ORIGINAL ARTICLE

The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX®

F. Borgström · O. Ström · J. Coelho · H. Johansson · A. Oden · E. V. McCloskey · J. A. Kanis

Abstract

Summary The study estimated the cost-effectiveness of risedronate compared to no treatment in UK women using the FRAX algorithm for fracture risk assessment. A Markov cohort model was used to estimate the cost-effectiveness. Risedronate was found cost-effective from the age of 65 years, assuming a willingness to pay for a QALY of £30,000.

Introduction The aim of this study was to assess the cost-effectiveness of risedronate for the prevention and treatment in a UK setting using the FRAX® algorithm for fracture risk assessment. A further aim was to establish intervention thresholds with risedronate treatment.

Methods The cost-effectiveness of risedronate was compared to no treatment in post-menopausal women with clinical risk factors for fracture using a Markov cohort model populated with data relevant for the UK. The model incorporated the features of FRAX® (the WHO risk assessment tool). The analysis had a health care perspective and quality adjusted life years was used as the main outcome measure.

Results Treatment was cost-effective from the age of 65 years, assuming a willingness to pay for a QALY of £30,000. Treatment was also cost-effective at all ages in women who had previously sustained a fragility fracture or in women with a parental history of hip fracture with a bone mineral density set at the threshold of osteoporosis. At the £30,000 threshold value for a QALY, risedronate was on average found to cost-effective below the 10-year probability of a major osteoporotic fractures of 13.0%.

Conclusions Risedronate is a cost-effective agent for the treatment of established osteoporosis (osteoporosis and a prior fragility fracture) in women from the age of 50 years and older and above 65 years in women with osteoporosis alone. The results support the treatment recommendations in recent UK guidelines for osteoporosis.

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

F. Borgström · O. Ström
Medical Management Centre, Karolinska Institute,
Stockholm, Sweden

F. Borgström (✉) · O. Ström · J. Coelho
I3 Innovus,
Klarabergsviadukten 90, Hus D,
111 60 Stockholm, Sweden
e-mail: fredrik.borgstrom@i3innovus.com

H. Johansson · A. Oden · E. V. McCloskey · J. A. Kanis
Centre for Metabolic Bone Diseases (WHO Collaborating Centre)
University of Sheffield Medical School,
Sheffield, UK

Introduction

Since the early 1990s, osteoporosis has been defined on the basis of bone mineral density (BMD), and the prevailing approach to treatment guidelines for osteoporosis has focused on BMD, existing prevalent fracture and age as the main determinants whether treatment should be recommended. However, there is now a movement from this approach towards assessment based on absolute fracture risk [1–8]. This has been facilitated by the development of new instruments for fracture risk assessment such as FRAX®, which allows estimation of the individual fracture risk based on more risk factors than the traditional T-score, age and prevalent fracture (e.g. smoking, body mass index (BMI), alcohol, parental fracture) [9]. The approach is intended to simplify the identification of patients eligible for treatment in clinical practice.

It has become increasingly common to place recommendations concerning the use of osteoporosis treatments in a health economic context in order to justify resource allocation and form the basis for 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 [10–14]. With the change towards absolute fracture risk, it is important to consider the health economic implications. Instead of estimating the cost-effectiveness for a range of BMD values for a patient population, it is, in the context of absolute fracture risk, more relevant to assess at what fracture probability treatment is cost-effective (i.e. the intervention threshold)

When incorporated in health economic analysis, the FRAX® improves the precision in fracture risk estimation beyond that previously possible [15]. In most previous cost-effectiveness studies of osteoporotic treatments, the fracture risk was derived based on a BMD value, prevalent fracture and age, whilst assuming that the weight of all other risk factors equalled that of the general population. By using FRAX®, it is now possible to assess the fracture risk based on a multiple combination of risk factors.

The aim of this study was to assess the cost-effectiveness of risedronate for the prevention and treatment in a UK setting using the FRAX® tool for determining fracture risk for patient groups with different risk factor profiles. A second aim was to establish intervention thresholds with risedronate treatment defined in terms of fracture probability.

Methods

The cost-effectiveness of risedronate was compared to no intervention in a UK setting by simulating costs and outcomes in cohorts of post-menopausal women from the age of 50 years 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). Costs and effects were discounted at 3.5% as recommended by NICE [16]. 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 risedronate 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 [17–25]. 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 the 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 site 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 [15, 34, 35]. The same approach was used to assess the risk of rib fractures.

