NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

The clinical effectiveness and cost effectiveness of technologies for the prevention of osteoporotic fragility fractures in postmenopausal women

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members prior to the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties.

A list of the sources of evidence used in the preparation of this document is given in Appendix A.

This overview summarises the background and evidence from two appraisals:

1) The clinical effectiveness and cost effectiveness of drugs for the primary prevention of osteoporotic fragility fractures in postmenopausal women
2) Strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis.

The overview also includes information relating to the use of drugs for the secondary prevention of osteoporotic fractures so that the Committee may consider the extent to which previous guidance should be updated in view of new data which has recently become available.

The aims of the Appraisal Committee meeting in September 2005 are:

- to discuss the clinical and cost effectiveness of bisphosphonates, SERMs and strontium ranelate for the primary prevention of osteoporotic fractures in postmenopausal women
- to discuss the clinical and cost effectiveness of strontium ranelate for the secondary prevention of osteoporotic fractures in postmenopausal women
- to consider the extent to which the published Technology Appraisal No. 87 requires updating.

1 Background

1.1 Remit and current guidance

In 2002 NICE received the remit to develop guidance for the prevention and treatment of osteoporosis and the prevention of osteoporotic fractures in postmenopausal women. The scope for this appraisal included the drugs alendronate, risedronate, etidronate, raloxifene and teriparatide.

In February 2004, the Appraisal Committee agreed that the existing evidence was sufficient to allow the development of guidance for women with previous fracture (secondary prevention). This was published in January 2005 (see Appendix B). However, the Appraisal Committee concluded that further evidence was required before issuing guidance on the use of drugs in women without a previous history of fracture for the following reasons.

- The cost of the strategy for identification of women at high risk of fracture needed to be included in the economic modelling.
- It was anticipated that the World Health Organization (WHO) would publish a full risk algorithm that would integrate all clinical risk factors in the calculation of absolute risk of fracture.

In 2004 NICE received the remit to develop guidance for strontium ranelate for the prevention of osteoporotic fractures in postmenopausal women. Because of the extension of the timelines for the primary prevention appraisal, the timelines for both appraisals now coincide.

A clinical guideline on osteoporosis ('Assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk') is in development. The guideline development group (GDG) have been closely involved in these appraisals.

1.2 The condition

Osteoporosis is a progressive, systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

Bone formation exceeds bone resorption in youth, but by the third decade of life there is a gradual loss of bone mass. Osteoporosis is therefore usually an age-related disease. It can affect both sexes, but women are at greater risk because bone loss is accelerated after the menopause.

Diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD), with reference to the number of standard deviations (T-score) from the BMD in an average 25-year-old woman:

- normal: T-score of –1 or above
- osteopenia: T-score of between –1 and –2.5
- osteoporosis: T-score of –2.5 or below
- established/severe osteoporosis: T-score of –2.5 or below with one or more associated fractures.

T-score measurements vary by site and method. It has been recommended that BMD should be measured at the femoral neck using dual-energy X-ray absorptiometry (DXA) to estimate fracture risk.

UK-specific data from 1998 indicate that there are 1.14 million women with osteoporosis in England and Wales. The National Osteoporosis Society, however, estimates that there are 3 million postmenopausal women with osteoporosis in the UK. Osteoporosis is most common in white women. Prevalence of osteoporosis increases markedly with age after menopause from approximately 2% at 50 years of age rising to over 25% at 80 years.

In the absence of fracture the condition is asymptomatic and often remains undiagnosed. Osteoporotic fractures occur most commonly in the vertebrae, hip and wrist and are associated with substantial disability, pain and reduced quality of life.

In women aged over 50 years, the lifetime risk of a vertebral fracture is estimated to be one in three, and one in five for hip fracture. Postmenopausal women with an initial fracture are at substantially greater risk of subsequent fractures. For instance, a woman with a vertebral fracture has an increased relative risk of 4.4 for a further vertebral fracture, 2.5 for a hip fracture, and 1.7 for a wrist fracture.

It is estimated that annually there are 180,000 osteoporosis-related symptomatic fractures in England and Wales. Of these, 70,000 are hip fractures, 25,000 are clinical vertebral fractures, and 41,000 are wrist fractures.

After a hip fracture, a high proportion of women are permanently unable to walk independently or perform other activities of daily living and, consequently, are unable to live independently. Hip fractures are also associated with increased mortality; estimates of the relative mortality risk vary from 2 to greater than 10 in the 12 months following hip fracture. However, it is unclear to what the extent this can be attributed to fracture alone as opposed to pre-existing comorbidity.

Vertebral fractures are associated with loss of height and curvature of the spine and may result in pain, breathing difficulties, gastrointestinal problems and difficulties performing activities of daily living. It is thought that the majority of vertebral fractures (50–70%) do not come to clinical attention. Vertebral fractures are also associated with increased mortality; UK-specific data indicate a 4.4-fold increase in mortality due

to vertebral fractures. However, as with hip fractures, it is unclear to what extent this may be due to comorbidities.

In addition to increasing age and low BMD, other clinical factors have been associated with an increased fracture risk, such as prior fracture, parental history of osteoporotic fracture, particularly hip fracture, systemic corticosteroid use, low body mass index, early menopause, smoking, rheumatoid arthritis, alcohol consumption and conditions affecting bone metabolism.

1.3 Current management

The aim of interventions for postmenopausal osteoporosis is to prevent further bone loss and reduce the risk of fractures. Interventions include lifestyle modifications, drug therapy and fall-prevention programmes.

Lifestyle factors such as regular weight-bearing exercise and adequate dietary calcium/vitamin D intake help to prevent deterioration of BMD.

Drug therapy may also be considered in postmenopausal women. Hormone replacement therapy (HRT) has, in the past, been prescribed widely for the prophylaxis of postmenopausal osteoporosis, but long-term use must be balanced against potential risks associated with HRT such as increased risk of breast cancer and thromboembolism.

Other drugs for osteoporosis include bisphosphonates (alendronate, risedronate and etidronate); selective oestrogen receptor modulators (SERMs), of which raloxifene is the only agent licensed for the treatment and prevention of osteoporosis; strontium ranelate; and parathyroid hormone (teriparatide).

2 The technologies

Alendronate is an oral bisphosphonate, licensed in the UK at a dosage of 5 mg/day for the prevention of postmenopausal osteoporosis and at a dosage of 10 mg/day for the treatment of postmenopausal osteoporosis. A once a week preparation (70 mg) is also licensed for the treatment of postmenopausal osteoporosis.

Risedronate is an oral bisphosphonate licensed at a dosage of 5 mg/day for the prevention and treatment of postmenopausal osteoporosis, and at a dosage of 35 mg once a week for the treatment of postmenopausal osteoporosis.

For alendronate and risedronate, there are special recommendations for administration to ensure adequate absorption and to prevent oesophageal adverse effects. These involve taking the drug with more than 100 ml of water separated from main meals and in an upright position, and remaining upright for some time after taking the drug. Common side effects of these drugs include gastrointestinal symptoms.

Etidronate is an oral bisphosphonate, licensed for the treatment of osteoporosis and prevention of bone loss in postmenopausal women. The drug is licensed at a dosage of 400 mg/day for 14 days of a 90-day cycle followed by calcium carbonate for the remaining 76 days.

Raloxifene is currently the only selective oestrogen receptor modulator licensed for the treatment and prevention of osteoporosis in postmenopausal women. The recommended dose is 60 mg/day. It should not be co-administered with systemic oestrogens and, in patients with breast cancer, should be used for osteoporosis treatment and prevention only after treatment of the breast cancer, including adjuvant therapy, has been completed.

Teriparatide is a recombinant human parathyroid hormone that stimulates new bone formation. It is licensed for the treatment of established osteoporosis in postmenopausal women. The recommended dose of teriparatide is 20 micrograms once daily by subcutaneous injection in the thigh or abdomen (using a pre-filled pen intended for 28 days use). The maximum total duration of treatment should not exceed 18 months.

Strontium ranelate is licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. It is composed of two atoms of stable strontium (an element with properties similar to calcium) and one molecule of ranelic acid. It is thought to have a dual effect on bone metabolism, increasing bone formation and decreasing bone resorption. The recommended dosage of strontium ranelate is 2g/day as a suspension in water, preferably before bed or at least 2 hours after eating.

Further details for all drugs are given in Table 1, acquisition cost are based on the British National Formulary (BNF) edition 49, March 2005. (NB. The costs used in the cost-effectiveness modelling were sourced from an earlier edition of the BNF.)

Table 1 Summary description of technologies

Generic name	Proprietary name	Manufacturer	Acquisition cost/4 weeks
Alendronate	Fosamax	Merck Sharpe & Dohme	£23.12 / £22.80 (once daily/once weekly)
Risedronate	Actonel	Procter & Gamble/ Aventis	£19.10/ £20.30 (once daily/ once weekly)
Etidronate	Didronel PMO	Procter & Gamble	£11.63 (£37.39 for 90 days)
Raloxifene	Evista	Eli Lilly	£19.86
Teriparatide	Forsteo	Eli Lilly	£271.88
Strontium ranelate	Protelos	Servier Laboratories Ltd	£25.60

3 Clinical effectiveness evidence

3.1 Previously reviewed interventions (bisphosphonates, raloxifene and teriparatide)

3.1.1 Efficacy

The clinical evidence for bisphosphonates, raloxifene and teriparatide was obtained during the development of the original osteoporosis appraisal including for both primary and secondary prevention, and much has already been the subject of consultation and consideration by the Appraisal Committee.

The systematic review on the clinical effectiveness of these interventions was undertaken for the development of the secondary prevention guidance in 2002. The Assessment Group updated this systematic review for bisphosphonates and raloxifene for the primary prevention appraisal. Six new publications were identified, two of which related to new studies, and four presented additional relevant data relating to three studies which had been included in the original assessment report. These new studies and all studies from the original assessment report were included in a meta-analysis, the results of which are summarised in Table 2.

Relative risks were pooled regardless of the T-scores and fracture status of the trial participants on the basis that there is no plausible reason for the efficacy of the drugs to be altered following a fracture and there is no evidence showing a clear difference in efficacy between women with osteoporosis and osteopenia.

Although observational data showing reductions in rates of fracture were available for etidronate, the RCTs were of insufficient size and duration to show significant reductions in this endpoint. The GDG consensus was that only RCT evidence should be used for estimates of efficacy.

The review of the clinical effectiveness of teriparatide was undertaken for the development of the secondary prevention guidance in 2002. The relative risks (RRs) from the main trial comparing teriparatide with placebo are summarised in Table 2.

Table 2 Relative risk of fracture compared with no treatment

From the Assessment Group meta-analysis (95% confidence intervals)

Drug	Vertebral fracture	Hip, pelvis and other femoral fractures	Proximal humerus, rib, sternum, scapula, tibia and fibula fractures
Alendronate[a]	0.56 (0.46–0.68)	0.62 (0.40–0.98)	0.81 (0.68–0.97)
Trials/participants	*4/7039*	*4/7881*	*6/9973*
Risedronate[a]	0.61 (0.50–0.75)	0.74 (0.59–0.93)	0.76 (0.64–0.91)
Trials/participants	*3/2301*	*3/11770*	*5/12399*
Etidronate[a]	0.40 (0.20–0.83)	0.50 (0.05–5.34)	1.04 (0.64–1.69)
Trials/participants	*3/341*	*2/180*	*4/490*
Raloxifene[a]	0.65 (0.53–0.79)	1.13 (0.66–1.96)	0.92 (0.79–1.07)
Trials/participants	*1/4551*	*2/6971*	*1/6828*
Teriparatide[b]	0.35 (0.22–0.55)	0.50 (0.09–2.73)	0.65 (0.43–0.98)
Trials/participants	*1/1326*	*1/1637*	*1/1637*

[a]Data taken from DSU report, March 2005, Appendix 3
[b]Data taken from the Assessment Report for the original appraisal[1]

3.1.2 Adverse events

For alendronate, gastrointestinal adverse events including nausea, dyspepsia, mild oesophagitis/gastritis and abdominal pain were reported in about one-third of the RCT participants, but this was only statistically significant relative to placebo in one study. This is consistent with post-marketing studies indicating that around one-third of alendronate users experience gastrointestinal adverse events. For risedronate, overall and gastrointestinal adverse events were similar in the risedronate and placebo groups in all RCTs.

