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ORIGINAL ARTICLE

The cost-effectiveness of strontium ranelate in the UK for the management of osteoporosis

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Abstract
Summary The cost-effectiveness of strontium ranelate was compared to no treatment in UK women using the FRAX® algorithm for fracture risk assessment. At a willingness-to-pay of £30,000 per quality-adjusted life-year (QALY), strontium ranelate was generally cost-effective in women with prior fracture at the threshold of osteoporosis from an age of 65 years.
Introduction The objectives of the study were to estimate the cost-effectiveness of strontium ranelate in the UK for the treatment of osteoporosis and to establish intervention thresholds for treatment using the FRAX® tool.
Methods The cost-effectiveness of strontium ranelate was compared to no treatment in postmenopausal women with clinical risk factors for fracture using a lifetime simulation model based on Markov cohort methodology that incorporated the features of FRAX®.
Results At a threshold of £30,000 per QALY, strontium ranelate was generally cost-effective in women from an age of 65 years with prior fracture at the threshold of osteoporosis (i.e., a T-score of −2.5 SD) and in women with a prior fracture (and no information on bone mineral density) from the age of 65 years. At a threshold of £20,000, strontium ranelate became cost-effective at a 10-year fracture probability of 25.7% and at 16.9% with a threshold of £30,000 for a QALY.
Conclusions Strontium ranelate is a cost-effective agent for the treatment of established osteoporosis in women over the age of 65 years. Cost-effective scenarios were also found for the prevention and treatment of fractures associated with osteoporosis, in younger women with additional clinical risk factors.

Keywords Cost-effectiveness · Fractures · FRAX · Osteoporosis · QALY

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Introduction

It has become increasingly common that recommendations concerning the use of treatments for osteoporosis have been placed in a health economic context in order to justify resource allocation and inform the development of clinical guidelines. An example is the National Institute for Health and Clinical Excellence (NICE), which has published several appraisals on the treatment and prevention of osteoporosis [1–5].

The vast majority of appraisals have examined cost-effectiveness in women according to the T-score for bone mineral density (BMD), and in the absence or presence of a prior vertebral fracture. There is a growing view that treatment guidelines for osteoporosis should be based on the absolute risk of fracture rather than on T-scores for BMD [6–12]. This change has been facilitated by new instruments for fracture risk assessment such as the FRAX® algorithm. The FRAX® tool allows estimation of the individual fracture risk based on more risk factors than

the traditional T-score, age, and prior fracture (e.g., smoking, body mass index (BMI), alcohol intake, parental history of hip fracture) [13]. This new approach is intended to simplify the identification of patients eligible for treatment in clinical practice. It is imperative to align health economic analysis to the paradigm shift in guidelines, by assessing intervention thresholds (i.e., at what fracture probability it is cost-effective to treat) using cost-effectiveness analysis.

Strontium ranelate, a divalent strontium salt of ranelic acid [14, 15], has been shown to reduce the risk of fracture in two large phase III clinical trials (the Spinal Osteoporosis Therapeutic Intervention study [SOTI] and the Treatment of Peripheral OSteoporosis Study [TROPOS]. Published estimates regarding the cost-effectiveness of strontium ranelate have not assessed intervention thresholds defined by fracture probabilities [1–5, 16].

Against this background, we wished to estimate the cost-effectiveness of strontium ranelate in the UK for the prevention and treatment of fractures associated with osteoporosis using the FRAX® tool to assess fracture risk for patients with different sets of clinical risk factors. A further aim was to establish intervention thresholds for treatment with strontium ranelate, i.e., the fracture probability at which treatment became cost-effective.

Methods

The cost-effectiveness of strontium ranelate was compared to no intervention in a UK setting by simulating costs and outcomes in cohorts of postmenopausal women at different ages of initiating treatment at different degrees of risk of an osteoporotic fracture. Health effects were measured as quality-adjusted life-years gained (QALYs, i.e., taking into account quality of life as well as life years) and major results are presented as the incremental cost-effectiveness ratio (ICER) which is defined as:

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{C_{\text{SR}} - C_{\text{NoTreat}}}{E_{\text{SR}} - E_{\text{NoTreat}}}$$

Costs and effects were discounted at 3.5% as recommended by NICE [17]. All costs were adjusted to reflect the price level of 2006. The analysis used a health care perspective.