The age-specific normal mortality rates for the general population in the UK were based on the 2004–2006 data [36]. The increase in mortality after hip and clinical vertebral fractures was derived from Odén et al. [37] and Johnell et al. [38].

Effect of treatment

The effects of risedronate on fracture risk used in the base-case analyses were derived by performing a meta-analysis

based on the three pivotal clinical studies studying the efficacy of risedronate on fracture risk compared to placebo [39–41]. The estimated relative risk (RR) of risedronate treatment from the meta-analysis were 0.66 (95% CI, 0.48–0.91) for hip fracture, 0.62 (95% CI, 0.50- 0.77) for vertebral fracture, 0.68 (95% CI, 0.42–1.08) for wrist fracture and 0.68 (95% CI, 0.70–0.98) for other osteoporotic fractures.

In a recent post hoc analysis, based on four randomised clinical trials, the fracture risk reduction of risedronate treatment was estimated in post-menopausal women with osteopenia (T-scores between −1 and −2.5 SD at the femoral neck) and no prevalent vertebral fractures [42]. The results showed that risedronate reduced the risk of fragility fractures by 73% (RR=0.27; 95% CI, 0.09–0.71). Using this efficacy for assigned all-fracture events, the cost-effectiveness was assessed for an osteopenic population in a sub-group analysis.

The duration of the intervention was set to 5 years, which is the most common treatment duration used in the majority of cost-effectiveness analyses [17–20, 23, 25]. After stopping treatment, the risk reduction was assumed to reverse in a linear manner over a 5-year period. Recent studies with the bisphosphonates suggest that this offset time may vary [43–45]. In view of this uncertainty, a 40% change in offset time was used in sensitivity analysis.

Side effects were not included in the base case since randomised studies of efficacy have shown few persistent differences between placebo and actively treated patients. In the NICE appraisal, it was assumed that side effects for bisphosphonates [46] 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 [46]. These assumptions were included in a sensitivity analysis.

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 [47, 48]. Therefore, it was assumed that 50% of the patients stopped treatment within the first year. These patients received 3 months of drug treatment for no health gain [13, 14, 35]. The remaining patients were assumed to stay on treatment for the whole intervention period. 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. [49]. Average in- 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 [50, 51] 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 [52, 53]. Nursing home costs were not included for fractures at other sites that might require admission to a nursing home.

The annual cost of medication was assumed to be £264.63 (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 bi-annually thereafter.

Quality of life

Quality of life losses in the first year after a hip, vertebral and a wrist fracture were based on empirical estimates [50, 51]. 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 was 35% and 7%. The reduction in QoL with other fractures was based on expert opinion [54]. 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 [51]. The quality of life in subsequent years after a vertebral fracture was reduced by 7% derived from empirical observations [55]. Wrist fractures were assumed to have no quality of life reduction in the second and subsequent years. These multipliers were used together with the population tariff values for the UK [56]. In a sensitivity analysis, a more conservative utility loss of 27% related the first year after a vertebral fracture was tested [13, 14].

The FRAX® algorithm

The FRAX® tool (http://www.shef.ac.uk/FRAX/index.htm) was developed by the World Health Organization Collaborating Centre at Sheffield, UK [9, 57, 58]. The clinical risk factors used were identified from a series of meta-analyses that identified clinical risk factors associated with an increase in fracture risk independently 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 oral glucocorticoids, rheumatoid arthritis, current cigarette smoking and high alcohol consumption (three 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 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 modelled clinical scenario. The FRAX® tool calibrated to the epidemiology of fracture and death in the UK was used in this study [9].

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 the FRAX® model. However, BMI was set to a fixed value of 26 kg/m^2, which is close to the average value for post-menopausal 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 maximum cost per QALY permitted (willingness to pay; WTP) was set at £30,000 per QALY. However, a WTP of £20,000 was also considered. Other clinical scenarios were modelled in sensitivity analyses. For these and other sensitivity analyses, 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 [1]. 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 BMI set to 26 kg/m^2. It should be noted that this was not a population simulation, but an array of all possible combinations.

