	15 (0.14)		15 (0.14)
History of VTE [n (% of history of VTE specified)]				
Yes	5 (11.63)	228 (2.58)	χ^2; df(1); p < 0.0001	233 (2.62)
No	38 (88.37)	8612 (97.42)		8650 (97.38)
Not known (% of stratum total)	5 (10.42)	1894 (17.64)		1899 (17.61)

χ^2 = chi-squared; **df** = degrees of freedom; **ND** = no data; **SD** = standard deviation.

the pattern of time to onset between the DVT and PE cases (t-test; p = 0.2222). The distribution of time to onset over the total analysis period for the 59 VTE cases was as follows: median 174 days (IQR 73–326); mean 208.03 days (SD 158.00). The distribution of time to onset over the total analysis period between the 38 DVT cases and 22 PE cases was not significantly different (t-test; p = 0.2222) [DVT: median 197.5 days (IQR 74–285); mean 206.87 days (SD 161.98), vs PE: median 234 days (IQR 131–351); mean 239.32 days (SD 161.98)].

During the first 12-month analysis period, there were a total of 48 incidents of VTE events

Table II. Summary of no. of cases identified with venous thromboembolism (VTE) events in the total Prescription-Event Monitoring (PEM) study period and the incidence of VTE events in the first 12-month analysis period

Incident event	Total PEM study period[a]		First 12-month analysis period		
	no. of cases initially reported during treatment or within 30 days of stopping[b]	no. of cases during treatment or within 30 days of stopping[b,c]	no. of cases during treatment or within 30 days of stopping[b]	patient-years exposed	Annual incidence per 1000 patient-years' treatment (95% Poisson exact CI)
VTE (DVT or PE)	67[d]	59[c]	48	7696.89	6.24 (4.60, 8.27)
DVT	44[e]	38[d]	31	7700.17	4.03 (2.74, 5.71)
PE	24[f]	22[e]	17	7707.80	2.21 (1.28, 3.53)

a Because of the time at which questionnaires were returned, the total time exposed was often >12 months.

b There were three events reported in three separate patients off-drug within 30 days after stopping; one DVT occurred 12 days after stopping, and two PEs (15 and 17 days after stopping). These three patients contributed 73, 131 and 21 days of patient-time exposed and all three were included within the first 12-month analysis.

c Excluding cases which, on follow-up, had not occurred.

d One patient had DVT and PE recorded and is only counted once in the combined VTE group.

e For six patients with DVT, follow-up revealed that DVT was excluded; therefore, these patients were not included in any further analysis.

f For two patients with PE, follow-up revealed that PE was excluded; therefore, these patients are not included in any further analysis.

DVT = deep vein thrombosis; **PE** = pulmonary embolism.

(31 DVT, 17 PE events) in the PEM cohort. The characteristics of patients with a VTE (cases) and those patients who did not experience a VTE are summarized in table I. Where age was reported, being aged ≥80 years was significantly associated with being a case {χ^2; degrees of freedom (df)[2]; $p = 0.012$}; the mean age of cases being significantly greater (t-test; $p = 0.0011$) than the mean age of the rest of the cohort. Sex was not associated with being a case (χ^2; df[1]; $p = 0.145$), although there was a higher proportion of males who were cases than non-cases (14.58% vs 8.65%, respectively). A history of VTE was significantly associated with being a case (χ^2; df[1]; $p < 0.0001$). The proportion with a history of VTE observed for the cases was over 4-fold greater than that for non-cases (risk ratio 4.51 [95% CI 1.96, 10.38]).