For etidronate, higher rates of gastrointestinal adverse effects were found in four RCTs, although the differences were not always statistically significant. However, non-RCT evidence and testimonies from clinical experts and patient experts suggested that etidronate may be associated with fewer gastrointestinal adverse effects than the other two bisphosphonates.

[1] *The Clinical Effectiveness and Cost Effectiveness of Prevention and Treatment of Osteoporosis*, Assessment report by Dr Matt Stevenson, ScHARR, University of Sheffield, February 2003.

For teriparatide, a proportion of women were reported to suffer mild discomfort at the injection site. A systematic review of teriparatide reported that treatment in a small proportion of women was associated with hypercalcaemia.

The most serious adverse effect associated with raloxifene is an approximately three-fold increase in the risk of venous thromboembolism.

In addition to the effect on fracture, raloxifene has been shown to reduce the incidence of invasive and non-invasive breast cancer with a relative risk (RR) of 0.38 (95% confidence interval [CI] 0.24–0.58). Raloxifene has also been shown to significantly increase the risk of venous thrombosis (RR 2.35; 95% CI 1.20–4.62).

3.2 Strontium ranelate

3.2.1 Efficacy

Three randomised, double-blind, placebo-controlled studies were identified.

- STRATOS investigated the efficacy and safety of different doses of strontium ranelate. A total of 353 osteoporotic women with at least one previous vertebral fracture and a lumbar T-score of less than –2.4 were randomised to receive placebo, or one of three dosages of strontium ranelate (0.5 g, 1 g or 2 g/day) for 2 years. Results showed that lumbar BMD, adjusted for bone strontium content (to account for strontium having higher atomic mass than calcium), increased in a dose-dependent manner and was significantly higher than in the placebo group. Vertebral fracture incidence was not affected in the first year of the study. During the second year of the study there were statistically significant effects in the 0.5 g and 2 g/day groups (0.5g/day RR 0.51 [95% CI, 0.31–0.84]; 2 g/day RR 0.56 [95% CI, 0.35–0.89]), but not in the 1 g/day group (RR 0.87 [95% CI. 0.59–1.26]). When the results were expressed in terms of the cumulative incidence over 2 years there was no significant effect of strontium ranelate on fracture incidence.

- SOTI investigated the efficacy of strontium ranelate in reducing the incidence of new vertebral fractures in a population of osteoporotic women with at least one prevalent vertebral fracture and a lumbar BMD of less than or equal to 0.840 g/cm^2 (lumbar T-score of less than or equal to –2.4). A total of 1649 women with a mean age of 69.3 years were randomised to receive either 2g/day of strontium ranelate or placebo. Follow-up was for 3 years.

- TROPOS was designed to demonstrate the efficacy of strontium ranelate in reducing the occurrence of incident osteoporosis-related peripheral fractures in a population of osteoporotic women with a femoral neck BMD of less than or equal to 0.60g/cm^2 (femoral neck T-score of less than –2.5). A total of 5091 women with a mean age of 76.8 years were randomised to receive either 2g/day of strontium ranelate or placebo. Follow-up was for 3 years. Pre-specified primary outcome was non-vertebral fracture, and pre-specified secondary outcome was the incidence of major non-vertebral osteoporotic

fractures. Vertebral fractures were not mandatory outcome, and data on vertebral fracture incidence were only obtained for part of the study population.

All participants in SOTI and TROPOS received Vitamin D supplements. They also received calcium supplements to maintain a daily calcium intake of at least 1500mg/day.

It was not possible for the Assessment Group to combine the results of the SOTI, STRATOS and TROPOS studies by meta-analysis as the SOTI and TROPOS studies did not publish the actual numbers of participants who suffered incident vertebral fracture, nor were these data available from the investigators. The efficacy data obtained from all three trials is summarised in Table 3, Table 4 and Table 5 below.

Table 3 Three-year vertebral fracture efficacy, relative risk calculated by the study investigators or published in the literature (95% CI)

Study	Reported in	Radiographic	Clinical
SOTI	Assessment Report	0.63 (0.52–0.67)	0.64 (0.49–0.85)
	Submission	0.59 (0.46–0.76)	0.62 (0.47–0.83)
TROPOS	Assessment Report	0.61 (0.51–0.73)	
	Assessment Report, with fracture	0.68 (0.53–0.85)	
	Assessment Report, without fracture	0.55 (0.42–0.72)	
SOTI + TROPOS pooled	Assessment Report	0.60 (0.53–0.69)	

Table 4 Three-year non-vertebral fracture efficacy, relative risk calculated by the study investigators or published in the literature (95% CI)

Study	Reported in	All non-vertebral fractures	Major osteoporosis-related peripheral fractures[a]	Patients with at least one incident osteoporosis-related peripheral fracture at 3 years
SOTI	Assessment Report	0.90 (0.71–1.15)		
TROPOS	Assessment Report			0.86 (0.73–1.02)
	Submission	0.84 (0.70–1.0)	0.81 (0.66–0.98)	
	Submission (without a previous fracture)	[redacted] CIC		
SOTI + TROPOS pooled	Assessment Report (Peripheral osteoporosis-related fractures)	0.84 (0.73–0.97)		

[a] Fractures occurring in wrist, pelvic-sacrum, ribs-sternum, clavicle, humerus, or proximal femur, taking into account the location of first fracture

Table 5 Three-year hip and other fracture efficacy, relative risk calculated by the study investigators or published in the literature (95% CI)

Study	Reported by	Hip	Wrist	Humerus
TROPOS	Assessment Report	[redacted][b]	[redacted] CIC	[redacted] CIC
	Assessment Report; Manufacturer	0.64 [a] (0.41–0.98)		
	Manufacturer	0.85 (0.61–1.19)	[redacted] CIC	

[a] Participants aged over 74 and osteoporotic at baseline

[b] based on the Assessment Groups own analysis based on patient numbers, which were provided CIC

3.2.2 Adverse events

The STRATOS study did not identify any differences between groups in the incidence of adverse events. Pooled data from the SOTI and TROPOS studies indicate that the most common adverse events (that is, those that occurred in more than 1% of the treatment or placebo group) were usually mild and transient. Nausea, diarrhoea and creatine kinase elevations were the most commonly reported clinical adverse events; they were generally reported at the beginning of therapy with no noticeable difference between groups thereafter.

The most serious adverse event associated with strontium ranelate therapy was an increased incidence of venous thromboembolism (VTE) and pulmonary embolism.

This was only identified when data from the SOTI and TROPOS studies were pooled (RR vs placebo 1.42; 95% CI 1.02–1.98). The risk of fatal pulmonary embolism was also increased but the difference did not achieve statistical significance compared with placebo (RR vs placebo 1.98; 95% CI 0.50–7.91). In addition, some nervous system disorders such as mental impairment, disturbed consciousness, memory loss and seizures were more common in patients randomised to strontium ranelate.

Strontium ranelate did not affect all-cause mortality (RR 1.02, 95% CI 0.69–1.50). However, there was an increased death rate due to cardiac disorders in patients receiving active treatment during the first year of therapy, but not thereafter. Deaths that could be related to thrombosis/embolism (including pulmonary embolism, cerebrovascular accident, and intestinal infarction) were also nominally more common in patients receiving active treatment.

3.2.3 Quality of life

Both the SOTI and the TROPOS studies recorded health-related quality of life every 6 months using the SF36 instrument; the SOTI study also used the quality of life in osteoporosis (QUALIOST) questionnaire. For the TROPOS study, no quality of life results were available.

In the SOTI study, strontium ranelate therapy was said to benefit quality of life as assessed by the QUALIOST specific scale and the General Health perception score of the SF36 general scale compared with placebo.

[redacted] (AIC).

3.2.4 Continuance and compliance

Compliance was reported to be 93% in the STRATOS study with no difference between groups, and compliance was 83% and 85% in the strontium ranelate and placebo groups of the SOTI study respectively. However, neither reported a definition of compliance and only the STRATOS study indicated how it had been measured. No data were available for the TROPOS study.

Participants in the SOTI and TROPOS studies were recruited into an open run-in study which may have increased compliance rates.

All three studies provided information on the proportion of participants who completed follow-up for the planned length of the study. In the STRATOS study, 73–77% of participants on active treatment and 81% on placebo completed the study. In the SOTI study, 76–77% of participants completed follow-up, as did 64–66% of participants in the TROPOS study, with no difference between treatment arms. However, while it is clear that in the STRATOS study this figure represents the

proportion who continued to take the study medication for the length of the study period, it is not clear whether all the participants who completed follow-up in the SOTI and TROPOS studies were still taking the study medication at the end of the 3-year period.

3.3 Conclusion – clinical effectiveness evidence

- The bisphosphonates alendronate and risedronate statistically significantly reduce the incidence of vertebral fractures, grouped non-vertebral fractures and hip fractures.
- The bisphosphonate etidronate statistically significantly reduces the incidence of vertebral fractures. RCT data do not show a statistically significant effect on the incidence of hip fracture. However, observational data support an effect on the incidence of hip fracture.
- Raloxifene statistically significantly reduces the incidence of vertebral fractures.
- Teriparatide statistically significantly reduces the incidence of vertebral and grouped non-vertebral fractures. The reduction seen on the incidence of hip fracture was not statistically significant.
- Strontium ranelate statistically significantly reduces the incidence of vertebral and grouped non-vertebral fractures. The effect on hip fracture incidence was not statistically significant. However, a subgroup analysis in women aged 74 and over showed a statistically significant effect on the incidence of hip fracture.

4 Cost effectiveness – primary prevention

The economic modelling for primary prevention was carried out in two steps.

1. The cost per QALY was estimated for the treatment of individual women over a range of absolute fracture risks using an updated version of the economic model from the earlier appraisal. It did not include the cost of any strategy for identification of women at high risk of fracture.
2. The impact of alternative approaches for identification of women who are at high risk of fracture on in the cost effectiveness of the interventions was explored.

This part of the overview presents the evidence in the following sequence.

- Section 4.1: Outline of the economic model used by the Assessment Group
- Section 4.2: Cost effectiveness in women without clinical risk factors.
- Section 4.3: The impact of clinical risk factors on cost effectiveness.
- Section 4.4: Integration of the identification costs with the cost effectiveness of alendronate for individual women using the net benefit approach.
- Section 4.5: Results of the economic modelling from the submissions.

4.1 Outline of the Assessment Group model

The Assessment Group used an updated version of the economic model that was used for the original appraisal.[2]

Costs per QALY were estimated for postmenopausal women in different age bands and at a T score of –2.5, or at other T-scores that nominally doubled risk. This model was similar to conventional state transition models, where hypothetical individuals pass through states using a set of time-dependent transition probabilities, and each state has its associated costs, mortality rates and health state utility values. The model simulated for each patient whether or not an event occurred in the forthcoming year and then a mean estimate was taken of costs and QALYs for each cohort. Factors such as prior fractures and current residential status were used to determine the probabilities of events in the next time period. The model simulated at 1-year intervals until either the patient died or a 10-year time horizon was reached. Treatment with the interventions was assumed to be for 5 years, with a linear decline of efficacy (fall time) after the 5-year treatment period.

