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SHORT COMMUNICATION

Nationwide registry-based analysis of cardiovascular risk factors and adverse outcomes in patients treated with strontium ranelate

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Abstract
Summary National registers showed that a large proportion of patients treated with strontium ranelate have conditions that may now contraindicate use. The risk of death in strontium ranelate-treated patients was significantly higher than that seen in users of other osteoporosis drugs even after adjusting for cardiovascular risk factor profile.
Introduction The European Medicines Agency (EMA) recently warned that strontium ranelate should be avoided in patients with ischaemic heart disease (IHD), peripheral vascular disease (PVD) or cerebrovascular disease (CVD), and in patients with uncontrolled hypertension. We investigated to what extent patients beginning strontium ranelate had cardiovascular conditions and determined the rates of MI, stroke and death.
Methods Using the Danish National Prescription Database, we identified all 3,252 patients aged 50+ who began strontium ranelate in 2005–2007 and 35,606 users of other osteoporosis drugs as controls. Hospital contacts and causes of death were retrieved from national registers.
Results Patients starting strontium were older than patients treated with other osteoporosis drugs and more likely to suffer from IHD, PVD or CVD (combined prevalence 19.2 % in female users and 29.5 % in male users). The adjusted risk of MI was not significantly increased (women: HR 1.05 [95 % CI 0.79–1.41, p=0.73]; men: 1.28 [0.74–2.20, p=0.38]). For stroke, the adjusted HR was 1.23 (0.98–1.55, p=0.07) in women and 1.64 (0.99–2.70, p=0.05) in men. All-cause mortality was higher in strontium users (women: adjusted HR 1.20 [1.10–1.30, p<0.001]; men: adjusted HR 1.22 [1.03–1.45, p<0.05]).
Conclusion Patients treated with strontium ranelate have an unfavourable cardiovascular risk profile compared with users of other osteoporosis drugs. However, only the risk of death differed significantly from the rates observed in users of other osteoporosis drugs adjusted for risk factor profile. A large proportion of patients currently treated with strontium ranelate have conditions that would now be considered contraindications according to EMA.

Keywords Drug safety · Epidemiology · Mortality · Osteoporosis · Strontium ranelate

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Introduction

In April 2013, the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) released a warning about increased risk of myocardial infarction (MI) in patients treated with strontium ranelate [1]. This still has to be legally approved by the EMA. The information was based on pooled data from studies in postmenopausal women, a single study in men and a study in osteoarthritis and led to the conclusion that strontium ranelate should be considered contraindicated in patients with a current or past history of

ischaemic heart disease, peripheral vascular disease (PVD) or cerebrovascular disease (CVD) and in patients with uncontrolled hypertension.

We hypothesised that a considerable proportion of patients currently receiving strontium ranelate would have baseline comorbid conditions that fell within these categories. The present analysis aimed at identifying the presence of CVD, PVD and prior MI in patients at the time strontium ranelate was prescribed. The use of antithrombotic agents such as aspirin and clopidogrel was also considered as a marker of increased cardiovascular-based risk. We subsequently calculated the rates of MI, stroke and death (all cause and cardiovascular) in "real-world" patients treated with strontium ranelate in order to estimate the numbers needed to harm (NNH). A comparison with event rates in patients receiving other osteoporosis drugs was also undertaken.

Study population and methods

Using the Danish National Prescription Database, we identified all 3,252 patients aged 50+ in Denmark who began treatment with strontium ranelate in the years 2005–2007 and 35,606 users of other osteoporosis drugs (oral bisphosphonates, raloxifene, parathyroid hormone analogues). Bisphosphonate users made up 98 % of the comparator group, with alendronate accounting for 89 % of bisphosphonate use. Danish hospital contacts and causes of death were retrieved from national registers under Statistics Denmark (project 702538). The look-back for chronic comorbid conditions dated back to 1977 for inpatient contacts and 1995 for outpatient contacts. The index date was defined as the first new prescription for an osteoporosis drug in the time period above. Strontium ranelate was commonly used as a second-line treatment choice, and both treatment-naïve patients and patients who had previously used other osteoporosis drugs were included in the analysis. Baseline co-medications included all prescriptions filled in the past 12 months before the index date. Primary endpoints for the study were incident MI or stroke. Secondary endpoints include total mortality and death from cardiovascular causes, including fatal MI and fatal stroke. We considered death as cardiovascular death when an International Classification of Diseases (ICD)-10 diagnosis group I was stated as a cause of death on the death certificate. Stroke and MI events were considered fatal events if the discharge date was the same as the date of death. We used the Cox proportional hazard analysis censored on death or date of changing from strontium ranelate to other osteoporosis drugs. In accordance with the Cox method, we calculated incidence rates based on the number of patients with events; thus, rates were based on the time to the first event.