The crude annual incidence of VTE was 6.24 cases (95% CI 4.60, 8.27) per 1000 patient-years exposed (table II). When data were stratified by age, the crude annual incidence rate of VTE in patients aged <70 years (n = 7) was 2.68 cases (95% CI 1.08, 5.52); in those aged between 70 and 79 years (n = 18) the rate was 6.47 cases (95% CI 3.77, 10.35) per 1000 patient-years exposed; and for patients aged ≥80 years (n = 23) the rate was 9.63 cases (95% CI 6.11, 14.45). Stratification of data by history of VTE revealed estimates of 32.60 cases (95% CI 10.59, 76.09) per 1000 patient-years exposed in patients with a past history of VTE, and 6.11 cases (95% CI 4.33, 8.39) per 1000 patient-years exposed in patients without a history of VTE. When the annual incidence rate between female and male cases was examined, the crude annual incidence rate of VTE in female patients (n = 41) was 5.83 cases (95% CI 4.19, 7.92) per 1000 patient-years exposed, while the corresponding estimate for male patients (n = 7) was 10.61 (95% CI 4.26, 21.85).

Time-to-Event Analysis

The distributions of times to onset for the 12-month analysis of VTE cases, for the whole PEM cohort and for the various subsets of patients, are given in figure 1.

Figures 2–5 show the cumulative hazard estimates for VTE events in the first 12 months of treatment for the whole cohort, and for the different strata defined by age, sex and past history of VTE. Whilst for each graph and each stratum the rate of VTE event appears fairly constant over time and appears to diverge between the age categories and VTE history, this separation is not significant until after month 10 (95% CI data not shown on the figures). There was statistical evidence of a difference in the estimate of time to event between strata defined by age (log rank test; $p = 0.0073$), with more cases observed than expected in the older age group (23 vs 14.72, respectively), and by past history of VTE (log rank test; $p = 0.0001$), with more cases observed than expected in those with a past history of VTE (5 vs 1.02, respectively). There was no difference between the strata defined by sex (log rank test; $p = 0.1424$). Note that the median survival time cannot be estimated using these graphs.

Causality Assessment and Sensitivity Analysis

Follow-up information was returned for 57 of the 67 patients with DVT or PE initially reported during the total PEM study period, although 8 of the 67 patients were later found to have not experienced a VTE event. When causality assessments were performed on the events, there was one event assessed as probably related to strontium ranelate and seven possibly related (see table III for information about these cases reported during the whole PEM study period). For all reports of VTE, the most commonly reported risk factors were immobility and fracture.

A sensitivity analysis was performed on cases other than those assessed as unlikely to be related to strontium ranelate, hereafter referred to as 'assessed' cases. There were 17 assessed cases in total, of which 12 occurred within the 12-month analysis period. A past history of VTE was significantly associated with being an assessed case (χ^2; df[1]; $p = 0.002$; 16.67% vs 2.60%), whilst sex was not significantly associated (χ^2; df[1]; $p = 0.966$). There was a tendency for assessed cases to be older, but not significantly so