Results

The cost-effectiveness of risedronate in women at the threshold of osteoporosis (i.e. at T-score of −2.5 SD at the femoral neck) is shown in Table 1. In women with osteoporosis, treatment was cost-effective from the age of 65 years, assuming a WTP of £30,000/QALY and from the age of 70 years with a WTP of £20,000/QALY. Treatment

Table 1 Cost-effectiveness of intervention with risedronate in women at the threshold of osteoporosis (T-score=−2.5) and corresponding 10-year risk of major osteoporotic fracture, 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)	Self-identifying								Opportunistic case finding			
	T-score=−2.5		T-score=−2.5		No BMD		T-score=−2.5		No BMD	
	No previous fracture		Previous fracture		Previous fracture		Parental history		Parental history	
	ICER	10-year risk (%) of major fracture	+ previous fracture	10-year risk (%) of major fracture	ICER	10-year risk (%) of major fracture	ICER	10-year risk (%) of major fracture	ICER	10-year risk (%) of major fracture
Base case										
50	40.8	6.38	26.6	12.00	44.7	7.15	24.2	11.61	38.4	6.67
55	43.0	7.98	29.0	14.30	45.6	9.23	24.9	14.45	38.1	8.72
60	40.5	9.69	28.0	16.56	40.6	11.80	23.4	17.39	33.8	11.26
65	24.5	12.32	16.5	20.03	22.3	15.99	13.7	21.92	19.1	15.60
70	18. 6	14.23	11.8	22.09	15.1	19.66	7.9	22.98	15.0	16.75
75	19.8	15.28	13.2	22.60	15.0	22.61	cs	29.33	10.5	21.89
80	18.0	16.93	11.4	23.75	11.1	26.72	cs	33.40	cs	29.82

BMI set to 26 kg/m^2

cs cost saving

was also cost-effective at all ages in women who had previously sustained a fragility fracture or in women with a parental history of hip fracture with a BMD set at the threshold of osteoporosis. Indeed, treatment was cost saving from the age of 75 years in women with a parental history at the threshold of osteoporosis. A prior fragility fracture or a parental history was a sufficiently strong risk factor to indicate that treatment was cost-effective from the age of 65 years even in women in whom BMD was not known.

The effect of different clinical risk factors at different T-scores for BMD is shown in Table 2 for women at the age of 70 years. In women at the threshold of osteopenia (a T-score of −1 SD), treatment with risedronate was cost-effective in the presence of any single CRF with the exception of current smoking. At the threshold of osteoporosis, treatment with risedronate was cost-effective in the presence of any single CRF using a WTP of £20,000. Prior fractures and a parental history of hip fracture were the strongest risk factors, the use of glucocorticoids and the presence of rheumatoid arthritis had a lesser impact on cost-effectiveness and current smoking and excessive alcohol intake were the weakest of the clinical risk factors.

In the presence of more than one clinical risk factor, the ICER depended on the weight of the clinical risk factor (data not shown). In the absence of information on BMD, the combination of the weakest two risk factors gave an ICER of less than £30,000 from the age of 70 years and below £20,000 from the age of 75 years. In the presence of the strongest two clinical risk factors (family history and prior fracture) and in the absence of information on BMD test, the ICER lay below £30,000/QALY at all ages and below £20,000/QALY from the age of 65 years. In women aged 70 years with a BMD test, the ICER was below £20,000/QALY gained over the whole range of T-score examined and was cost saving with a T-score of −3.0 SD or less.

Probabilistic sensitivity analyses

In Fig. 1, a number of probabilistic analyses using the distribution of treatment efficacy are presented in the form of acceptability curves. The ICER fell below a threshold of £20,000 in 75.3% of the simulations in the in women aged 70 years without previous fracture. With a willingness to pay for a QALY set at £30,000, treatment was cost-effective in at least 98% of simulations in all base case scenarios.