Simulation model

A suitable framework for assessing the cost-effectiveness of strontium ranelate is a previously developed model extensively used to evaluate the cost-effectiveness of treatments for osteoporosis and hormone replacement therapy in several countries, including the UK [16, 18–25]. This model is based on Markov cohort methodology and has been used to compute intervention thresholds and predict fracture rates and mortality making it well validated and calibrated. Furthermore, it is suggested as a reference model for the economic evaluation of osteoporotic treatments [26–29].

A patient started a model simulation in the healthy state and passed through the model in yearly cycles between the different health states until 100 years of age or death. In each cycle, patients had a probability of a fracture of the hip, forearm, spine, or other sites or dying. The transitions were assumed to occur in the middle of each cycle, i.e., the model was half-cycle-corrected. When a fracture occurred, the patient moved to the corresponding fracture health state (i.e., *hip*, *vertebral*, *wrist*, or *other fracture*). The long-term consequences of hip and vertebral fractures were considered in separate health states. Wrist fracture and other osteoporotic fracture were assumed to have an impact on costs and morbidity only in the first year after fracture, and the patient was thus considered to have regained full health 1 year after the fracture. After a hip fracture, the patient was only at risk for another hip fracture or dying. After a vertebral fracture, the patient was at risk of sustaining a hip or a vertebral fracture or dying. This conservative simplification was adopted because there are few available data on the costs and effects of multiple fractures and, given the low probability of having a vertebral or a wrist fracture after a hip fracture, this discrepancy will have a minor impact on the cost-effectiveness.

Population fracture risks and mortality

Fracture of the spine, rib, pelvis, humerus, forearm, hip and other femoral fractures, tibia, and shoulder girdle were considered to be osteoporotic, since they are associated with low BMD and increase in incidence with age [30, 31]. The incidence of fractures was taken from Singer et al [32] except for rib and vertebral fractures, which are inconsistently reported in the UK [33]. The incidence of a clinical vertebral fracture was calculated by assuming that the ratio of clinical vertebral fracture to hip fracture would be similar in the UK compared to Sweden [34–36]. The same approach was used to assess the risk of rib fractures. This assumes a proportionality of fractures at different sites in different countries, an assumption consistent with the available information [30].

The age-specific normal mortality rates for the general population in the UK were based on the years 2004–2006 [37]. The increase in mortality after hip and clinical vertebral fractures was derived from Odén et al. [38] and Johnell et al. [39]. Age-specific fracture rates and mortality were assumed to remain stable over the lifetime of individuals. The assumption on mortality underesti-

mates lifetime risk, but has little impact over the intervention period.

Effect of treatment

The effects of strontium ranelate on fracture risk were taken from the published results in the SOTI and TROPOS phase III studies [14, 15]. The relative risk was 0.60 (95% CI, 0.53–0.69) for vertebral fracture and 0.84 (95% CI, 0.73–0.97) for non-vertebral fractures. A post hoc subgroup analysis in women over 74 years of age with a T-score of −2.4 SD at the femoral neck gave a RR for hip fracture of 0.64 (95% CI, 0.41–0.98) [14]. The results based on the post hoc group were incorporated in a separate analysis. For the base case, we took a conservative position in assuming that treatment exerted effects on all patients equally.

An intervention for 5 years was modeled as has been used in studies for other osteoporosis agents [16, 18–20, 23, 25, 40]. After stopping treatment, the risk reduction was assumed to reverse in a linear manner over a 5-year period as also assumed in many health economic analyses [16, 18–20, 23, 25, 40]. The assumption arises because it is unlikely that the fracture risk-reducing effect of strontium ranelate treatment stops immediately after treatment is stopped and it also unlikely that the effect persists forever. Recent studies with the bisphosphonates suggest that this offset time may vary [41–43]. For strontium ranelate, several studies have shown that the BMD, at both lumbar and femoral sites, decreases after stopping treatment, but after 1 year, there was still a beneficial effect on the BMD compared to BMD at baseline at a time that the skeletal load of strontium has markedly decreased [44–47]. In view of uncertainty over offset time, a 40% change in offset time was used in sensitivity analysis.