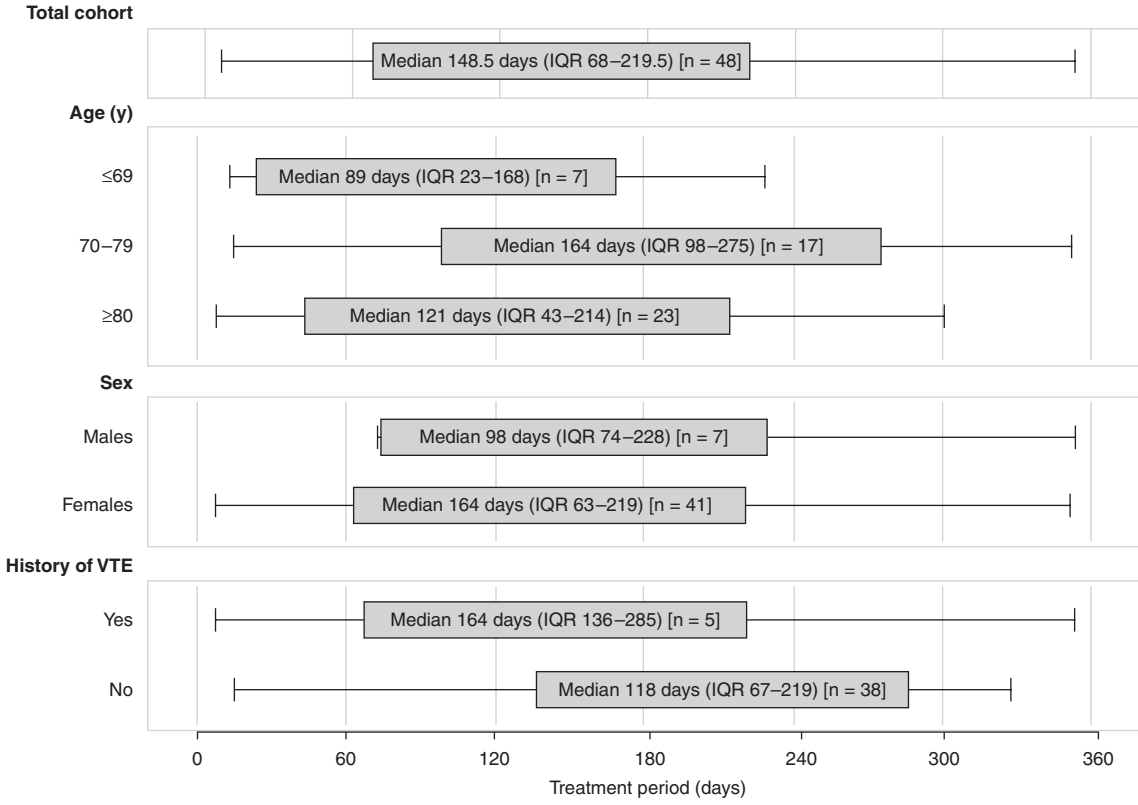

Fig. 1. Box plots of distribution of time to event for venous thromboembolism (VTE) cases within the first 12-month analysis period for the strontium ranelate cohort, by risk factor (age, sex, history of VTE). The boxes represent the interquartile range (IQR) and the whiskers represent the minimum and maximum treatment period.

(χ^2; df[1]; $p = 0.338$). When compared with the reported VTE events, there was no difference in the distribution of age, past medical history or sex (all $p > 0.05$). No significant difference was found in the distribution of time to onset of VTE events between reported and assessed events for the whole cohort (t-test; $p = 0.8562$). The crude incidence rate of VTE for assessed cases in the 12-month analysis period was 1.56 cases (95% CI 0.80, 2.72) per 1000 patient-years exposed. Incidence rates for strata defined by age, sex and past medical history of VTE were not calculated because of small numbers within each stratum. It is important to note that these assessed cases include those nine cases that could not be given a causality classification because of incomplete information, and which may not have been related to strontium ranelate.

Discussion

This analysis has estimated the crude annual incidence rate of VTE within this population of patients prescribed strontium ranelate by GPs as 6.24 cases (95% CI 4.60, 8.27) per 1000 patient-years exposed. This is similar to the recent UK GPRD study by Breart et al.,[5] in which the crude annual incidence of VTE in strontium ranelate-treated osteoporotic women ($n = 2408$) was 7.0 per 1000 patient-years. These estimates are both higher than a recent background rate estimate of the incidence of VTE in 20- to 79-year-olds in the general UK population (which comprise treated and untreated patients, and patients without osteoprosis) of 0.75 reports per 1000 patient-years.[8] However, of note is that both strontium ranelate studies consisted of mainly