Sub-group analysis of osteopenic patients

The cost-effectiveness of risedronate in post-menopausal women with osteopenia and no prevalent vertebral fracture is shown in Table 3. The ICER was below £30,000/QALY gained in all scenarios, i.e. between T-scores −1 and −2.5 SD and ages between 50 and 80 years. The apparent low cost-effectiveness ratios achieved at the relative low 10-year risk of fractures compared to the base cases are directly related to the 73% reduction in fragility fractures with risedronate treatment in this sub-group analysis.
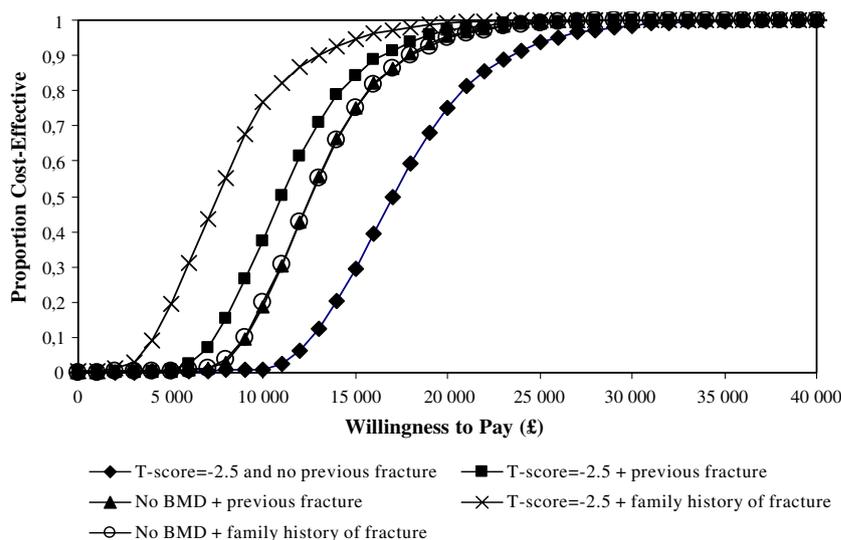
Sensitivity analysis

Sensitivity analysis showed that 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 in the NICE appraisal, were included, this had a very modest effect on cost-effectiveness using the lifetime horizon. Moderate effects on cost-effectiveness were observed with changes in the assumptions concerning efficacy, 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. 2 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

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

BMI set to 26 kg/m^2

	T-score (SD)							
	0.0	−0.5	−1.0	−1.5	−2.0	−2.5	−3.0	−3.5
No risk factor	44.0	39.4	35.0	30.3	25.2	18.6	12.4	6.6
Prior fracture	31.4	27.9	24.8	21.2	17.2	11.8	6.8	1.8
Family history	27.1	23.8	20.6	16.9	12.9	7.99	3.3	cs
Glucocorticoids	30.5	27.8	24.4	21. 0	16.4	10.9	5.3	cs
Rheumatoid arthritis	33.5	30.1	26.4	22.6	18.2	12.6	7.4	2.5
Alcohol >3 units daily	36. 6	32.3	28.1	23.7	18.9	12.7	7.2	1.9
Current smoking	51.6	45.8	40.1	33.9	26.4	17.5	8.8	0.4

Fig. 1 Probabilistic sensitivity analysis presented as acceptability curves

which treatment became cost-effective at different ages with a mean value of 18.6% at a WTP of £20,000 and 13.0% and at a WTP of £30,000. Thus, with a WTP of £20,000, any recommendations for intervention should ensure that individuals have a fracture probability that exceeds 18.6%.

Discussion

The principal finding of the present study is that cost-effective scenarios are found for the treatment of osteoporosis and established osteoporosis (i.e. osteoporosis with fracture) with risedronate in post-menopausal women. In the case of a prior fracture, the ICER lay below a WTP of £30,000 at the threshold of osteoporosis from the age of 50 years and fell below the more stringent WTP of £20,000 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. At a

WTP threshold of £20,000, treatment with risedronate was cost-effective in women with a family history from the age of 65 years in women with a T-score of −2.5 SD or less and also in the absence of BMD. Our finding of good cost-effectiveness for the treatment of osteoporosis is not surprising, given that many treatments in osteoporosis or established osteoporosis, including risedronate, have been shown to be cost-effective in a UK setting [19, 20, 59].