In the NICE appraisal, it was assumed that side effects for strontium ranelate were the same as those assumed for the bisphosphonates [48], which was assumed to be 23.5 additional GP consultations per 1,000 patient months in the initial treatment period and 3.5 GP consultations subsequently, and the use of a proton pump inhibitor. Symptoms were assumed to persist for 1 month with a utility loss equivalent to a multiplier of 0.91 [48]. These assumptions were included in a sensitivity analysis. Venous thromboembolic events (VTEs) were shown to have a borderline significant increase in incidence with strontium ranelate (1.4; 95% CI, 1.0–1.0) based on a pooled analysis of the 3-year follow-up of SOTI and TROPOS [12]. However, based on the 5-year follow-up, the significant increase in risk of VTE was not maintained (1.3; 95% CI, 0.9–1.9) [49]. Because the assumed treatment duration in this study was 5 years, we did not include VTE in the model. Neither were other side effects included in the base case since the randomized studies of efficacy have shown few persistent differences between placebo and actively treated patients.

Studies show that up to 50% of patients do not follow their prescribed treatment regimen and/or discontinue treatment within 1 year with existing pharmacological agents [50, 51]. Therefore, the long-term persistence with strontium ranelate was set at 50%. The remaining 50% were assumed to receive 3 months of drug treatment for no health gain [4, 5, 35]. A persistence rate of 70% and 30% was assumed for sensitivity analysis (base case ±40%).

Costs

Costs of fracture were taken from Stevenson et al [52]. Average in-patient and out-patient costs used were £10,760 for hip fracture, £9,236 for pelvic fracture, £13,771 for other femoral fractures, £1,706 for vertebral fracture, £527 for forearm fracture, £147 for ribs and sternal fractures, £141 for scapular fractures, £1,112 for humeral fractures, and £3,864 for fractures of the leg. These did not include any cost for home help. Costs were age-weighted [53, 54] and included nursing home admissions after hip fracture that increased from 6.7% between the age of 50 and 59 years to 22.6% at the age of 90 years or more [55, 56]. Nursing home costs were not included for fractures at other sites that might require admission to a nursing home.

The cost of strontium ranelate was assumed to be £333.71 per annum (as given in the British National Formulary). The cost for case finding was 3 min of GP time to administer the questionnaire on risk factors (£5.76), a BMD test at the femoral neck with dual energy X-ray absorptiometry (£35), and a 10-min consultation with a general practitioner to start treatment (£19.20). Conservatively, all patients treated were assumed to have a BMD test before treatment and 2-yearly thereafter.

Quality of life

Utility losses in the first year after a fracture at the hip, spine, or forearm were based on empirical estimates [53, 54]. A hip fracture has shown to reduce the quality of life by 20% the year after fracture. The corresponding estimates for vertebral and wrist fracture were 35% and 7%. Utility losses for other fractures were based on expert opinion [57]. The quality of life in subsequent years after a hip fracture was assumed to be 90% of that of a healthy individual which also corresponds to a recent empirical study [54]. Wrist fractures were estimated to have no quality of life reduction in the second and subsequent years. The quality of life in subsequent years after a vertebral fracture was reduced by 7% derived from empirical observations [58]. These multipliers were used together with the population tariff values for the UK [59]. In sensitivity analysis, a more

conservative utility loss of 27% which has been used in the NICE appraisal the first year after a vertebral fracture was used [4, 5].