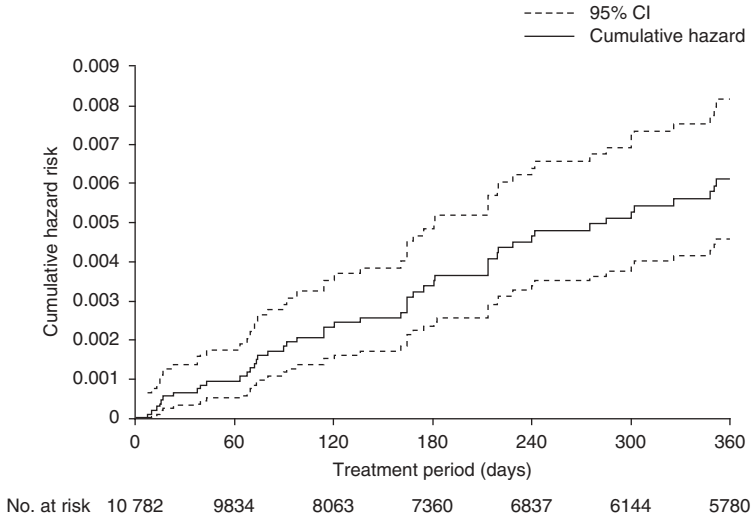

Fig. 2. Nelson-Aalen cumulative hazard plot for venous thromboembolism events (deep vein thrombosis or pulmonary embolism) in the first 12 months since starting treatment for the whole strontium ranelate cohort.

older individuals (PEM cohort: mean age 73.26 years [SD 11.45]; UK GPRD strontium ranelate cohort: mean age 74.1 years [SD 10.1]), and epidemiological investigations have demonstrated that increasing age leads to an exponential increase in VTE risk.[9] The UK GPRD study by Huerta et al.[8] provided a background rate estimate of 2.3 cases per 1000 patient-years in patients aged 70–79 years. The recent UK GPRD study by Breart et al.[5] reported annual incidence rates of 5.2 per 1000 patient-years for women aged between 75 and 80 years without osteoporosis, and of 7.2 per 1000 patient-years for women of a similar age with untreated osteoporosis. Other estimates, outside of the UK, of the background annual incidence of VTE in patients

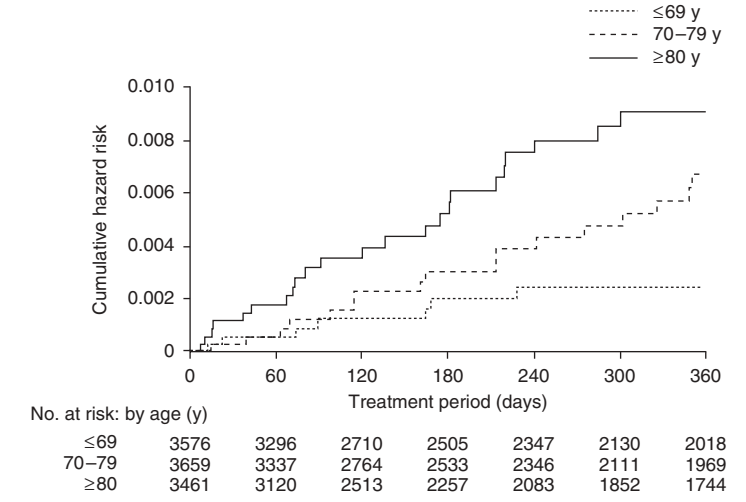

Fig. 3. Nelson-Aalen cumulative hazard plots for venous thromboembolism events (deep vein thrombosis or pulmonary embolism) in the first 12 months since starting treatment for the strontium ranelate cohort, by age.

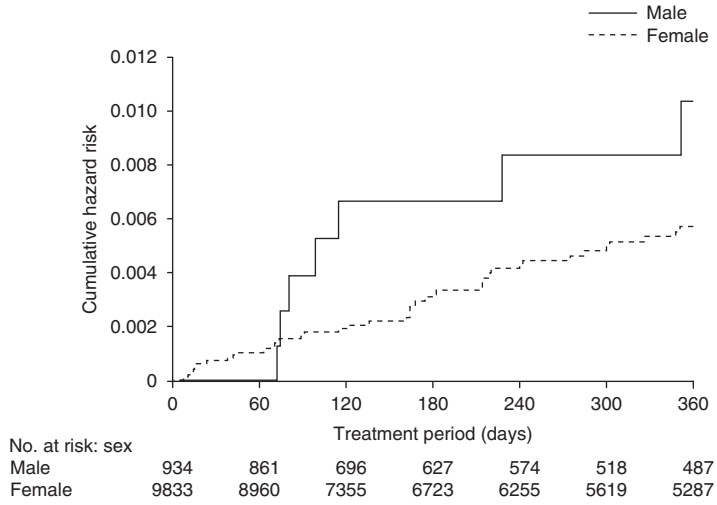

Fig. 4. Nelson-Aalen cumulative hazard plots for venous thromboembolism events (deep vein thrombosis or pulmonary embolism) in the first 12 months since starting treatment for the strontium ranelate cohort, by sex.