We also performed a post hoc analysis testing whether adverse outcomes that were statistically significant remained so when restricting the analysis to female patients without a history of MI, PVD or CVD and who did not use antithrombotic drugs (low-cardiovascular risk group). In a sensitivity analysis, we repeated the main analysis without censoring on change of osteoporosis drug. We also performed a matched analysis, where the effect of age was incorporated as a matching criterion rather than controlled for as a covariate in the Cox analysis.

Ethics committee permission was not required, and the study was not a clinical trial.

Results

Baseline comparison

Patients beginning strontium ranelate were significantly older than patients who initiated treatment with osteoporosis drugs in general (Table 1). Furthermore, they were significantly more likely to have had hospital contacts for diabetes (4.9 %), PVD (6.2 %) or CVD (11.3 %). In addition, 6.8 % had a history of MI. Dementia was also more prevalent in strontium users as was ulcer disease. The combined prevalence of MI, PVD and CVD was 19.2 % in female strontium users and 29.5 % in male strontium users (Fig. 1). Antiplatelet drugs including aspirin and clopidogrel were used by 47 % of strontium users (Table 1). Prior MI, PVD, CVD or current use of antiplatelet drugs was found in more than 50 % of the female and more than 60 % of the male strontium users.

Cardiovascular outcomes based on the National Hospital Discharge Register

The absolute incidence rate for MI was 13.3 per 1,000 patient years (female strontium ranelate users, Table 2) and 11.1 per 1,000 patient years (female users of other osteoporosis drugs), while the rate of stroke was 21.8 per 1,000 patient years (female strontium ranelate users) and 15.5 per 1,000 patient years (female users of other osteoporosis drugs). In men, the absolute incidence rate per 1,000 patient years for MI was 30.3 (strontium ranelate) and 24.8 (other osteoporosis drugs), and for stroke, 34.1 (strontium ranelate) and 21.2 (other osteoporosis drugs).

The Cox proportional hazards analysis showed that differences in the risk of MI and stroke were largely explained by differences in baseline comorbid conditions and age, though risk increases for stroke had p values of 0.05 and 0.07. The risk of MI was not significantly increased when comparing with users of other osteoporosis drugs in women (HR 1.05 [95 % CI 0.79–1.41, p=0.73], when adjusted for age, MI, CVD, Charlson index, statins, antiplatelet drugs, antihypertensives, antidiabetics and index year). The same was true in men (adjusted HR 1.28 [0.74–2.20, p=0.38]).

For stroke, the adjusted HR was 1.23 (0.98–1.55, p=0.07) in women and 1.64 (0.99–2.70, p=0.05) in men. Risks of fatal MI

Table 1 Baseline demographics

	Comparator group, *N*=35,606		Strontium ranelate, *N*=3,252		*p* value
	Number	Percent	Number	Percent	
Age (mean and SD), [range]	71.8 (10.2) [50–103]		74.0 (10.2) [50–100]		<0.0001
Male gender	6,413	18.0	383	11.8	<0.0001
Prior fracture	15,598	43.8	1,726	53.1	<0.00001
Prior osteoporosis treatment	0	0.0	1,558	47.9	<0.00001
Prior myocardial infarction	2,283	6.4	222	6.8	0.352
Cardiac failure	7,084	19.9	718	22.1	0.003
Diabetes, without complications	1,876	5.3	145	4.5	0.049
Diabetes, with complications	608	1.7	44	1.4	0.156
Paralysis	315	0.9	31	1.0	0.705
Peripheral vascular disease	1,871	5.3	201	6.2	0.026
Cerebrovascular disease	3,550	10.0	367	11.3	0.018
Renal failure	326	0.9	24	0.7	0.333
Liver disease, mild	1,534	4.3	174	5.4	0.007
Liver disease, severe	272	0.8	25	0.8	0.928
Ulcer disease	2,520	7.1	356	10.9	<0.00001
Collagen and rheumatic disorders	6,483	18.2	638	19.6	0.049
Pulmonary diseases	6,771	19.0	622	19.1	0.872
Malignancy	4,541	12.8	451	13.9	0.07
Solid metastatic tumour	344	1.0	29	0.9	0.769
Dementia	607	1.7	86	2.6	<0.00001
AIDS	7	0.0	0	0.0	1
Charlson index (median, [range])	1 [0–16]		1 [0–16]		0.002
Charlson index ≥3	8,303	23.3	835	25.7	0.003
Medications in past year					
Antihypertensives	18,442	51.8	1,701	52.3	0.582
Platelet inhibitors including aspirin	14,461	40.6	1,542	47.4	<0.00001
Antidiabetics	1,885	5.3	135	4.2	0.005
Statins	6,329	17.8	511	15.7	0.003