The FRAX® algorithm

The FRAX® tool (http://www.shef.ac.uk/FRAX/index.htm) was developed by the World Health Organization [13, 60]. The clinical risk factors used were identified from a series of meta-analyses that identified clinical risk factors (CRFs) associated with an increase in fracture risk independent of age and BMD at the femoral neck. These included low BMI (in part dependent on BMD), a prior fragility fracture, a parental history of hip fracture, long-term use (e.g., for 3 months or more) of glucocorticoids given orally, rheumatoid arthritis, other secondary causes of osteoporosis, current cigarette smoking, and high alcohol consumption (3 or more units/daily). The weight of the various risk factors differs for hip fracture and other fracture outcomes and in the presence or absence of information on BMD. The FRAX® algorithms estimate both the 10-year probability of hip and a major osteoporotic fracture (hip, clinical spine, forearm, and proximal humerus) as well as the relative risk of fracture and death (before the fracture) compared to the normal population. The relative risks were used to adjust the population fracture risk for any modeled clinical scenario. The FRAX® tool calibrated to the epidemiology of fracture and death in the UK was used in this study [13].

The starting point in the model was the fracture and death hazard in the population with no clinical risk factors and with no BMD test. In the simulations, the incidence of fracture and risk of death was then adjusted to reflect the risk in the target patient groups based on the presence or absence of clinical risk factors according to FRAX®. However, BMI was set to a fixed value of 26 kg/m^2—close to the average value for postmenopausal women.

Clinical vignettes

We examined the cost-effectiveness of intervention in women with a prior fracture as an example of "self-identifying" patients and women with a parental history of hip fracture as an example of "opportunistic assessment". Both scenarios were examined with and without information on BMD. The cost, however, of BMD testing was retained in the examples without information on BMD. The threshold at which strontium ranelate was assumed to be considered cost-effective was set at a willingness to pay (WTP) of £30,000 per QALY. However, a WTP of £20,000 was also considered. Other clinical scenarios were modeled in sensitivity analysis.

For these and other sensitivity analysis, we examined the changes in cost-effectiveness for women at the age of 70 years, as used in an earlier evaluation of alendronate [25].

Intervention thresholds

For the purpose of determining intervention thresholds, probabilities of a major osteoporotic fracture (rather than hip fracture) were computed, for reasons previously argued [61]. Intervention thresholds at each age were determined from the relationship between fracture probabilities and the cost-effectiveness of all possible combinations of CRFs at T-scores between 0 and −3.5 SD in 0.5 SD steps (512 combinations) with a BMI set to 26 kg/m^2. Note that this was not a population simulation, but an array of all possible combinations.

Results

The results from the cost-effectiveness analysis with strontium ranelate for a 5-year intervention in women at the threshold of osteoporosis are presented in Table 1. In women with osteoporosis (i.e., a femoral neck T-score equal to −2.5 SD), the ICER was above a WTP threshold of £30,000/QALY, except at the age of 70 years. In women with a BMD set at the threshold of osteoporosis and who had previously sustained a fragility fracture, treatment was cost-effective from the age of 65 years, except at the age of 80 years. Similarly, treatment was cost-effective from the age of 65 years in women with a prior fracture in the absence of information on BMD. In women with a parental history of hip fracture, treatment was cost-effective from the age of 65 years with or without information on BMD.

As expected, cost-effectiveness was improved when the post hoc analysis of efficacy was considered, but the conclusions were broadly similar in that cost-effectiveness was noted in women from the age of 65 years for all clinical scenarios using a WTP of £30,000. For women at the threshold of osteoporosis and a parental history of hip fracture, treatment was cost-effective at all ages. With a WTP of £20,000 treatment was generally cost-effective from the age of 70 years.

The effect of different clinical risk factors at different T-scores for BMD for women at the age of 70 years is shown in Table 2. In women at the threshold of osteopenia (a T-score of −1 SD) treatment with strontium ranelate was cost-effective in the presence of prior fracture or family history. At the threshold of osteoporosis, treatment with strontium ranelate was cost-effective in the presence of any single CRF using a WTP of £30,000, with the exception of current smoking. The strongest risk

Table 1 Cost-effectiveness of intervention with strontium ranelate in women at the threshold of osteoporosis, with or without a clinical risk factor (prior fracture or parental history of hip fracture) and in women with a clinical risk factor without BMD