aged 70–79 years range from 3.0 to 7.0 cases per 1000 patients,[8,9,19] and increases to ten cases per 1000 patients in older individuals.[19] Other investigators have also provided similar estimates and shown the background annual incidence rate to be 4.1 per 1000 patient-years in patients aged >65 years,[20] and 7 per 1000 patient-years in patients ≥85 years.[21] Stratification of the PEM data by age provides estimates of 2.68, 6.47 and 9.63 cases per 1000 patient-years exposed for strontium ranelate-treated patients aged ≤69 years, 70–79 years and ≥80 years, respectively; these

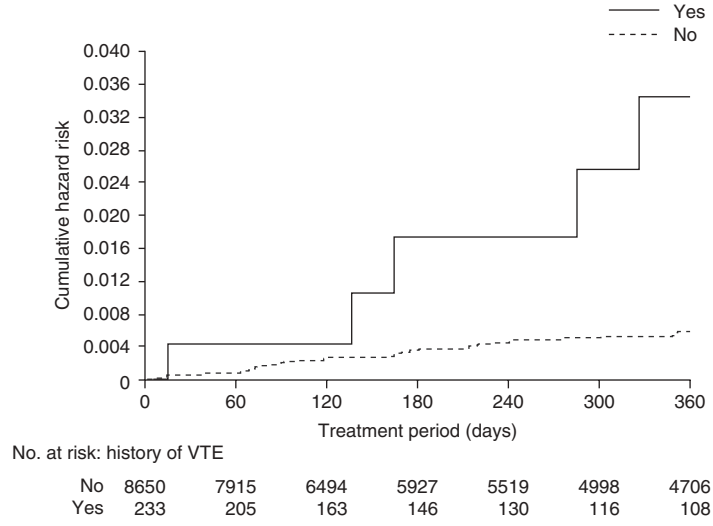

Fig. 5. Nelson-Aalen cumulative hazard plots for venous thromboembolism (VTE) events (deep vein thrombosis or pulmonary embolism) in the first 12 months since starting treatment for the strontium ranelate cohort, by history of VTE.

Table III. Summary of causality assessments (possible and probable) for venous thromboembolism (VTE) events reported during the total Prescription-Event Monitoring study period

Case no.	Event	Time to onset (days)	Causality assessment	Was event reason for stopping?	ADR[a]	Risk factors[b]
1	Deep vein thrombosis	Unknown	Probable	No	No	1
2	Deep vein thrombosis	161	Possible	Yes	No	2
3	Deep vein thrombosis	63	Possible	Yes	No	0
4	Deep vein thrombosis	15	Possible	No	Yes	1
5	Deep vein thrombosis	393	Possible	Yes	No	0
6	Deep vein thrombosis	440	Possible	Yes	No	3
7	Deep vein thrombosis	413	Possible	No	No	1
8	Deep vein thrombosis	Unknown	Possible	Yes	No	1

a ADR (as reported by the general practitioner).

b Risk factors included immobility, past medical history, current smoker and concomitant medication.

ADR = adverse drug reaction.

estimates were similar to estimates reported elsewhere.[5,8,9,19-21] Some of the variation in these estimates may be due to the differences in the age cut-offs, definitions used and the populations studied; however, our data support increasing age as an important risk factor relevant for VTE.