4.1.1 Costs included in the current model

- Costs associated with fractures (see table 24 of strontium ranelate assessment report, page 63).
- Cost associated with death due to hip fracture (see table 24 of strontium ranelate assessment report, page 63)
- Drug costs (from BNF edition 48).
- GP costs for initial prescribing; costs for reviewing medication were as follows:
    - no GP costs for women aged 75 years and over (as these are assumed to be seen by a GP annually);
    - one-third of women below 75 years would require one GP appointment per annum (based on GP opinion that two-thirds of women over 50 routinely see their GP for other reasons) this was costed at £18.
    - Costs related to switching drug because of adverse effects were explored in a sensitivity analysis.
- DXA scans for diagnosis and treatment decision (£35 per DXA). No follow-up DXA scans for monitoring treatment were included in the model. This was considered to reflect clinical practice in the UK, based on the limited DXA availability, and preferential use of DXA for diagnosis. The original model included a DXA scan after 2 years of treatment for monitoring.

[2] Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, Technology appraisal No.87 issued January 2005

- Nursing home care as a result of fracture (see table 24 of strontium ranelate assessment report, page 63).

4.1.2 Utility multipliers used in the model

The utility weights used in the current model were based on a recently published study, assuming an initial utility in the year of fracture and a higher utility in subsequent years (Table 6). The utility multipliers for hip and vertebral fracture were lower, that is, more favourable to the interventions, than in the original model.

Table 6 Utility multipliers used in the modelling

Fracture type	Utility in 1st year following fracture	Utility in 2nd year following fracture
Vertebra (clinical)	0.626	0.909
Hip, pelvis and femoral shaft	0.792	0.813
Forearm, clavicle, scapula sternum and ribs	0.977	0.999
Humerus	0.794	0.973
Tibia and fibula	0.794	0.926

4.1.3 The current model differed from the original model as follows:

- **More fracture sites were considered.** In addition to hip, clinical vertebral, proximal humerus and wrist fractures, the current model includes rib, sternum, scapula, clavicle, humeral shaft, tibia, fibula, pelvis and femoral (other than hip) fractures.
- **Risk factors were aggregated and quantified as absolute risk.** The original model used T-score and age separately to stratify different levels of fracture risk. The current model uses an algorithm derived from a WHO study (see Appendix 12 of strontium ranelate Assessment Report) to aggregate different risk factors into absolute fracture risk. The WHO study involved the analysis of age, sex and the prevalence of several other clinical risk factors in 12 cohorts from Europe, North America and Asia, with a total of 60,000 people and 250,000 patient years. The WHO study results were made available to the Assessment Group under confidentiality. It was originally envisaged to use a 10-year absolute risk. However, the Assessment Group used an annual fracture risk, assumed constant over a 5-year period. This was done because fracture risk changes within a 10-year timeframe for postmenopausal women. For example, the use of a 10-year risk could allow women for whom treatment would not be cost effective between 70 and 74 years to receive treatment because of the large benefits gained between 75 and 80 years.

Absolute fracture risk is not the only determinant of cost effectiveness of interventions. The following parameters also change with age and need to be considered:

- the baseline proportion of fractures at each site
- the impact of clinical risk factors on hip and on non-hip fracture risk
- the mortality risk
- the baseline utility values
- the probability of entering a nursing home.

It was therefore necessary to establish the cost effectiveness for different age bands separately.

Due to the large number of cost-effectiveness estimates to be generated for different levels of absolute risk and age bands, only **single point RR** were used (Table 2). Where confidence intervals spanned unity, no effect was assumed. For strontium ranelate the following RR were used in the model: vertebral fractures: 0.60; hip, pelvis and other femoral fractures: [redacted] (CIC); wrist, proximal humerus, rib, sternum, scapula, tibia and fibula fractures: 0.84.

In the absence of evidence to the contrary, it was assumed that relative risks remain constant at all ages. There is, however, little evidence for the very elderly and this is noted as a caveat in the cost-effectiveness results produced for women aged 80 years and older in the published guidance on secondary prevention.

4.2 Cost effectiveness results in women without clinical risk factors (excluding identification costs)

The original modelling stratified women by T-score and age, and did not integrate these two factors. For the current modelling, a risk algorithm derived from the WHO study was used to quantify absolute risk from age and T-score (Table 7). Other relevant clinical risk factors were also considered (see Section 4.4). The WHO risk algorithm methodology is currently academic-in-confidence and the information that has been made available to NICE is summarised in the strontium Assessment Report (pages 15–22 and Appendix 12).

Table 7 Absolute annual risk of osteoporotic fracture (%) for women with no other clinical risk factors

Adapted from Tables 68–74 in Appendix 10 of the Strontium ranelate Assessment Report.

	T-score								
Age band	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**
50–54	6.0	3.6	2.3	1.5	1.1	0.9	0.7	0.6	0.5
55–59	5.5	3.5	2.3	1.7	1.2	1.0	0.8	0.7	0.6
60–64	5.3	3.5	2.5	1.8	1.3	1.1	0.8	0.7	0.6
65–69	5.9	4.1	3.0	2.3	1.7	1.4	1.1	0.9	0.8
70–74	7.0	5.2	3.9	3.0	2.4	1.9	1.5	1.3	1.1
75–79	8.5	6.4	4.9	3.8	2.9	2.3	1.8	1.6	1.4
80–84	10.0	7.6	5.9	4.5	3.5	2.8	2.2	1.9	1.6

Fracture risk increases with increasing age and with worsening BMD (i.e. decreasing T-score). Table 7 shows that a 50-year-old woman with a T-score of –3.5 has a similar absolute fracture risk to an 80-year-old woman with a T-score of –1.

The following drugs are currently licensed for the primary prevention of osteoporotic fractures:

- alendronate
- risedronate
- etidronate
- raloxifene
- strontium ranelate.

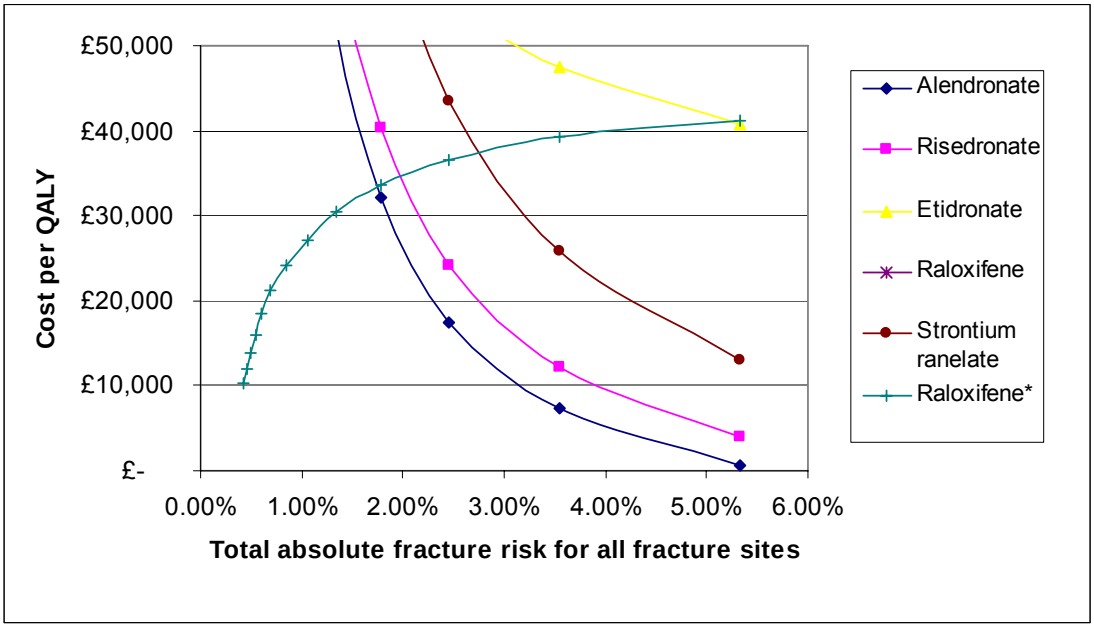
The results of the Assessment Group's modelling for these interventions for all age bands are shown in Figures 1–7 (pages 4–7) of the Addendum Assessment Report. Figure 1 and Figure 2 below illustrate the results for two of the age bands considered, 60–64 and 75–79 respectively. It should be noted that these figures show the cost effectiveness for each drug **in comparison with no treatment**. They should not be used to infer differences between the drugs in terms of incremental cost effectiveness.[3]

For most of the interventions, the incremental cost effectiveness ratio (ICER) versus no treatment decreases with increasing absolute risk (as illustrated in Figure 1 and Figure 2 below). An exception to this is raloxifene when the beneficial effect on risk of breast cancer is included.

[3] An incremental analysis based on the intervention with the highest net benefit at a cost effectiveness threshold of £20,000 per QALY gained is shown in Tables 2–8 (pages 8–11) of the Addendum Assessment Report. This suggests that alendronate is ranked above other interventions where the risk of fracture is sufficiently high for treatment to be cost effective. An exception to this is the case of younger women at low risk of fracture where the beneficial effects of raloxifene on breast cancer come into play.

Figure 1 Cost effectiveness of interventions by absolute annual fracture risk for women aged 60–64 with no clinical risk factors (primary prevention)

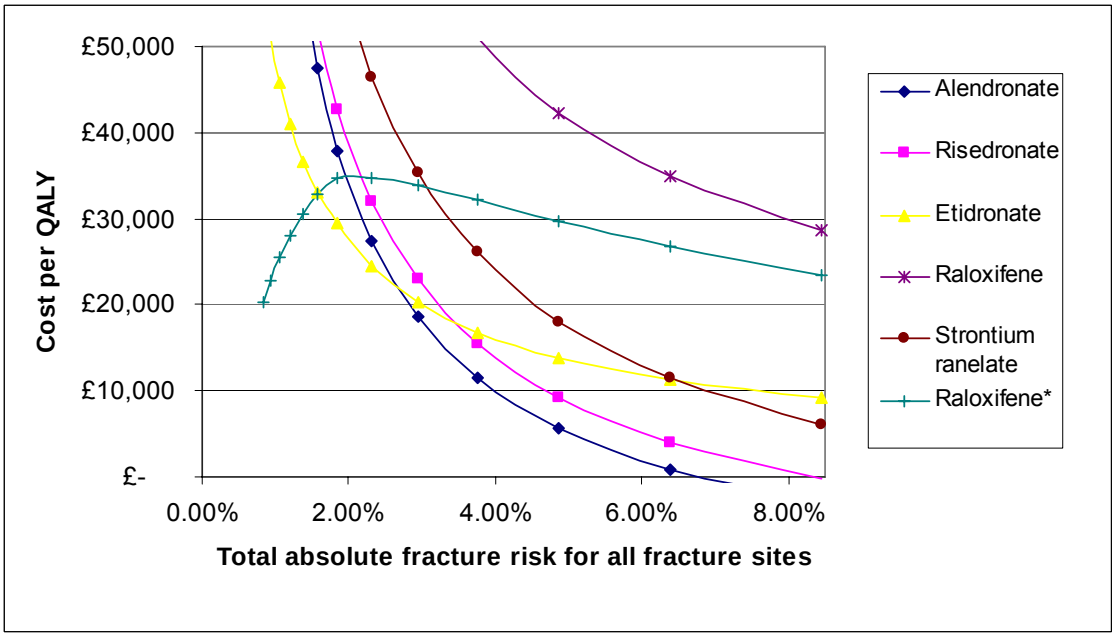
Figure 3 in Addendum Assessment Report.