Age (years)	Cost (£000)/QALY gained				
	T-score=−2.5	Self identifying		Opportunistic case finding	
	No previous fracture	T-score=−2.5 + previous fracture	No BMD + previous fracture	T-score=−2.5 + parental history	No BMD + parental history
Base case					
50	61.3	42.5	60.8	33.5	50.1
55	62.9	44.2	58.1	33.9	49.1
60	59.3	42.8	52.5	32.0	43.8
65	36.2	26.3	29.6	19.4	24.9
70	28.7	20.6	21.5	17.5	22.5
75	39.1	29.6	27.4	18.4	25.3
80	47.3	37.5	29.1	14.6	17.7
Post hoc					
50	48.2	31.5	54.1	28.9	48.2
55	50.6	34.3	51.1	29.7	46.6
60	47.3	32.9	44.5	27.8	40.6
65	28.3	19.5	23.8	16.3	22.2
70	21.2	14.1	15.5	10.2	15.7
75	26.4	18.4	16.8	1.9	8.6
80	26.7	18.9	12.4	cs	cs

BMI set to 26 kg/m^2

cs cost saving

factors were prior fractures and a parental history of hip fracture, whereas current smoking and excessive alcohol intake were the weakest of the clinical risk factors. As expected, cost-effectiveness was improved when the post hoc analysis of efficacy was included.

When more than one clinical risk factor was included the ICER depended on the weight of the clinical risk factor (see Table 3). In the absence of information on BMD, the combination of the weakest two risk factors gave an ICER of less than £30,000 (£27,300) at the age of 70 years. In the

Table 2 Cost-effectiveness of intervention with strontium ranelate (cost (£000)/QALY gained) in women aged 70 years with clinical risk factors according to T-score for femoral neck BMD

	T-score (SD)							
	0.0	−0.5	−1.0	−1.5	−2.0	−2.5	−3.0	−3.5
Base case								
Prior fracture	34.2	31.7	29.8	27.6	24.5	20.6	17.1	13.8
Family history	30.9	28.7	26.6	24.3	21.2	17.5	14.2	10.9
Glucocorticoids	36.4	34.6	32.3	30.4	26.6	22.4	18.3	14.0
Rheumatoid arthritis	37.3	34.9	32.5	30.0	26.3	22.0	18.1	14.4
Alcohol >3 U daily	41.1	37.9	35.0	32.2	28.2	23.3	18.9	14.8
Current smoking	62.7	58.4	54.5	50.5	44.3	36.6	29.1	21.8
Post hoc analysis								
Prior fracture	32.4	29.3	26.5	23.3	19.1	14.1	9.3	4.5
Family history	28.7	25.6	22.6	19.1	14.9	10.2	5.7	1.2
Glucocorticoids	34.3	31.8	28.5	25.4	20.2	14.5	8.6	2.1
Rheumatoid arthritis	35.2	32.1	28.7	25.2	20.4	15.0	9.9	5.0
Alcohol 3 or more units daily	38.4	34.4	30.5	26.4	21.2	15.2	9.8	4.5
Current smoking	58.1	52.5	46.9	40.8	32.7	23.2	13.6	3.9

Table 3 Cost-effectiveness of treatment with strontium ranelate in women aged 70 years and two weak clinical risk factors (current smoking and excessive alcohol intake) or two strong risk factors (family history and prior fracture)

BMD T-score	Base case		Post hoc analysis	
	Weak CRFs[a]	Strong CRFs[b]	Weak CRFs[a]	Strong CRFs[b]
No BMD	–	++	+	++
−1.0	–	++	–	++
−1.5	–	++	–	++
−2.0	–	++	+	++
−2.5	+	++	++	++
−3.0	+	++	++	++
−3.5	++	++	++	++

++ denotes cost-effectiveness at a WTP of £30,000; + denotes cost-effectiveness at a WTP of £20,000; – cost-ineffective

[a] Current smoking and alcohol intake

[b] Prior fracture and parental fracture

presence of the strongest two clinical risk factors (family history and prior fracture) and in the absence of information on BMD, the ICER was below £20,000/QALY at the age of 70 years (Table 3). In women aged 70 years with a BMD test and two weak CRFs, the ICER was below £30,000/QALY gained with a T-score of −2.5 SD or less and below £20,000/QALY gained with a T-score of −3.5 SD or less. With two strong CRFs, treatment was cost-effective irrespective of BMD. As expected, more cost-effective scenarios were found using the post hoc analysis. However, the analyses using the post hoc efficacy needs to be interpreted with some caution for ages below 74 years of age since the post hoc population only consisted of women above this age.