The annual incidence of VTE events reported in phase III clinical studies of strontium ranelate over 5 years is estimated to be 0.7%,[1] which is equivalent to seven cases per 1000 patient-years exposed. The current crude incidence from the strontium PEM cohort appears to be similar at 6.24 cases per 1000 patient-years exposed. This current analysis may still underestimate the incidence of VTE in patients taking strontium ranelate. It is noteworthy that there is likely to be a difference in the recording and reporting of adverse event data between clinical trials compared with observational studies.[14] It is also important to acknowledge the differences in study setting; published data previously mentioned are derived from other observational studies conducted in various countries in which differences in diagnosis in clinical practice and case definition are likely. In this analysis of PEM data, a narrow case definition was used that relied on the GP specifying that the patients had a DVT or PE on the Green Form; however, these events are recognized to be clinically difficult to diagnose.[7] With regard to available data from the UK, the incidence rates in this PEM cohort appear higher than that seen in the general UK population.[8]

These data should also be considered in relation to other treatments for postmenopausal osteoporosis. The MORE (Multiple Outcomes of Raloxifene Evaluation) and RUTH (Raloxifene Use for The Heart) clinical trials have evaluated the incidence of VTE with long-term raloxifene treatment. In the MORE study, the incidence of VTE in the first year of treatment with raloxifene was 5.1 per 1000 woman-years, compared with 0.8 per 1000 woman-years for the placebo group.[22] The RUTH study determined the annualized incidence of VTE with raloxifene as 0.39%, which is equivalent to 3.9 cases per 1000 patient-years exposed, compared with 2.7 cases per 1000 patient-years exposed in the placebo group.[23] It should be noted that, in both the MORE and RUTH studies, patients were younger than in other osteoporosis studies, with a mean age of 66 and 55 years, respectively, and that history of VTE was an exclusion criteria for participating in both studies. The SPC for raloxifene (Evista®) states that VTE events occurred at a frequency of approximately 3.22 cases per 1000 patient-years across all placebo-controlled trials.[24] Alendronate is a bisphosphonate indicated for the treatment of postmenopausal osteoporosis to prevent fractures.[25] A recent GPRD study has estimated the annual incidence of VTE in postmenopausal women receiving

alendronate treatment to be 7.2 per 1000 patient-years,[5] which is similar to the incidence found for strontium ranelate in this PEM study. Hormone replacement therapy can be used as both postmenopausal osteoporosis prevention and treatment.[26] A randomized controlled trial to examine the long-term use of estrogen plus progestin in healthy postmenopausal women estimated the annualized incidence of VTE as 0.34%, which is equivalent to 3.4 cases per 1000 patient-years, compared with 1.6 per 1000 patient-years for placebo.[27] Other trials have also shown an increase in the risk of VTE for postmenopausal women treated with HRT.[26] These observations suggest that whilst VTE incidence is associated with postmenopausal osteoporosis treatment, other risk factors related to the indication itself may be important. A similar conclusion has been reached by Breart et al.[5] in the recent UK GPRD study in which the authors reported a significantly increased relative risk of VTE in untreated osteoporotic women compared with non-osteoporotic women (annual incidence 5.6 and 3.2 per 1000 patient-years, respectively; hazard ratio 1.75 [95% CI 1.09, 1.84]; p = 0.030), but no significant difference in VTE risk between untreated and strontium ranelate-treated osteoporotic women (adjusted hazard ratio 1.09 [95% CI 0.60, 2.01]).[5]

Due consideration should be given to the difference in the characteristics of the populations being studied; the population in this PEM study may differ from patients included in clinical trials as the major clinical trials for strontium ranelate were limited to women with postmenopausal osteoporosis and excluded patients that had used other osteoporosis treatments for >2 weeks in the past 12 months, or if they had severe diseases or conditions recognized to interfere with bone metabolism.[28,29] Patients involved in clinical trials also have continued close monitoring and follow-up during treatment whereas the PEM study reflects the use of strontium ranelate in the general practice setting, in patients irrespective of their co-morbidities and concomitant/previous medication use, or adherence to treatment regimens. Strontium ranelate was also prescribed for indications other than the licensed indication of postmenopausal osteoporosis, including use in males, in this PEM study. Males only accounted for around 8.7% of the cohort, and while there is some evidence of sex having a slight effect on VTE risk at different ages, there is no consistent difference between sex on VTE risk.[8,9,19] This analysis supports these findings that sex is not an important risk factor for VTE events in this strontium ranelate PEM cohort.