The cost-effectiveness was also estimated for women with osteopenia without prevalent vertebral fractures based on a post hoc analysis of four clinical trials that studied the efficacy of risedronate [42]. The cost-effectiveness results showed that the ICER fell below £30,000 already at the age of 50 years and a T-score of −1, which are patients usually not considered being at high risk of fracture. The cost-effectiveness is primarily driven by the high efficacy (73% risk reduction) estimated in the post hoc analysis. Also, to be considered is that the risk reduction of vertebral fractures solely was not found to be significant (HR, 0.44; 95% CI, 0.11–1.78) in the post hoc analysis. However, non-vertebral fractures were shown to have a significant risk reduction

Table 3 Cost-effectiveness of intervention with risedronate (cost (£000)/QALY gained) in women with osteopenia and no prevalent fractures and corresponding 10-year risk of major osteoporotic fracture

Age (years)	T-score=−1		T-score=−1.5		T-score=−2		T-score=−2.5	
	ICER	10-year risk (%) of major fracture	ICER	10-year risk (%) of major fracture	ICER	10-year risk (%) of major fracture	ICER	10-year risk (%) of major fracture
50	29.5	3.72	25.2	4.31	20.7	5.14	15.9	6.38
60	28.7	5.58	24.6	6.43	19.8	7.79	14.9	9.69
70	12.3	8.36	10.1	9.48	7.2	11.38	3.9	14.23
80	12.2	9.95	8.2	11.62	3.6	13.69	cs	16.93

BMI set to 26 kg/m^2

cs cost saving

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

| | Cost (£000)/QALY gained | | | | |
| | Self-identifying | | | Opportunistic case finding | |
	T-score=−2.5 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					
Base case	18.6	11.8	13.9	7.9	13.8
10-year time horizon	38.7	26.3	31.2	17.5	30.5
Offset time +40% (7 years)	16.5	10.1	12.2	6.4	12.1
Offset time—40% (3 years)	21.1	13.9	15.9	9.7	15.9
Non-adherence +40% (70%)	20.5	13.9	16.0	9.3	15.4
Non-adherence—40% (30%)	17.7	10.9	12.9	7.3	13.1
Higher utility for vertebral fracture	19.5	12.6	14.7	8.3	14.5
Side effects	19.8	13.4	14.9	9.9	14.9

(HR, 0.09; 95% CI, 0.01–0.71) which was higher than the overall fracture risk reduction [42]. Using the separated efficacy of vertebral and non-vertebral fractures yields similar cost-effectiveness ratios compared to using the overall efficacy. When only assuming a fracture risk reduction for non-vertebral fractures, the ICER was almost doubled.

The current indication for risedronate in the UK is for the prevention of hip and vertebral fractures in the treatment of established osteoporosis (i.e. patients with prevalent fracture) and for the prevention of vertebral fractures in patients with osteoporosis. Given a threshold value of £30,000 for a QALY, the results in this study supports the indication for treatment of established osteoporosis at all ages between 50 and 80 years. The preventive indication is supported by the results from about 65 years and older. However, this is under the conservative assumption that the patient does not have any other CRF than low BMD. Adding a risk factor would increase the fracture risk

and thus also improve the ICER and lower the limit when it would be cost-effective to treat.

The estimated cost-effectiveness of risedronate treatment in this study is well aligned and supports the recommendations in recently issued treatment guidelines. For example in the Royal College of Physicians guidelines for the treatment and prevention of osteoporosis [60–62], the recommendation is that BMD tests should be performed in post-menopausal women with strong risk factors for fracture and that treatment is to be considered where the T-score for BMD ≤−2.5 SD. For women with a prior fragility fracture, treatment is also recommended without necessarily measuring BMD [62]. Similar approaches to case finding have also been recommended by the European Community and the International Osteoporosis Foundation [63, 64].

There are two other studies published that have assessed the cost-effectiveness of risedronate in the UK [19, 65]. In Iglesias et al. [19], risedronate was shown to be cost saving compared to no treatment in 75-year-old women with