Sensitivity analysis

Changes in time horizon and assumptions concerning side effects had marked effects on cost-effectiveness (Table 4). The ICERs were more than doubled when a 10-year rather than a lifetime horizon was used. When side effects, as assumed by NICE, were included, this had a lesser, though marked effect on cost-effectiveness using the lifetime horizon, but had a more marked adverse effect on cost-effectiveness with the shorter time horizon. Moderate effects on cost-effectiveness were observed with changes in the assumptions concerning offset time, adherence, and utility weights for spine fracture.

Intervention thresholds

At each age, there was a close correlation between the probability of a major osteoporotic fracture as determined by FRAX® and cost-effectiveness. The relationship is illustrated in Fig. 1 for women at the age of 50 years.

The point estimates for the correlations permit the calculation of the mean fracture probability for any willingness to pay as shown in Table 5 for a WTP of £20,000 and £30,000. There was rather little difference in the threshold probability at which treatment became cost-effective at different ages with a mean value of 37.8% at a WTP of £20,000 and 21.6% and at a WTP of £30,000. Thus, with a WTP of £30,000, any recommendations for intervention should ensure that individuals have a fracture probability that exceeds 21.6%. When the post hoc analysis of efficacy was used, threshold probabilities were lower. Thus, treatment became cost-effective with a fracture probability of 22.1% at a WTP of £20,000 and 16.0% and at a WTP of £30,000.

Discussion

The principal finding of the present study is that cost-effective scenarios are found for the treatment of osteoporosis and established osteoporosis with strontium ranelate in postmenopausal women. In the case of a prior fracture, the ICER lay below £30,000 in women at the threshold of osteoporosis from the age of 65 years. Cost-effectiveness improved, as expected with lower T-scores. However, cost-effectiveness was shown from the age of 65 years for women with a prior fracture even in the absence of information on BMD. Assuming a WTP per QALY of £20,000 treatment with strontium ranelate was cost-effective from the age of 65 years in women with a T-score of –2.5 SD or less. Our finding of good cost-effectiveness for the treatment of osteoporosis is not surprising, given that many treatments in osteoporosis or established osteoporosis, now including strontium ranelate, have been shown to be cost-effective in a UK setting [19, 20, 40].

Table 4 Sensitivity analysis of the cost-effectiveness of strontium ranelate in women aged 70 years

	Cost (£000)/QALY gained				
	T-score=−2.5	Self identifying		Opportunistic case finding	
	No previous fracture	T-score=−2.5 + previous fracture	No BMD + previous fracture	T-score=−2.5 + parental history	No BMD + parental history
Base case efficacy					
Base case	28.7	20.6	21.5	17.5	22.5
10-year time horizon	64.3	46.9	53.1	36.8	52.8
Offset time +40% (7 years)	26.5	18.9	19.7	15.9	20.6
Offset time −40% (3 years)	31.5	22.6	23.6	19.4	24.8
Non-adherence +40% (70%)	30.8	22.9	23.9	18.9	24.1
Non-adherence −40% (30%)	27.8	19.5	20.4	16.8	21.7
Higher utility for vertebral fracture	30.4	22.1	22.8	18.5	23.6
Side effects	46.3	28.2	29.6	23.2	32.1
Post hoc analysis					
Base case	21.2	14.1	15.6	10.2	15.7
10-year time horizon	49.2	34.0	40.5	23.6	39.0
Offset time +40% (7 years)	18.9	12.3	13.7	8.6	13.8
Offset time −40% (3 years)	23.9	16.2	17.7	12.1	17.9
Non-adherence +40% (70%)	23.2	16.2	17.7	11.6	17.3
Non-adherence −40% (30%)	20.3	13.2	14.6	9.6	14.9
Higher utility for vertebral fracture	22.2	14.9	16.4	10.7	16.4
Side effects	31.3	18.4	20.4	12.8	20.9