* indicates that breast cancer effects were included

Figure 2 Cost effectiveness of interventions by absolute annual fracture risk for women aged 75–79 with no clinical risk factors (primary prevention)

Figure 6 in Addendum Assessment Report.



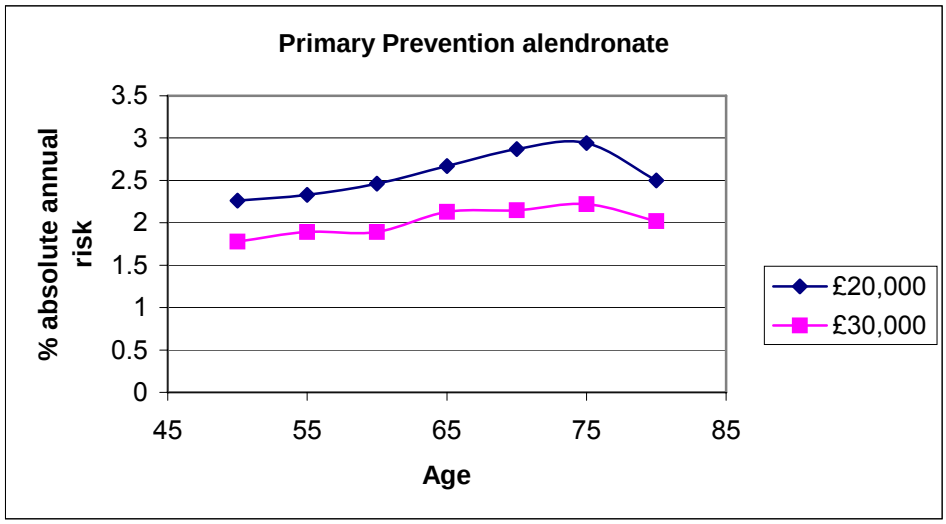
* indicates that breast cancer effects were included

4.2.1 Thresholds for intervention

The Assessment Group calculated the absolute risk at which treatment becomes cost effective (intervention thresholds), assuming different levels of willingness to pay for an additional QALY (Figure 3). These maximum acceptable ICERs were taken from Sections 6.2.6.10 and 6.2.6.11 of the *Guide to the methods of technology appraisal* published by NICE in April 2004, and were £20,000 and £30,000 per QALY.

Figure 3 Absolute risk-intervention thresholds for alendronate for women with no clinical risk factors, for maximum acceptable ICERs of £20,000 per QALY and £30,000 per QALY

Data taken from Tables 48–54 from the strontium Assessment Report.



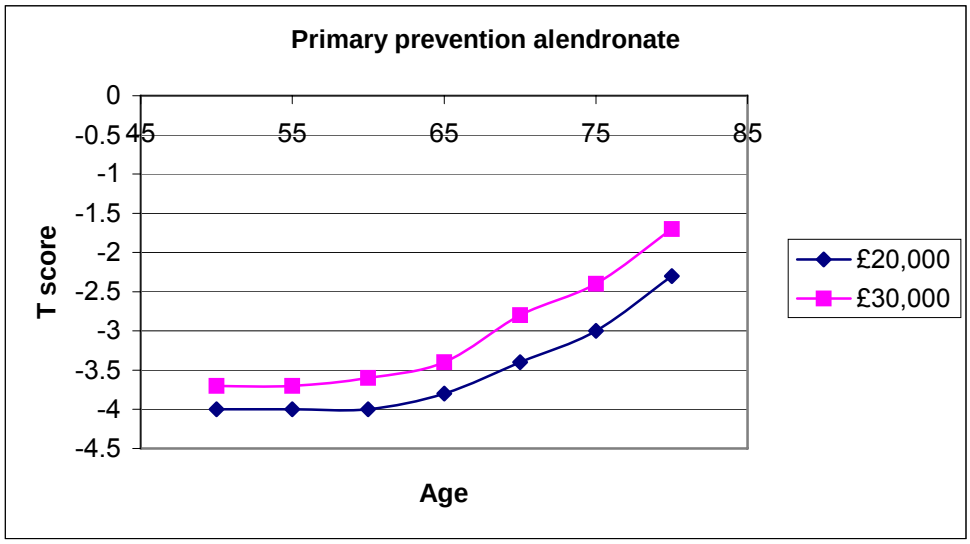
As shown in Figure 3, the intervention thresholds in terms of absolute risk of fracture were fairly constant across age, and increase only slightly with age before declining at age 80. The initial increase is due to the fact that the interaction between hip fracture risk and BMD is age-dependent with a Z-score change of –1 having a bigger impact on hip fracture risk at lower ages. This means that the hip fracture contribution to risk is larger than at higher ages, and since hip fractures are more expensive to treat and have a worse impact on quality of life, treatment is relatively more cost effective. The other factors that influence this relationship are changes in baseline utility, mortality and the probability of nursing home entry with age. At age 80 the decline in threshold is due to hip fracture having a greater impact on mortality and nursing home entry. However, without confidence intervals around the intervention thresholds, it is uncertain if the differences seen between age bands are relevant.

The concept of expressing cost effectiveness by absolute fracture risk may still be unfamiliar. Therefore, the same intervention thresholds are illustrated for different T-scores and ages (assuming no other clinical risk factors) in Figure 4. If willingness to pay for an additional QALY is £20,000, women under the age of 65 must have a T

score of –4 for treatment to be cost effective in primary prevention. As age increases, less severe T-scores are needed to reach cost effectiveness.

Figure 4 T-score thresholds for alendronate for women with no clinical risk factors, for maximum acceptable ICERs of £20,000 per QALY and £30,000 per QALY

Data taken from Tables 48–54 from the strontium Assessment Report.



The absolute risk intervention thresholds shown in Figure 3 can be transposed onto the age/T-score matrix to illustrate the groups of women that can be treated cost effectively (Table 8). This indicates that the following groups can be treated with alendronate cost effectively assuming a maximum acceptable ICER of £20,000 per QALY:

- all women with a T-score of less than –4
- women over the age of 70 with a T-score of less than –3.5
- women over the age of 75 with a T-score of less than –3
- women over the age of 80 with a T-score of less than –2.5.

However, these results did not consider the cost of identifying women at high risk of fracture. This is addressed in Section 4.4.

Table 8 Absolute annual risk of osteoporotic fracture (%), no prior fracture, no clinical risk factors

T-score/age combinations highlighted for which treatment with alendronate is cost effective according to the current modelling, assuming £20,000 per QALY highlighted in dark grey and £30,000 per QALY highlighted in light grey.

Age	T-score								
	–5	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**
50–54	6.0	3.6	2.3	1.5	1.1	0.9	0.7	0.6	0.5
55–59	5.5	3.5	2.3	1.7	1.2	1.0	0.8	0.7	0.6
60–64	5.3	3.5	2.5	1.8	1.3	1.1	0.8	0.7	0.6
65–69	5.9	4.1	3.0	2.3	1.7	1.4	1.1	0.9	0.8
70–74	7.0	5.2	3.9	3.0	2.4	1.9	1.5	1.3	1.1
75–79	8.5	6.4	4.9	3.8	2.9	2.3	1.8	1.6	1.4
80–84	10.0	7.6	5.9	4.5	3.5	2.8	2.2	1.9	1.6

A comparison between the cost per QALY for alendronate in primary prevention, derived from the original modelling carried out in November 2003 and the cost per QALY derived from the current modelling shows little net change, despite the changes to the modelling methodology (Table 9).

Table 9 Cost per additional QALY (£) for alendronate; no previous fracture, T-score –2.5

November 2003 data from November 2003 overview, Table 5.

	Age 50	**Age 60**	**Age 70**	**Age 80**
Absolute risk (%)	0.9	1	1.9	2.8
Alendronate Nov 03	–	–	34,403	12,343
Alendronate July 05	>50,000	>50,000	35,000	12,000

4.2.2 Summary of cost effectiveness in primary prevention

4.2.2.1 Bisphosphonates

For all age bands, the results for alendronate led to the most favourable cost per QALY results, followed by the results for risedronate. This is because the efficacy profile for these two drugs is very similar (Table 2). For alendronate, the absolute risk intervention thresholds were approximately 2% and between 2.5% and 3% for £30,000 and £20,000 per QALY, respectively, depending on age. Intervention thresholds for risedronate would be very similar. The modelling does not provide confidence intervals around the cost per QALY estimates. Therefore a judgement needs to be made about the true difference between these drugs. Also, the incremental cost effectiveness of these two drugs has not been established.

The third bisphosphonate, etidronate, became more cost effective with increasing age, and followed the alendronate and risedronate results more closely from age 70 onwards (note: no effect of etidronate on hip fracture incidence was assumed in line with RCT evidence; however, observational studies indicate that etidronate is efficacious for hip fracture prevention). Up to age band 65–69 the intervention threshold for etidronate would be >6% absolute fracture risk, assuming a maximum

acceptable ICER £20,000 per QALY. From age 70 onwards the intervention thresholds for etidronate would be similar to those for alendronate and risedronate.

4.2.2.2 Strontium ranelate

At all age bands, strontium ranelate led to less favourable cost per QALY data than alendronate and risedronate. Costs per QALY were lower than for etidronate at younger ages, but higher than etidronate at older ages. It needs to be considered that for etidronate no effect on hip fracture was assumed, whereas for strontium ranelate, the midpoint efficacy estimate was used, although it was not statistically significant. The latter was done because a significant effect on hip fracture for women over the age of 74 has been published for strontium ranelate. Up to age band 65–69 the intervention thresholds for strontium ranelate would be approximately 2% higher than those for alendronate and risedronate. Above the age of 70 the difference in intervention thresholds declined to approximately 1%.

4.2.2.3 Raloxifene

In the main clinical trial carried out to establish raloxifene's effect on vertebral fracture, raloxifene was also shown to reduce the incidence of invasive and non-invasive breast cancer. The cost effectiveness of raloxifene depends on whether this beneficial effect on breast cancer incidence is included. When the breast cancer effect was included, raloxifene was cost effective at low fracture risk (less than 1%) and the cost per QALY increased with increasing fracture risk. This indicates that the cost effectiveness is entirely driven by the beneficial effect on breast cancer incidence. When the effect on breast cancer was excluded, the cost per QALY for raloxifene was lower than £30,000 compared to no treatment only at age 75 and above plus an annual fracture risk of 7% or more.

4.3 The impact of other clinical risk factors

Apart from age and BMD, other clinical risk factors affect the risk of fracture. About [redacted] (AIC) of women have at least one clinical risk factor. The clinical risk factors listed in Table 10 have been shown to have a strong and consistent association with an increased risk of fracture. The increased risks in Table 10 show, however, only an indication of the magnitude of their impact. The WHO algorithm, and therefore the Assessment Group's modelling, uses age-specific risks, and the impact of some of these factors changes with age. Furthermore, the analysis of the WHO study cohorts has allowed the assessment of interactions between the clinical risk factors. (For more detail about the WHO study see strontium ranelate Assessment Report, Appendix 12.)

Table 10 The increased risk of osteoporotic fracture associated with clinical risk factors

Adapted from Table 22 from DSU report issued for the primary prevention appraisal in March 2005.