Fig. 2 Correlation between the 10-year probability of a major osteoporotic fracture and cost-effectiveness of risedronate at the age of 50 years in women (BMI set to 26 kg/m²). Each point represents a particular combination of clinical risk factors
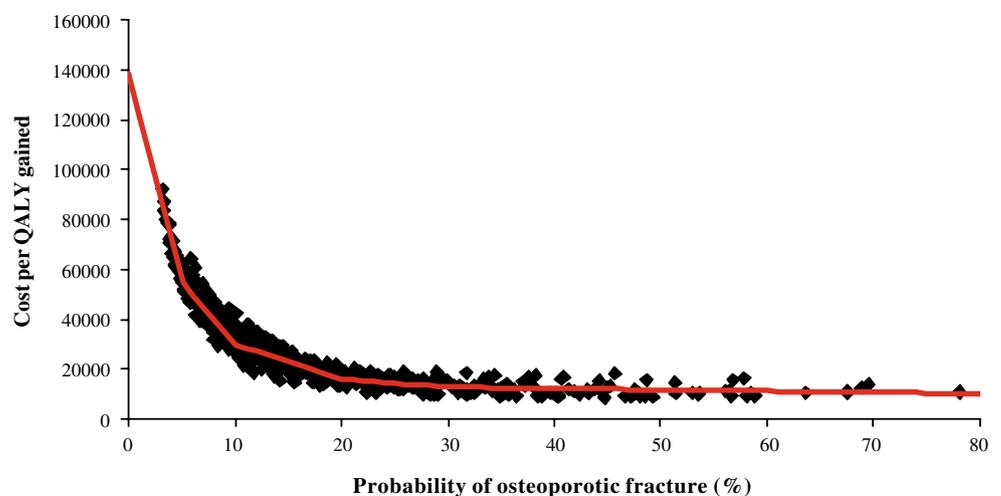
Table 5 Probability (mean and 95% confidence intervals; CI) within 10 years of a major osteoporotic fracture (%) by age at or above which treatment with risedronate becomes cost-effective

Age (years)	10-year probability of osteoporotic fracture (%) with BMD at a WTP of			
	£20 000/QALY		£30 000/QALY	
	Probability	95% CI	Probability	95% CI
50	17.1	12.1–29.4	10.0	8.6–14.9
55	19.8	16.1–29.3	14.3	10.6–18.0
60	23.0	17.5–33.2	16.5	12.6–20.8
65	18.0	14.4–23.9	11.9	9.4–15.4
70	16.1	12.9–19.2	9.9	8.9–12.9
75	17.9	13.8–23.3	13.3	9.7–17.4
80	18.3	14.7–24.3	15.2	11.6–18.9

established osteoporosis, and in Kanis et al. [19], the cost per QALY gained was estimated to £10,363 for 70-year-old women with a T-score of −2.5 SD and a prevalent vertebral fracture. It is not entirely straightforward to compare these results with the current study since there are differences in model structures, data input and assumptions. One key difference is the method to assess fracture risk for the target patients in the analyses. In most previous studies, the fracture risk for the target patient population in the analysis has been based on age, BMD and prevalent vertebral fracture. All other risk factors have been assumed to be at the same level as in the general population. With the use of FRAX®, the presence of CRFs included have to be defined, which means that at a given age and BMD value, FRAX® will render somewhat lower fracture risks compared to the old approach and thus yield somewhat higher cost-effectiveness ratios.

Another recent cost-effectiveness estimation of risedronate was performed in the NICE appraisal [13, 14]. The appraisal results appear to show poorer cost-effectiveness than our results. Even though much of the data regarding costs and quality of life are the same, a direct comparison to our results is not straightforward. For example in the NICE reports, the cost-effectiveness is estimated over a range of age and range of T-scores, 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 or at 60 years). Also, there are differences in the assumed time horizon (the time patients are followed in the model simulations) and the approach of estimating fracture risk. In the NICE analyses, the simulation model uses a 10-year time horizon, whereas a lifetime horizon is used in our study. The large impact of reducing the time horizon to 10 years is shown in the sensitivity analyses (the ICER is doubled). Although the NICE model does consider deaths occurring after 10 years, it does not include the long-term consequences of fracture. Another difference relates 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 modelled in sensitivity analyses. For example, the inclusion of side effects of risedronate had a small impact on cost-effectiveness using the assumptions that side effects were the same as NICE assumed for the bisphosphonates.

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 [57, 66, 67]. 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 risedronate became cost-effective at or above a 10-year fracture probability of 18.6% and at or above 13.0% with a WTP of £30,000.

This study presents the cost-effectiveness of risedronate 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 due to the lack

of head to head trials 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, which are mainly driven by a lower drug price. Because of the low drug price, generic alendronate is generally considered as the first line treatment option in the UK. However, this study shows that there are cost-effective scenarios for treatment with risedronate compared to no treatment, making it a viable option for patients that are not candidates for receiving 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.

Conflicts of interest JAK, FB, OS, EMcC, HJ and AO act as advisors to and have received funding from many pharmaceutical companies involved in marketing products for treatment of osteoporosis.

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