It is not known what the incidence of VTE is in the patients for whom no questionnaire was returned; if it is higher or lower than the current estimate then the true incidence may be greater than or less than the estimate provided in this analysis. We are unable to ascertain what effect the warnings in the product information have on the prescribing of strontium ranelate to patients who have had a previous VTE or those who are at an increased risk of VTE. However, this analysis identifies a past history of VTE as an important risk factor significantly associated with being a case, with a correspondingly high estimate of incidence rate of 32.6 cases per 1000 patient-years exposed. The 'warnings and precautions for use' section of the SPC states that strontium ranelate should be used with caution in patients at increased risk of VTE, including those with a past history of VTE.[1] The results from this study support this precaution for use. This has been supported by observations elsewhere. A high incidence of VTE has been observed previously in women with a history of VTE at a background rate of 12.6 cases per 1000 patient-years, although in a cohort study of 4337 women aged 18–55 years, which is a lower age range than that found in this PEM study.[30]

The sensitivity analysis shows that the selected patient characteristics were unlikely to contribute to variation between the crude incidence estimates for the reported cases and the assessed cases, with the estimate for the assessed cases being much lower than for reported cases in the 12-month analysis period (1.56 cases per 1000 patient-years exposed). One explanation may simply be the smaller numbers included within the calculation. An alternative explanation may be related to the absence of information on other risk factors. The descriptions of cases

assessed point to the presence of other risk factors such as immobility or smoking. Information on these factors was not collected for the entire cohort and therefore has not been included in the analysis.

Conclusions

This analysis has provided an estimate of the incidence of VTE in patients treated with strontium ranelate in the real-life general practice setting. The annual incidence rates of VTE events is similar to estimates in populations of similar ages, and corresponds to the incidence found in patients from phase III clinical studies and observational cohort studies of strontium ranelate on this topic. The crude annual incidence rate of VTE in the PEM cohort is higher than the background annual incidence rate found in the UK population; however, it is similar to estimates in populations of similar age and populations receiving treatment for postmenopausal osteoporosis. Also, we acknowledge the potential for underestimating the incidence in this population. Nevertheless, this analysis contributes to the ongoing postmarketing safety assessment of this product.

In terms of recommendations for practice, GPs need to be aware that some patients have a predefined risk of VTE and may require routine optimization of treatment with regular review of concurrent illness (and newly prescribed medications) that may affect the benefit-risk balance of this treatment. Furthermore, high-risk patients need to be monitored for signs or symptoms of VTE, with appropriate treatment measures initiated where appropriate.

Acknowledgements

Michael Perrio is now an employee of GlaxoSmithKline.

We would like to thank all the staff at the DSRU who contributed to this study, Dr Victoria Cornelius for advice on the analysis, and Mr Shayne Freemantle for data management and IT support. We thank the GPs who have participated in this study, without whose general support PEM would not be possible. We also thank the Prescription Pricing Division of the National Health Service Business Services Authority for their important participation.

The DSRU is a registered independent charity (no. 327206) that works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or publication of the studies undertaken by the DSRU. The DSRU has received unconditional donations from the manufacturer of strontium ranelate (Servier).