Guidance for the treatment and prevention of osteoporosis has been provided in the UK by the Royal College of Physicians (RCP) [62–64]. The RCP recommends that BMD testing should be undertaken in postmenopausal women with strong risk factors for fracture and that treatment is to be considered where the T-score for BMD ≤−2.5 SD. A less stringent T-score is recommended for glucocorticoid-induced osteoporosis [64] and treatment is also recommended for women with a prior fragility fracture without necessarily measuring BMD. Similar approaches to case finding have been recommended by the European Community and the International Osteoporosis Foundation [65, 66]. The results of the present analysis strengthen the foundations of these guidelines from a health economic perspective for the treatment of strontium ranelate in women aged 65 years or more.

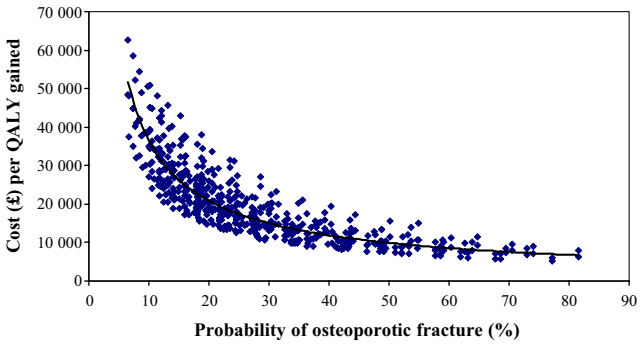

Fig. 1 Correlation between the 10-year probability of a major osteoporotic fracture and cost-effectiveness of strontium ranelate at the age of 70 years in women (BMI set to 26 kg/m^2). Each point represents a particular combination of clinical risk factors. The *upper panel* shows the base case, and the *lower panel* results derived from the post hoc analysis

Direct comparisons with the results in the NICE appraisals are problematic because their evaluations provide estimates of cost-effectiveness over a range of age and range of T-scores (e.g., patients below −3.0 SD), whereas our analysis provides the cost-effectiveness for a specific T-score (e.g., at −3.0 or at −3.5 SD) and a specific age (e.g., at 55 years or at 60 years). Although a direct comparison is difficult, it is clear that the results in this study contrast markedly with those of the NICE appraisals [4, 5]. The assessment of NICE consistently found higher ICERs for any clinical scenario, so that the T-score at which intervention was recommended was consistently more stringent than estimated in our analysis.

Table 5 Ten-year probabilities (mean and 95% confidence intervals (CI)) of a major osteoporotic fracture (percent) by age at or above which treatment with strontium ranelate becomes cost-effective

Age (years)	10-year probability of osteoporotic fracture (percent) with BMD at a WTP of			
	£20,000/QALY		£30,000/QALY	
	Probability	95% CI	Probability	95% CI
Base case				
50	46.1	16.6–138	17.0	10.0–51.6
55	47.5	19.3–112	19.7	14.4–52.5
60	46.5	22.0–91.6	23.8	16.4–52.8
65	27.8	18.1–52.9	17.1	12.4–25.2
70	25.0	17.0–40.0	15.4	10.3–21.0
75	35.3	21.4–137	26.2	16.0–39.7
80	36.4	20.9–94.4	32.1	17.3–69.5
Post hoc analysis				
50	19.6	14.6–99.6	13.4	9.6–18.5
55	25.1	18.0–61.4	17.1	13.2–22.4
60	27.1	19.3–49.2	19.0	14.9–26.5
65	20.5	16.3–30.3	14.6	10.7–18.8
70	18.3	14.3–24.2	12.1	9.4–16.1
75	21.6	16.1–29.1	17.0	12.0–22.9
80	22.7	17.0–30.3	19.0	14.2–25.8