and fatal stroke were not significantly different between patients treated with strontium ranelate compared with other osteoporosis drugs (p=0.14 to 0.79, Table 2). Results did not change materially by performing the analyses without censoring at the date of switching drugs. An age-matched cohort analysis, performed as a sensitivity analysis, produced the same results as the above, with the only exception that the increased risk of stroke in female strontium ranelate users became statistically significant (adjusted HR 1.31 [1.01–1.68], p=0.04).

Mortality outcomes based on the National Cause of Death Register

All-cause mortality was significantly higher in strontium users of both genders (women: adjusted HR 1.20 [1.10–1.30, p<0.001]; men: adjusted HR 1.22 [1.03–1.45, p<0.05]), compared with patients treated with other osteoporosis drugs. The risk of cardiovascular death did not differ significantly, though p values were below 0.10 (women: adjusted HR 1.20 [0.99–1.45, p=0.06]; men: adjusted HR 1.42 [0.96–2.09, p=0.08]). Findings were confirmed in a matched cohort analysis with age as a matching criterion.

In a post hoc analysis restricted to female gender, no use of antiplatelet drugs and no prior CVD, MI or PVD, the all-cause mortality risk was also significantly increased in the strontium cohort (adjusted HR 1.23 [1.04–1.46, p<0.05]). The mortality rate in this subgroup at low cardiovascular risk was 31.6 deaths per 1,000 patient years in strontium users and 27.6 per 100 patient years in users of other osteoporosis drugs.

Discussion

This study shows that, as a group, patients in Denmark treated with strontium ranelate have an unfavourable cardiovascular risk profile compared with users of other osteoporosis drugs.

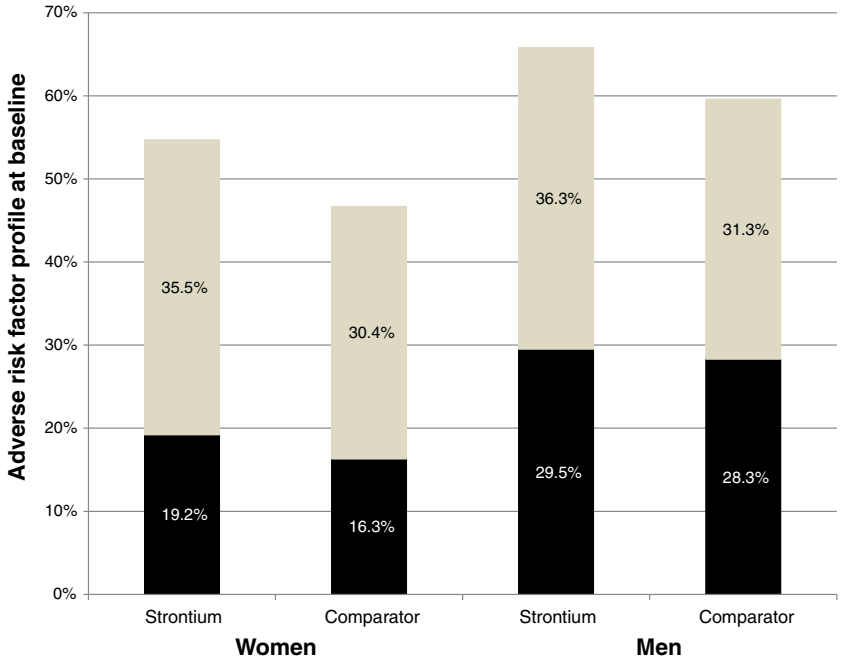

Fig. 1 Combined prevalence (*black bars*) of cerebrovascular disease, peripheral vascular disease and prior myocardial infarction at baseline in strontium group and comparator group, shown separately for men and women. *Grey bars* indicate patients who filled prescriptions for antiplatelet drugs including aspirin at baseline but who did not have a history of MI, CVD or PVD. Please see Table 1 for additional comorbid conditions and medications