Clinical risk factors	Increased risk of hip fracture	Increased risk of osteoporotic fracture
Parental history of hip fracture	2.28	1.54
Current smoking	1.60	1.13
Ever used systemic corticosteroids	2.25	1.66
Alcohol intake > 2 units daily	1.70	1.36
Rheumatoid arthritis	1.73	1.47
Prior fracture after age of 50	1.62	1.76

Although a low body mass index has been shown to be predictive of fracture risk when BMD is not known, the Assessment Group omitted it from their analyses, because the correlation between body mass index and BMD seen in a UK study was low ($r^2 = 0.1$). Also, since body mass index is not a predictive factor once BMD is known, the omission only affects those women who do not receive DXA scans. The effect of this simplification was judged to be small. However it is acknowledged that some women for whom a low body mass index is the sole risk factor may not have a DXA scan recommended.

4.3.1 Absolute risk of fracture and cost effectiveness in the presence of clinical risk factors

The presence of any of these clinical risk factors contributes to a woman's absolute fracture risk. Although the absolute fracture risk provides a single measure for a woman's risk, it does not provide a single indicator of cost effectiveness. This is because the absolute risk covers all fracture sites included in the analysis, but different fracture sites have different impacts on quality of life, costs and mortality. Hip fracture in particular has a much greater impact on costs and mortality than fractures at other sites. Therefore, the cost effectiveness is dependent on the contribution from each fracture site to the total risk of fracture and in particular on the ratio of hip fracture risk to non-hip fracture risk at any given absolute fracture risk.

For individuals with different clinical risk factors, any absolute fracture risk can be reached at different T-scores. T-score and clinical risk factors have different impact on the hip fracture risk, and this difference of impact also varies with age. The ratio of hip fracture risk to non-hip fracture risk at any given absolute fracture risk is therefore complex and is derived from two main factors:

- the relative risk associated with the clinical risk factors, and
- the relative risks associated with the T-score.

If the contribution of the T-score to absolute risk is large, it is possible that – at a given absolute fracture risk – women without clinical risk factors can be treated more cost effectively than women with clinical risk factors. This is because T-score strongly relates to hip fracture risk which is the main driver of cost effectiveness. This

effect is particularly pronounced at younger ages, as the effect of some risk factors on hip fracture changes with age.

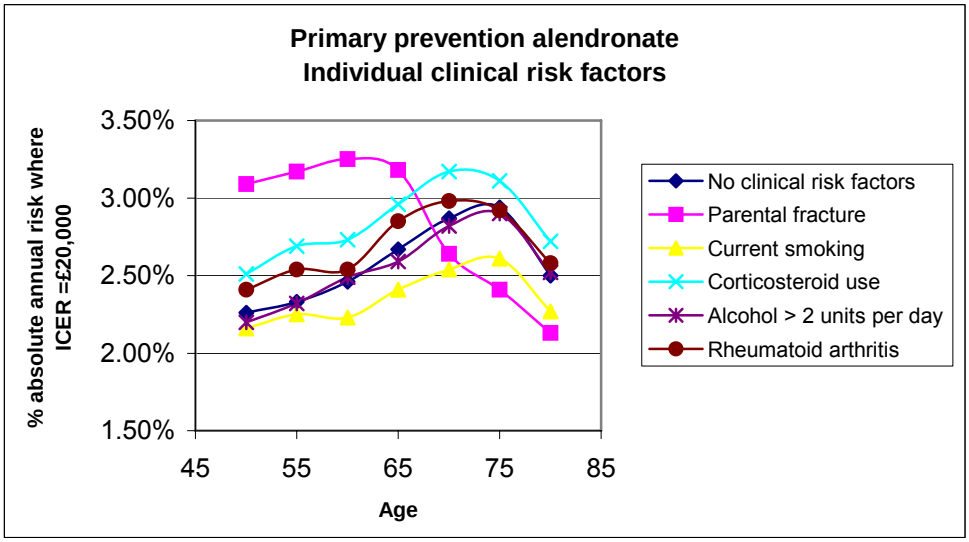
At the same absolute risk, different costs per QALY (and intervention thresholds) are therefore possible, depending on which risk factors contribute to absolute risk.

4.3.2 Cost-effectiveness results for women with clinical risk factors

Because of the complexity of calculating cost effectiveness based on absolute fracture risk, the Assessment Group calculated intervention thresholds (i.e. the absolute risks at which treatment becomes cost effective at a specified maximum acceptable ICER) for alendronate for all clinical risk factors separately (Figure 5).

Figure 5 Absolute risk intervention thresholds for alendronate for women with one clinical risk factor (assuming maximum acceptable ICER £20,000 per QALY)

Data taken from Tables 48–54 in the strontium Assessment Report.



The intervention thresholds increased from an absolute risk of 2.25% to approximately 3% with age for most clinical risk factors, and declined again around age 80. When corticosteroid use or rheumatoid arthritis were the risk factors, the intervention thresholds were slightly higher, which means that treatment is less cost effective than with other or no risk factors at the same level of absolute risk. For parental hip fracture a different pattern was observed: the intervention thresholds were approximately 3.25% at ages below 65 years, and declined sharply from age 70 onwards, to absolute risk levels below the intervention thresholds seen for other clinical risk factors. This is because the RR associated with parental hip fracture increases for hip fracture with age but decreases for non-hip fractures with age. The net effect of this is that the cost effectiveness of treatment increases with age, due to a larger proportion of the absolute risk being hip fracture risk.

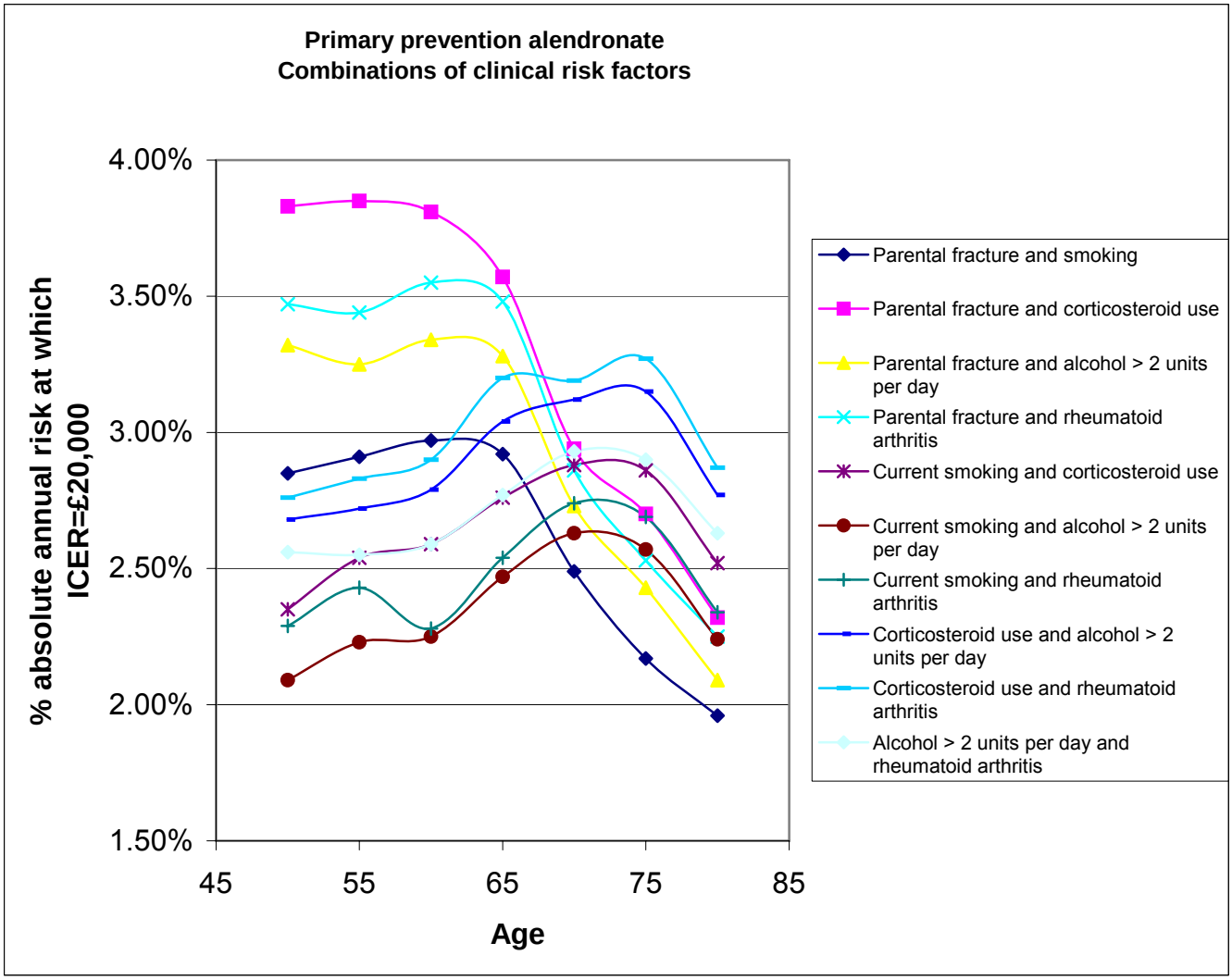
About [redacted]% (AIC) of women over 50 have two clinical risk factors. The intervention thresholds for women with two clinical risk factors follow the same trend as described

for women with one clinical risk factor, depending on whether parental fracture is one of the risk factors present (Figure 6).

The data for women with three or more clinical risk factors are not shown in this overview as only [redacted]% (AIC) of women fall into this group. The data follow the same trend as above: if parental fracture is one of the clinical risk factors, then they follow the trend for parental fracture. If parental fracture is not included, the intervention thresholds are similar to the intervention thresholds associated with the use of corticosteroids.

Figure 6 Absolute risk intervention thresholds for alendronate for women with two clinical risk factors (assuming maximum acceptable ICER £20,000 per QALY)

Data taken from Tables 48–54 in the strontium Assessment Report.



In general, clinical risk factors increase the intervention thresholds slightly above those obtained with no risk factors. When parental hip fracture contributes to absolute risk, the intervention thresholds are increased below age 70, and

decreased above age 70, compared with the intervention thresholds without clinical risk factors.

4.3.3 Summary (Section 4.3)

Using the WHO algorithm, clinical risk factors other than age and BMD can be quantified and aggregated into absolute risk. Although this provides an overall measure of fracture risk, it does not give a precise indicator of cost effectiveness.

This is because different risk factors have different relative effects on hip and non-hip fractures, and this ratio also varies with age. The impact on hip fracture risk is particularly important as hip fracture has a much greater impact on costs and mortality than fractures at other sites. Therefore, at the same absolute risk, different costs per QALY are possible, depending on which risk factors contribute to absolute risk.

4.4 Integration of identification approaches in the cost-effectiveness modelling

Women who have not had a fracture, but who may be at high risk of fracture, do not usually come to clinicians' attention. Although the responsibility for defining an appropriate strategy for identifying cases is the responsibility of the Guideline Development Group, the Appraisal Committee needs to consider the impact of the costs of identifying cases on the cost effectiveness of the technologies under appraisal. If the identification of cases costs more than the net benefit accrued by the summation of all individuals who can be cost-effectively treated, the entire pathway would not be cost effective.

4.4.1 Net benefit modelling

In order to combine the data on the cost effectiveness of treatment for individuals with the cost of identification of women for treatment, the Assessment Group calculated net benefit (for details see Strontium ranelate Assessment Report, page 60, and pages 100-101).