It is difficult to determine why the results of the present study and those of NICE differ, but ultimately reasons reside in either the construct of the model or the assumptions used to populate the model. The most apparent difference related to the model construct is the use of different time horizons, i.e., the time the patients are followed in the model simulations. The NICE model predominantly uses a 10-year time horizon which, as shown in our sensitivity analysis and elsewhere [25], has a large effect on the cost-effectiveness. The NICE model do take account of deaths occurring after 10 years abut none of the other consequences of fracture. Unfortunately, there are no data that test the sensitivity of the NICE model to changes in the time horizon and inclusion of other consequences of death beyond 10 years. In health economic analysis, all consequences related to the intervention should be considered regardless at what point in time they occur. In chronic diseases, the most appropriate approach is to model over remaining lifetimes [Drummond and NICE guidelines].

Another difference relate to the estimation of risk based on clinical risk factors. For example, in the NICE model, BMI was treated as dichotomous rather than a continuous variable, the CRFs were given equal weighting on fracture risk and no account was taken of the effects of the clinical risk factors on the death hazard.

There are also differences in the assumptions used to populate the model. Most of these were modeled in sensitivity analyses. For example, the inclusion of side effects of strontium ranelate had a small impact on cost-effectiveness using the assumptions that side effects were the same as NICE assumed for the bisphosphonates. We also included the results of the post hoc analysis, which had a much larger effect on cost-effectiveness. The relevance of such a post hoc subgroup analysis is debatable but a number of studies in the field of osteoporosis suggest that greater efficacy is observed in those patients at higher risk [14, 67–69].

To date, treatment of osteoporosis has largely been directed by the level of BMD. The appreciation that age and a variety of clinical risk factors modulate risk and therefore cost-effectiveness, reinforce the view that treatment should be directed on the basis of fracture probability, rather than on a BMD threshold [60, 70, 71]. The preferred metric is the probability of fracture, e.g., the 10-year fracture probability that integrates not only fracture hazards, but also competing death hazards. From a health economic perspective, an intervention threshold represents the fracture probability at which treatment becomes cost-effective. Intervention thresholds have previously been estimated for the UK [27, 28], but were based on hip fracture probability alone and not on specific interventions. The present study uses the FRAX® tool to determine the average fracture probability above which treatment becomes cost-effective. At a WTP of £20,000, intervention with strontium ranelate became cost-effective at or above a 10-year fracture probability of 25.7% and at or above 16.9% with a WTP of £30,000. If the post hoc analysis is considered then the respective probabilities were 18.3% and 12.6%. Such data

could be used to inform clinical practice guidelines, as has been done in the case of alendronate [11].

In post marketing research, a few cases of DRESS syndrome have been reported (some of which have had fatal consequences) which potentially could be related to strontium treatment [72, 73]. However, the DRESS is a very rare event (one per 570,000 patient years of exposure) and is unlikely to impact the ICER. For this reason and because more research is needed to establish the causative link between strontium ranelate and DRESS, we chose not to incorporate it in the cost-effectiveness analysis.

This study presents the cost-effectiveness of strontium ranelate compared to a no treatment alternative. Other interventions were thus not considered in the analysis. It could be argued that the large number of untreated patients in clinical practice makes "no treatment" a relevant comparator. A direct comparison between different osteoporotic agents in a cost-effectiveness context is problematic because there are currently no head to head trials available using a fracture outcome. The value of an incremental analysis between the individual treatments is therefore questionable, since any resulting hierarchy of treatments is dependent largely on price, but otherwise relatively meaningless in clinical terms. This is clearly shown in a recent study which estimated the cost-effectiveness of other osteoporotic medications [25]. The study showed that the cost-effectiveness of generic alendronate generates lower cost-effectiveness ratios mainly due to lower drug price. Because of the low price of generic alendronate, it has to be considered as a first-line treatment option in the UK. However, this study shows that there are cost-effective scenarios for treatment with strontium ranelate making it a credible option for patients that are unable to take alendronate for some reason. Ultimately, the decision of which treatment that is most suitable for an individual patient in clinical practice has to be based on factors such as shown differences in shown efficacy of each agent at different fracture sites, patient preferences, gastrointestinal tolerance, and the health condition of the patient.

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