While strontium ranelate users had increased rates of MI, stroke and death, only the latter differed significantly from the rates observed in users of other osteoporosis drugs when allowance was made for baseline differences in risk factor profile. Importantly for health policy, our study indicates that a large proportion of patients currently treated with strontium ranelate have conditions that, based on the concerns raised by the EMA, should now be considered contraindications against its use. If we include use of antiplatelet drugs as a proxy for the presence of significant cardiovascular disease—a caution that does not follow directly from the EMA document [1]—the proportion of high cardiovascular risk patients is above 50 % in both men and women. The high proportion is surprising for two reasons. First, prescribers are already advised to exert

Table 2 Cox proportional hazards analysis censored at death, end of study and change from strontium ranelate to other osteoporosis treatment. Adjusted hazard ratio (HR): Adjusted for age, index year, myocardial infarction (MI), cardiovascular disease (CVD), Charlson index, statins, platelet inhibitors, antihypertensives and antidiabetics in the past year

		Comparator group (rate per 1,000 py)	Strontium ranelate (rate per 1,000 py)	Unadjusted HR		*p* value	Adjusted HR		*p* value
Hospital discharge register									
MI (*N*=713)	Men	24.8 (21.5–28.5)	30.3 (16.6–50.9)	1.226	(0.713–2.109)	0.46	1.276	(0.740–2.200)	0.38
	Women	11.1 (10.1–12.2)	13.3 (9.9–17.5)	1.187	(0.888–1.585)	0.25	1.053	(0.787–1.408)	0.73
Fatal MI (*N*=93)	Men	4.4 (3.1–6.1)	2.2 (0.1–12.1)	0.491	(0.067–3.583)	0.48	0.497	(0.068–3.643)	0.49
	Women	1.2 (0.9–1.6)	2.4 (1.1–4.5)	1.952	(0.957–3.978)	0.07	1.726	(0.844–3.531)	0.14
Stroke (*N*=924)	Men	21.2 (18.2–24.5)	34.1 (19.8–54.5)	1.622	(0.986–2.668)	0.06	1.635	(0.991–2.697)	0.05
	Women	15.5 (14.3–16.8)	21.8 (17.4–27)	1.404	(1.119–1.76)	<0.05	1.234	(0.983–1.548)	0.07
Fatal stroke (*N*=80)	Men	1.5 (0.8–2.6)	2.0 (0.1–11.2)	1.292	(0.169–9.881)	0.81	1.320	(0.167–10.428)	0.79
	Women	1.5 (1.1–1.9)	1.3 (0.4–3)	0.882	(0.354–2.196)	0.79	0.752	(0.301–1.878)	0.54
Register of causes of death									
Death (*N*=7,670)	Men	100.6 (96.3–105.1)	129.1 (109–151.9)	1.314	(1.11–1.555)	<0.01	1.221	(1.031–1.447)	<0.05
	Women	47.9 (46.6–49.2)	65 (59.9–70.4)	1.449	(1.331–1.578)	<0.001	1.196	(1.098–1.302)	<0.001
Cardiovascular death (ICD-10 group I) (*N*=1,470)	Men	18.2 (16.4–20.2)	24.8 (16.5–35.8)	1.368	(0.93–2.011)	0.11	1.416	(0.96–2.089)	0.08
	Women	9.3 (8.7–9.9)	13.4 (11.1–16)	1.526	(1.265–1.841)	<0.001	1.198	(0.992–1.446)	0.06