The total net benefit for each identification approach and age band was calculated by subtracting the cost of identification (risk assessment and DXA scanning) from the net benefit of treating all women that can be treated cost effectively. Where the total net benefit is positive, the identification and treatment approach is cost effective on a population level. If the net benefit is negative, an identification and treatment strategy is not cost effective. As with the intervention thresholds mentioned earlier, the net benefit approach requires an assumption about the cost per QALY that society is prepared to pay. The Assessment Group modelled this for two maximum acceptable ICERs, £20,000 and £30,000 per QALY.

4.4.2 GP costs

It was assumed that the initial assessment, comprising questions regarding age, weight, height and other clinical risk factors, was undertaken during a GP consultation arranged for different reasons (i.e. opportunistically, without active call-

up). GP consultations (costed at £1.92/min) were modelled as described in the strontium Assessment Report, page 102.

4.4.3 Modelling of the RCP selective case-finding approach

The approach currently used in the UK for the identification of women for osteoporosis treatment is a selective case finding strategy recommended by the Royal College of Physicians (RCP). The RCP approach consists of three stages:

- opportunistic GP-assessment of the presence of specified clinical risk factors
- referral for DXA scan if any risk factor is present
- treatment if DXA indicates that the individual is osteoporotic (T-score -2.5 or below).

In order to establish the cost involved in such an identification approach, the percentage of women who would be eligible for the BMD scan needs to be known. For this, prevalence data on individual risk factors and combinations of risk factors in the population of postmenopausal women were made available from the WHO data under confidentiality (Table 2 in the strontium Assessment Report, page 7).

4.4.3.1 Results

The results of the identification modelling are described in the Strontium ranelate Assessment Report, pages 103–107. The RCP approach was modelled using alendronate as the treatment to be used in the cases identified. The RCP approach led to negative net benefits for women under the age of 65 or 70, depending on the maximum acceptable amount to pay for an additional QALY (Table 11), Above these age bands, the RCP approach led to positive net benefits. Assuming a 100% uptake of the RCP approach, the net cost of the RCP approach is £285 million for one cohort of postmenopausal women over 10 years (this cost includes the cost for assessment, DXA scan and net cost of treatment, for all ages as this is current practice). The total net cost is unaffected by the maximum amount acceptable to pay for an additional QALY because the decision to treat is not made on cost-effectiveness grounds, but on whether the woman has a T-score of –2.5 or below. Assuming 100% uptake of the RCP approach, 2 million DXA scans would be carried out over 10 years in women with no previous fracture.

4.4.4 Modelling of alternative approach using WHO algorithm

Using the WHO algorithm, clinical risk factors can be quantified. Also, absolute risk can be estimated without knowledge of BMD, and a separate algorithm exists for the calculation where BMD is known. Therefore, it may be possible to make treatment decisions without the use of DXA scanning, for women where the addition of BMD information would not alter the treatment decision. This would lead to three different options at the risk assessment stage.

1. No treatment (or investigation) is given (that is, the estimated fracture risk is much below the intervention threshold).

2. Treatment is given without DXA scan (that is, the estimated fracture risk is much above the intervention threshold).
3. A DXA scan is carried out and treatment is given if the absolute risk is above the intervention threshold (as specified in Sections 4.2 and 4.3).

In order to establish if women should be given no treatment, treatment without a DXA scan or a DXA scan, the Assessment Group ran the model for each age band and risk factor combination and calculated which of the three options gave the highest net benefit. This had to be done for all combinations of risk factors because the T-score thresholds for cost-effective treatment vary with different clinical risk factors.

4.4.4.1 Results

The results of the identification modelling are described in the Strontium ranelate Assessment Report, pages 103–107. As with the RCP approach, the WHO approach led to negative net benefits for women under the age of 65 or 70, depending on the maximum acceptable amount to pay for an additional QALY (Table 11), which means that for these age bands the WHO approach would not be considered cost effective. Above these age bands, the WHO approach led to positive net benefits, and this net benefit was higher than the RCP approach, as DXA scanning is more efficiently targeted at high-risk women and the treatment is given on cost-effectiveness grounds (Table 11). Assuming a 100% uptake of the WHO approach, 1.6 million DXA scans would be carried out over 10 years in women who are currently aged 70 and over with no previous fracture (assuming a willingness to pay of £20,000 per QALY, which is 20% less than with the RCP approach).

However, the identification approach using the WHO algorithm costs more than the RCP strategy. Assuming a 100% uptake, the net cost of the WHO approach for one cohort of women aged 50 and above over 10 years is £381 million if willingness to pay for an additional QALY is £20,000 or £839 million if willingness to pay is £30,000 per QALY. This cost includes the cost of assessment, cost of DXA scan and net cost of treatment for age bands with positive net benefit. It is also assumed that capacity exists for this volume of scanning.

Table 11 Cost effectiveness of identification approaches expressed as net benefit (£ million), assuming a 100% uptake for both approaches and alendronate as treatment

	Maximum acceptable ICER			
Age band	**RCP £20k**	**RCP £30k**	**WHO £20K**	**WHO £30K**
50–64	–*	–*	–*	–*
65–69	–*	3.9	–*	8.2
70–74	24.1	63.2	28.7	90.0
75–59	82.3	131.8	122.2	263.1
80 +	196.8	285.5	492.0	887.0
*Net benefit negative				

Table 12 illustrates the identification and treatment options that are cost effective (assuming a maximum acceptable ICER of £20,000 per QALY).

Table 12 Cost-effective identification and treatment strategies based on the WHO algorithm (assuming a maximum acceptable ICER of £20,000 per QALY)

Age band	Risk factors					
	None	Smoking	Any 1	Any 2	PH plus 1 more	Any 3
50–69	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
70–74	n.t.	DXA	DXA	DXA	DXA	DXA
75–79	DXA	DXA	DXA	DXA	T	T
80+	DXA	DXA	T	T	T	T

n.a.= no assessment
n.t.= no treatment
DXA = refer for DXA scan. The resulting T-score is used to re-assess the risk, and treatment is given if the absolute risk is above the intervention threshold (as in Sections 4.2 and 4.3),
T= treat without DXA
PH = Parental history of hip fracture

For women who are referred for DXA scanning, different T-score thresholds apply depending on the clinical risk factors involved (see section 4.3). This may be impractical in clinical practice. Therefore, the Assessment Group have transformed this very accurate, but complex approach into a simplified version, by which only one T-score threshold is applied to each age band and clinical risk factors number (Table 13). This results in a small loss of net benefit (<1%), which could be considered acceptable because of the gains derived from the logistical improvement.

Table 13 Cost-effective identification and treatment strategies based on the simplified WHO algorithm (assuming a maximum acceptable ICER of £20,000 per QALY)

Note that 'parental history of hip fracture' counts as two clinical risk factors due to its greater effect at ages 70 and above.

	Number of clinical risk factors			
Age	0	1	2	3 or more
50-69	No opportunistic case finding			
70-74	Reassure/Lifestyle advice	DXA & treat at T-score ≤ -2.8	DXA & treat at T-score ≤ -2.3	DXA & treat at T-score ≤ -1.7
75-79	DXA & treat at T-score≤ -3.0	DXA & treat at T-score ≤ -2.3	DXA & treat at T-score ≤ -1.5	Treat
80+	DXA & treat at T-score ≤ -2.3	DXA & treat at T-score ≤ -1.5	Treat	Treat

Whilst some women can be cost-effectively treated below the age of 70 years, the benefit of treating these women is outweighed by the costs of the identification approach.

4.4.5 Sensitivity analyses

Sensitivity analyses carried out using alendronate as treatment and a maximum acceptable ICER of £20,000 per QALY revealed that time taken for risk assessment, and an increase in the cost of DXA did not substantially change results.

Compliance, however, affected the cost effectiveness of the treatment pathway, with identification and treatment becoming not cost effective when compliance dropped to somewhere between 50 and 25% (Table 14).

Compliance in clinical trials for osteoporosis has been far above 50% (as reported in the first Assessment Report to the original appraisal). Data on compliance with osteoporosis therapy in clinical practice is more varied. Studies from the US, some of them large, indicate that compliance is between 25 and 55%, depending on dosing regimen. However, several other studies, some of which are from the UK, indicate that compliance is around 70% (for references see Appendix A).

Table 14 Total net benefit of identification strategy (£ million), for age 70–74

Compliance	1-month drug cost	6-month drug cost
100%	28.8	28.8
75%	17	15.4
50%	5.2	2
25%	–6.5	–11.3

4.4.6 Summary (Section 4.4)

Using the prevalence data for risk factors from the WHO study, the Assessment Group modelled the existing identification approach (RCP) and an alternative approach using the WHO algorithm. The latter enabled treatment decisions without DXA scanning for some women with clinical risk factors, where knowledge of BMD would not change the treatment decision.

The Assessment Group modelled the identification approaches using the net benefit approach. The total net benefit for each identification approach and age band was calculated by subtracting the cost of identification (risk assessment and DXA scanning) from the net benefit of treating all women that can be treated cost effectively. Where the total net benefit is positive, the identification and treatment approach would be cost effective on a population level.

Both the RCP and the WHO approach were not cost effective for populations of women below the age of 70 (at a maximum acceptable ICER of £20,000 per QALY). For women aged 70 and above, the net benefit obtained with the WHO approach was higher than with the RCP approach. However, the total cost was higher with the WHO approach.

4.5 Cost-effectiveness data from submissions

In 2002 the manufacturers of alendronate, risedronate, etidronate and raloxifene submitted cost-effectiveness data for the interventions from their own economic models, the results of which are summarised in Table 15. The details of these manufacturer models were discussed at previous Committee meetings.

For the strontium ranelate appraisal, the manufacturer submitted two models, one of which was similar to the Assessment Group model but only covered secondary prevention. This will be discussed in section 5 of this overview.

The other model is a Markov cohort model, and does not retain the individual's prior history. Therefore, a post vertebral fracture state and post hip fracture state have been included. However, transitions from the post vertebral fracture state are restricted to hip fracture and death, and transitions from the post hip fracture state are limited to death. This model assumes a lifetime horizon, with a cycle length of 1 year. Treatment duration is 3 years and fall time is 3 years (as opposed to 5 years treatment and 5 years fall time in the assessment group model); Increasing the treatment and fall time, increased the cost per QALY. Utility data and the cost data used are different from the first submission model and favour the intervention. The utility data are the same as those used in the current Assessment Group model. Hip fracture costs were assumed to be higher in this model, favouring the intervention. A detailed critique of these two submission models can be found in Appendix 7 of the Strontium ranelate Assessment Report.

The results of the submission model for strontium ranelate are shown in Table 15. Further stochastic sensitivity analysis found the result robust, with the ICER falling below £30,000 per QALY on 67% of occasions for patients without previous vertebral fracture.

Table 15 Incremental cost per additional QALY (£) for interventions for primary prevention of osteoporotic fractures

From the manufacturers' submissions received in 2002.