References

1. Servier Laboratories Limited. Protelos: summary of product characteristics. Servier, 2008 Jan 23 [online]. Available from URL: http://www.medicines.org.uk/EMC/medicine/15410/SPC/Protelos/ [Accessed 2010 May 12]
2. European Medicines Agency. Protelos (strontium ranelate): European public assessment report summary for the public. Doc. Ref.: EMEA/528138/2009 [online]. Available from URL: http://www.ema.europa.eu/humandocs/PDFs/EPAR/protelos/121604en6.pdf [Accessed 2010 May 12]
3. Halil M, Cankurtaran M, Yavuz BB, et al. Short-term hemostatic safety of strontium ranelate treatment in elderly women with osteoporosis. Ann Pharmacother 2007; 41 (1): 41-5
4. Grosso A, Douglas I, Hingorani A, et al. Post-marketing assessment of the safety of strontium ranelate: a novel case-only approach to the early detection of adverse drug reactions. Br J Clin Pharmacol 2008 Nov; 66 (5): 689-94
5. Breart G, Cooper C, Meyer O, et al. Osteoporosis and venous thromboembolism: a retrospective cohort study in the UK General Practice Research Database [online]. Available from URL: http://www.springerlink.com/content/c72l383648v82320/fulltext.pdf [Accessed 2010 May 12]
6. Kroegel C, Reissig A. Principle mechanisms underlying venous thromboembolism: epidemiology, risk factors, pathophysiology and pathogenesis. Respiration 2003; 70: 7-30
7. Lopez JA, Kearon C, Lee AYY. Deep vein thrombosis. Hematology Am Soc Hematol Educ Program 2004; 439-56
8. Huerta C, Johansson S, Wallander MA, et al. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med 2007; 167: 935-43
9. White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107: I4-8
10. Anderson F, Spencer FA. Risk factors for venous thromboembolism. Circulation 2003; 107: I-9-16
11. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism. Arch Intern Med 2000; 160: 809-15
12. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism. Arch Intern Med 2002; 162: 1245-8
13. Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism Study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med 2006; 21: 1525-497
14. Shakir SAW. Prescription-event monitoring. In: Mann RD, Andrews EB, editors. Pharmacovigilance. 2nd ed. Chichester: John Wiley & Sons Ltd, 2007: 307-16

15. Shakir S. Causality and correlation in pharmacovigilance. In: Talbot J, Waller P, editors. Stephens' detection of new adverse drug reactions. 5th ed. Chichester: John Wiley & Sons Ltd, 2004: 329-43
16. CIOMS/WHO. International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS, 2002
17. Royal College of Physicians of London. Guidelines on the practice of ethics committees in medical research involving human subjects. 3rd ed. London: Royal College of Physicians of London, 1996
18. General Medical Council. Frequently asked questions supplement to 'confidentiality: protecting and providing information'. London: General Medical Council, 2004: 9
19. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998; 158: 585-93
20. Naess IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007; 5 (4): 692-9
21. Tsai A, Cushman M, Rosamond W, et al. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med 2002 May 27; 162: 1182-9
22. Grady D, Ettinger B, Moscarelli E, et al. Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. Obstet Gynecol 2004 Oct; 104: 837-44
23. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006 Jul 13; 355 (2): 125-37
24. Daiichi Sankyo UK Ltd. Summary of product characteristics: Evista. Daiichi Sankyo UK Ltd, 2008 Sep 17 [online]. Available from URL: http://www.medicines.org.uk/EMC/medicine/595/SPC/Evista+60mg+film-coated+tablets/ [Accessed 2010 May 12]
25. Merck Sharpe & Dohme Ltd. Summary of product characteristics: Fosamax. Merck Sharpe & Dohme Ltd, 2009 Apr 21 [online]. Available from URL: http://www.medicines.org.uk/EMC/medicine/1175/SPC/Fosamax/ [Accessed 2010 May 12]
26. Hallworth R. Prevention and treatment of postmenopausal osteoporosis. Pharm World Sci 1998; 20 (5): 198-205
27. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA 2002; 288 (3): 321-33
28. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004 Jan 29; 350 (5): 459-68
29. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis. Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005; 90 (5): 2816-22
30. Spannagl M, Heinemann L, DoMinh T, et al. Comparison of incidence/risk of venous thromboembolism (VTE) among selected clinical and hereditary risk markers: a community-based cohort study. Thromb J 2005 Jul 20; 3: 8

Correspondence: Ms *Vicki Osborne*, Research Fellow, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton SO31 1AA, UK.
E-mail: vicki.osborne@dsru.org