Py patient years

caution when prescribing strontium ranelate to patients at risk of venous thromboembolic events, and this would be expected to select for a slightly healthier subset of osteoporosis patients. Second, our study did not seek to identify patients with uncontrolled hypertension—another patient group in which EMA had voiced concerns—due to limitations in ICD-10 coding. The choice of strontium ranelate rather than bisphosphonates in patients with cardiovascular risk factors may perhaps have been influenced by the initial reports on risk of atrial fibrillation with bisphosphonates. As further discussed below, it is important to acknowledge that observations of adverse outcomes in a randomised clinical trial can not be refuted by an analysis of observational real-world data. Accordingly, the main purpose of the present analysis was to estimate the rate of cardiovascular events in strontium ranelate users. These estimates can be used in risk-benefit considerations, in which they are related to the relative risk estimates demonstrated in clinical trials. This may be illustrated with a practical example. The EMA reported a RR of 1.6 [1] against placebo for the outcome of MI in postmenopausal women with osteoporosis. To calculate the number needed to harm in a real-world setting, we used the observed rate of 13.3 events per 1,000 patient years for MI in strontium ranelate-treated women in Denmark. This translates to 5.0 excess events per 1,000 patient years or a NNH of 200 women treated for a year.

Interestingly, we observed an increased all-cause mortality in strontium users, even when restricting the analysis to women without a past history of CVD, MI and PVD. The mechanism linking strontium ranelate to cardiovascular and thromboembolic events is elusive [2] and does not appear to be explained by changes in blood counts or viscosity [3]. Strontium ranelate is, albeit infrequently, associated with inflammatory conditions such as uveitis [4] or, very rarely, DRESS syndrome [5].

In common with all observational studies, this report has limitations in that the decision to treat patients with strontium ranelate rather than other osteoporosis drugs is not random. Instead, the decision may have been based on the patients having experienced adverse effects on oral bisphosphonates, a mechanism that would channel strontium ranelate towards a more fragile subset of patients. Additional limitations include the absence of information on height, weight and lifestyle factors, including alcohol and smoking habits. Further, the number of strontium ranelate users was low so the confidence intervals on rates and risk estimates were wide. However, the study had acceptable power to pursue the outcomes of interest. For example, for MI, a retrospective power calculation using the event rates from Table 2 and the same distribution between men and women indicated that with a type 1 error of 5 %, our study had 80 % power to detect a relative risk of 1.57 in women and 2.08 in men. An additional limitation to the study is that the criteria for use of strontium ranelate will vary between countries; hence, the absolute or relative risks may not apply directly to countries with different prescription patterns, for example, first-line use in younger patients.

On the other hand, the strengths of the study include extensive information on past hospital contacts—going back almost 30 years in time—and the complete information on filled prescriptions for other drugs that could influence the risk of adverse outcomes.

Also, the study outcomes stroke and MI will almost certainly be treated in hospitals, and the validity of the registers for these outcomes is generally high, though better for MI events than for stroke [6, 7]. Use of an active comparator cohort offers the clear advantage of a high likelihood of patients in the study cohorts having osteoporosis, given the Danish reimbursement criteria requiring DXA scans or low trauma fractures. However, bisphosphonates may, in themselves, be linked to a lower mortality [8, 9] and lower risk of MI [10], which could slightly inflate the risk estimates observed with strontium ranelate. However, mortality effect sizes did not differ appreciably between strontium and bisphosphonates in the meta-analysis of placebo-controlled trials [9].

This study highlights that a large proportion of strontium ranelate-treated patients will fall within the categories of comorbid conditions [1] that would justify a change in their medication to other types of osteoporosis drugs. However, our analysis also points toward an increased mortality even in cardiovascular low-risk women treated with strontium ranelate, compared with other osteoporosis drugs. This does not provide evidence of causality. It may be that strontium ranelate failed to produce the reduction in mortality that has been linked to bisphosphonate use.

In conclusion, baseline cardiovascular diseases are common in patients treated with strontium ranelate, with more than half of strontium ranelate users being current users of antiplatelet drugs or having a history of cerebrovascular disease, peripheral vascular disease or myocardial infarction. Moreover, this observational study shows an increased confounder-adjusted mortality risk in patients treated with strontium ranelate compared with other osteoporosis drugs.

Conflicts of interest BA has served as an investigator in clinical trials and on advisory boards and/or speaker panels for pharmaceutical companies that produce osteoporosis drugs (clinical trials: Amgen and NPS Pharmaceuticals; advisory boards: Amgen, Merck and Takeda-Nycomed; speakers panels: Amgen, Nycomed, Eli Lilly and Merck). PV has received unrestricted research grants and travel grants from Servier, travel grants from Novartis, Eli Lilly, and Amgen, as well as unrestricted research grants from MSD. ELG has received speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim and Pfizer and serves on advisory boards for AstraZeneca, Bayer and Bristol-Myers Squibb.

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