Intervention	Age 50	Age 60	Age 70	Age 80
Alendronate, T-score < –2.5	–	–	8,622	–
Risedronate, T-score = –2.5	–	96,600	40,600	35,500
Risedronate, T-score <–2.5	–	53,600	13,500	600
Etidronate (incl observational data), T-score= –2.5	–	–	18,634	–
Raloxifene*, RR = 1	13,500	13,700	16,600	22,300
Raloxifene*, RR = 2	12,900	15,400	17,900	21,100
Raloxifene*, RR = 4	12,000	13,700	15,000	15,600
Strontium ranelate T-score = –2.5	–	–	24,681	–
* including the effect on breast cancer				

5 Cost effectiveness – secondary prevention

The scope for the appraisal of strontium ranelate for the prevention of osteoporotic fractures in postmenopausal women with osteoporosis included both primary and secondary prevention. The economic modelling in the strontium ranelate appraisal differed in two aspects from the model underpinning the published guidance for secondary prevention[4]: firstly in the quantification of fracture risk, and secondly in that an updated version of the model was used. Therefore, it is necessary to

[4] Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. *Technology Appraisal Guidance* No. 87 issued January 2005.

consider the extent to which the existing guidance should be reviewed. This overview therefore includes the strontium ranelate data as well as data generated by the Assessment Group to facilitate such an update for the other drugs that were previously appraised.

The NICE guidance on the secondary prevention of osteoporotic fractures was issued after the scope and protocol for the strontium ranelate appraisal had been published (see Appendix B). Because bisphosphonates are recommended as treatment options for certain risk groups in the secondary prevention guidance, the bisphosphonate alendronate was used as a comparator in the appraisal of strontium ranelate.

The evidence is presented in the following sequence.

- Section 5.1: Cost effectiveness of strontium ranelate and alendronate (for different ages and T-scores with no other risk factors).
- Section 5.2: Cost effectiveness of the other interventions (for different ages and T-scores with no other risk factors).
- Section 5.3: The impact of other clinical risk factors on the cost effectiveness of alendronate in secondary prevention.
- Section 5.4: Comparison of new modelling results with existing guidance.
- Section 5.5: Comparison of the Assessment Group and submission models.

5.1 Cost effectiveness of strontium ranelate and alendronate

As a first step, the cost effectiveness of strontium ranelate for secondary prevention was estimated for postmenopausal women at different ages and T-scores, and without any other clinical risk factors. To provide an additional comparator in line with the current guidance, the cost effectiveness of the bisphosphonate alendronate was also modelled for secondary prevention. The economic model used is described in Section 4.1 of this overview. Prior fracture was added as a risk factor when the absolute risk of (further) fracture was calculated. Table 16 summarises how absolute risk changes with age and T-score, for women with a previous fracture. Other clinical risk factors are discussed in Section 5.4.

Table 16 Absolute annual risk of osteoporotic fracture (%)

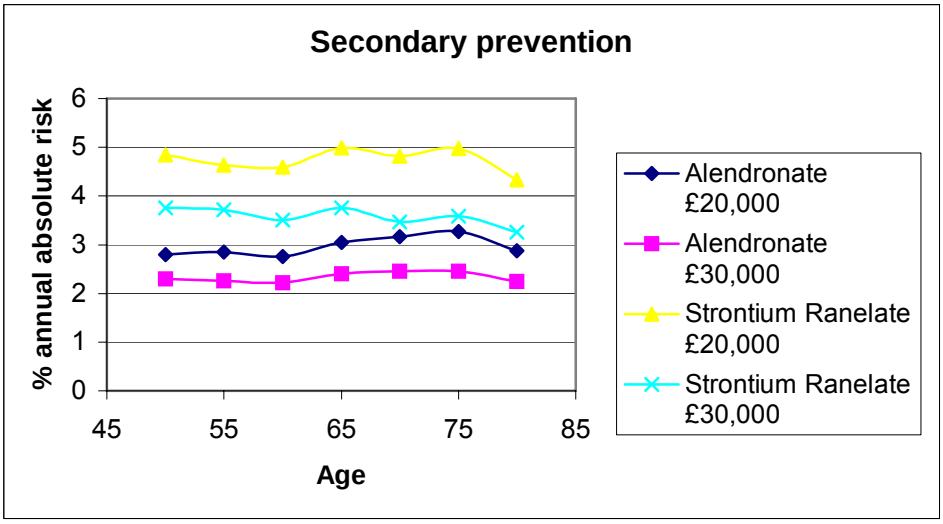
Adapted from Tables 68–74 in Appendix 10 of the Strontium ranelate Assessment Report, for women with prior fracture, but no other clinical risk factors.

	T-score												
Age band	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
50–54	12.0	7.1	4.4	3.0	2.2	1.7	1.4	1.1	1.0	0.9	0.8	0.8	0.7
55–59	10.2	6.5	4.3	3.0	2.3	1.8	1.4	1.2	1.0	0.9	0.9	0.8	0.8
60–64	9.3	6.2	4.3	3.1	2.3	1.8	1.5	1.2	1.0	0.9	0.9	0.8	0.7
65–69	9.7	6.8	5.0	3.7	2.9	2.3	1.8	1.5	1.3	1.2	1.1	1.0	0.9
70–74	11.0	8.2	6.2	4.8	3.8	3.0	2.4	2.1	1.8	1.6	1.5	1.3	1.2
75–79	12.6	9.6	7.4	5.7	4.5	3.6	2.9	2.5	2.1	1.9	1.7	1.5	1.3
80–84	14.5	11.1	8.6	6.7	5.3	4.1	3.4	2.9	2.5	2.1	1.8	1.6	1.4

The Assessment Group calculated cost per QALY for individuals at specific absolute risks of fracture and at different ages, and then calculated intervention thresholds (assuming maximum acceptable ICERs of £20,000 and £30,000 per QALY) for strontium ranelate and alendronate. Alendronate led to more favourable cost per QALY data and therefore lower intervention thresholds: If willingness to pay for an additional QALY is £30,000 the intervention thresholds were around 2.5% for alendronate and around 3.5% for strontium ranelate. At a maximum acceptable ICER of £20,000 per QALY the intervention thresholds were around 3% for alendronate and around 4.5% for strontium ranelate (Figure 7).

Figure 7 Absolute risk thresholds for secondary prevention

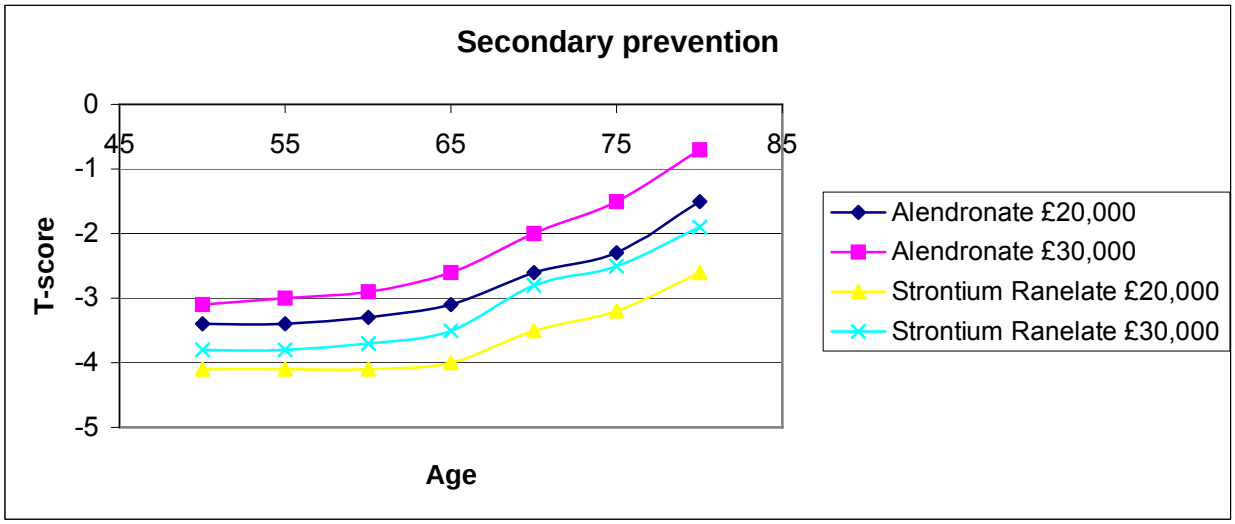
Data for alendronate and strontium ranelate, each compared with no treatment for women with previous fractures but no other clinical risk factors, taken from Tables 27–40 of the Strontium ranelate Assessment Report.



Intervention thresholds can also be illustrated for different T-scores and ages (Figure 8). As age increases, less severe T-scores are needed to reach the above-mentioned levels of cost effectiveness. T-score thresholds needed for alendronate to be cost effective were always higher than T-score thresholds needed for strontium ranelate, indicating more favourable cost effectiveness for alendronate.

Figure 8 T-score thresholds for secondary prevention

Data for alendronate and strontium ranelate, each compared with no treatment for women with previous fractures but no other clinical risk factors, taken from Tables 27–40 in the Strontium ranelate Assessment Report.



The probabilistic sensitivity analysis carried out by the Assessment Group compared alendronate and strontium ranelate directly with each other (Figures 9–14 in the Strontium ranelate Assessment Report). Alendronate was 20% likely to be the optimal choice at a maximum acceptable ICER of £30,000 for age 50; 40% for age 60 and 90% for ages 70 and 80. The corresponding figures for strontium ranelate were 0% for ages 50 and 60, and 10% for ages 70 and 80.

5.2 Cost per QALY data for other interventions

In order for the Appraisal Committee to be able to review the extent to which the existing guidance needs to be updated, the Assessment Group used the same model for the estimation of the cost effectiveness of the drugs previously appraised for the secondary prevention of osteoporotic fractures. The data for all age bands are shown in Figures 8–14 on pages 12–15 of the Addendum Assessment Report. Figure 9 and Figure 10 illustrate the results for two age bands, 60–64 and 75–79, respectively.

Figure 9 Cost per QALY for interventions

Each intervention compared with no treatment by absolute annual fracture risk for women aged 60–64 with previous fracture but no other clinical risk factors (secondary prevention) (Figure 10 in the Addendum Assessment Report).

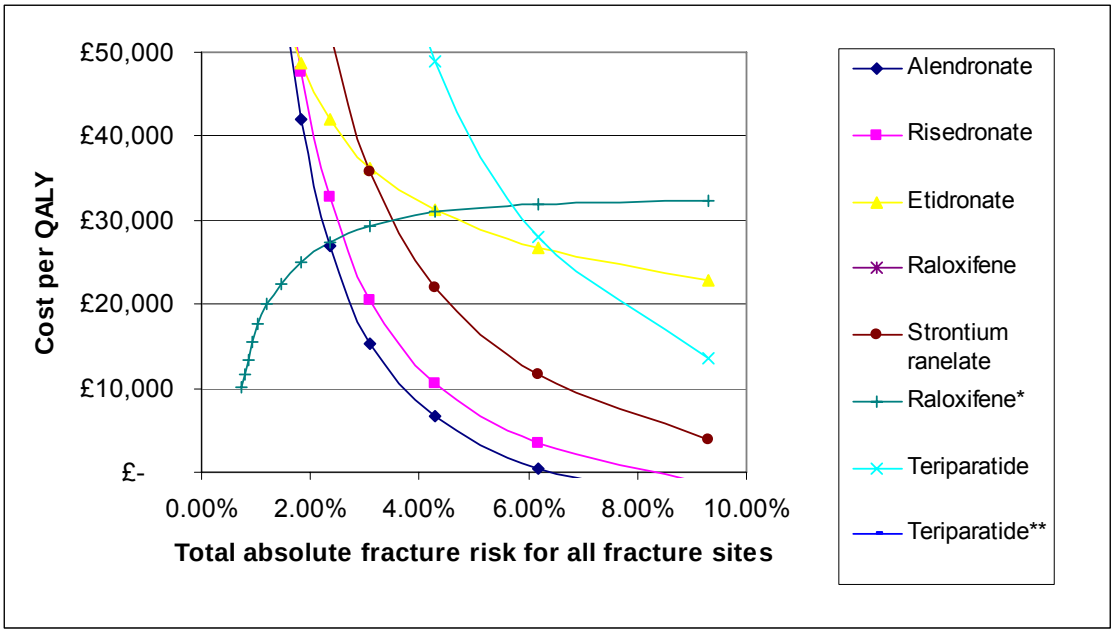
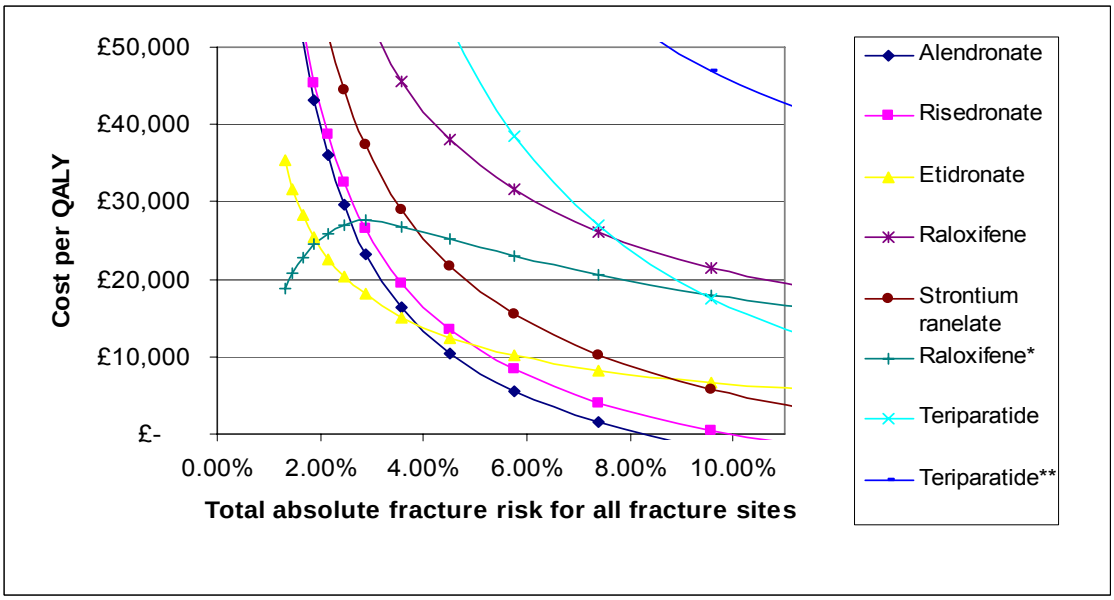


Figure 10 Cost per QALY for interventions

Each intervention compared with no treatment by absolute annual fracture risk for women aged 75–79 with previous fracture but no other clinical risk factors (secondary prevention) (Figure 13 in the Addendum Assessment Report).



* indicates that breast cancer effects were included
** indicates that the effect on hip fracture was excluded

The relative cost effectiveness was the same as for primary prevention for alendronate, risedronate, etidronate, strontium ranelate and raloxifene (see Section 4.3).

An additional drug, teriparatide, is licensed for secondary prevention. The efficacy of teriparatide for reducing hip fracture incidence has a wide confidence interval and the effect is not statistically significant (RR = 0.50; 95% CI 0.09–2.73).

In the original modelling, the uncertainty around the RR was incorporated, but it was not practicable to do this in the current modelling. However, the Assessment Group provided data for the following alternative assumptions: (1) no effect on hip fracture incidence (in line with the other RR where the 95% CI spanned unity); and (2) using the midpoint RR (as with strontium ranelate). When no effect on hip fracture incidence was assumed, a cost per QALY of £30,000 was only reached when absolute risk of fracture was 14.51% in women 80 and over. When the midpoint efficacy for hip fracture was used, intervention thresholds can be established across all age bands (Figure 11). These intervention thresholds are more than twice as high as the thresholds needed for bisphosphonates. Figure 12 expresses intervention thresholds by T-score.

Figure 11 Absolute risk thresholds for teriparatide

For women with previous fracture but no other clinical risk factors. Assuming an effect on hip fracture, data taken from Tables 13–19 in the Addendum Assessment Report

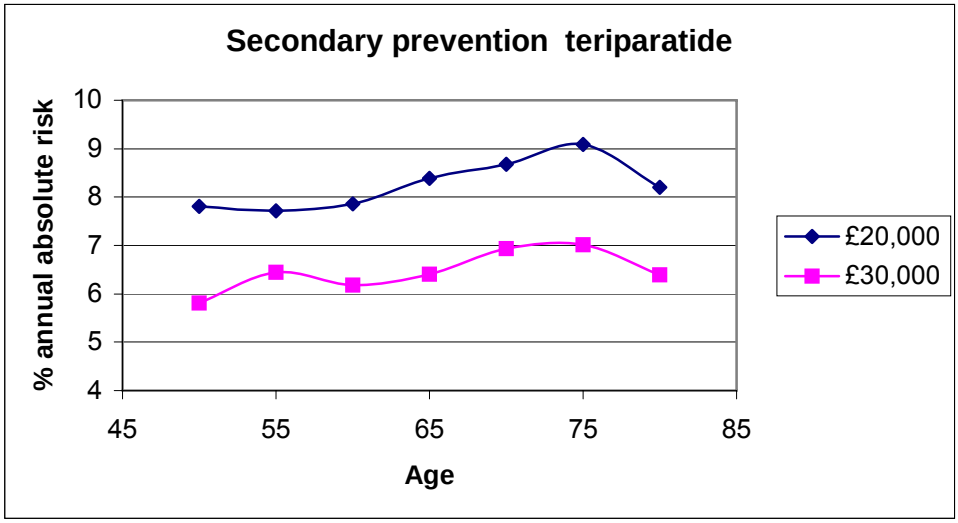
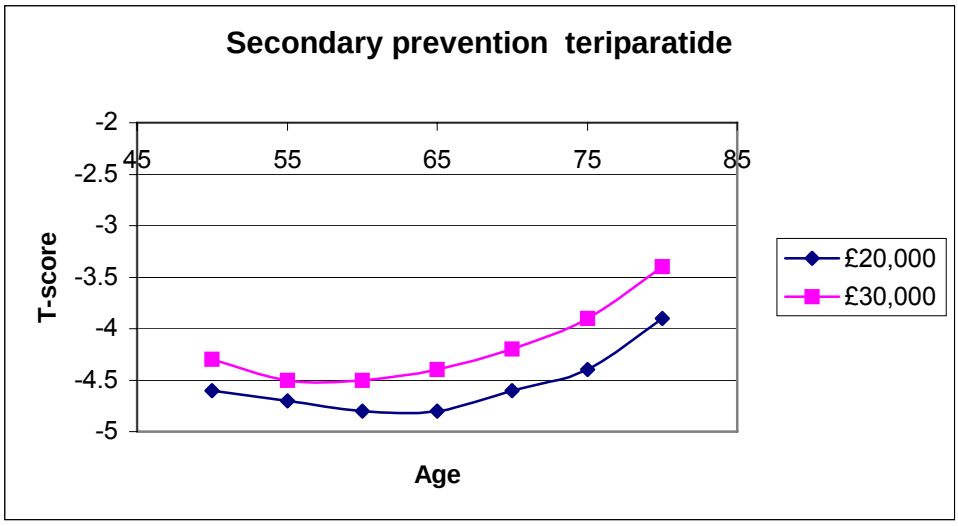


Figure 12 T-score thresholds for teriparatide

Assuming an effect on hip fracture, data taken from Tables 13–19 in the Addendum Assessment Report for women with previous fracture but no other clinical risk factors.



5.2.1 Summary (Sections 5.1 and 5.2)

Assuming different levels of willingness to pay for an additional QALY, absolute risk intervention thresholds at which treatment of individual women becomes cost effective are as follows.

- For **alendronate**, the absolute risk intervention thresholds were approximately 2.25–2.5% and 3% for maximum acceptable ICERs of £30,000 and £20,000 per QALY respectively, depending on age.
- The cost effectiveness of **risedronate** was similar to that of alendronate.
- **Etidronate** was similarly cost effective at age 70 and above.
- Absolute risk intervention thresholds for **strontium ranelate** were generally 1–1.5% higher than for bisphosphonates.
- Intervention thresholds for **raloxifene** depended on whether or not the breast cancer effect was included in the modelling.
- When the effect on hip fracture was excluded for **teriparatide**, costs per QALY were very high, and intervention thresholds were far above 10%. When the effect on hip fracture was included, intervention thresholds were between 6% and 7% (for a maximum acceptable ICER of £30,000 per QALY).

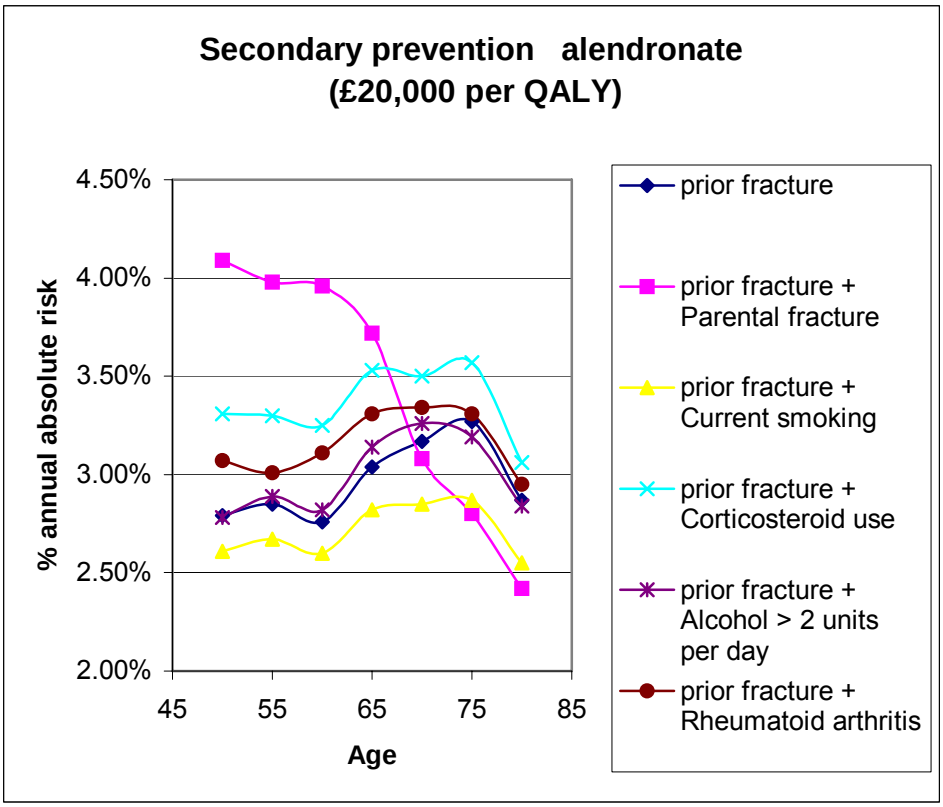
5.3 The impact of other clinical risk factors

For the reasons given in Section 4.3, absolute risk alone does not precisely predict cost effectiveness when clinical risk factors other than age and low T-score are to be considered. This is because clinical risk factors have different impacts on the hip fracture risk and the ratio of hip fracture to non-hip fracture, and this also varies with age.

Figure 13 and Figure 14 show the absolute risk intervention thresholds for different risk factors and combinations of risk factors for a maximum acceptable ICER of £20,000 and £30,000 per QALY.

Figure 13 Intervention thresholds for alendronate

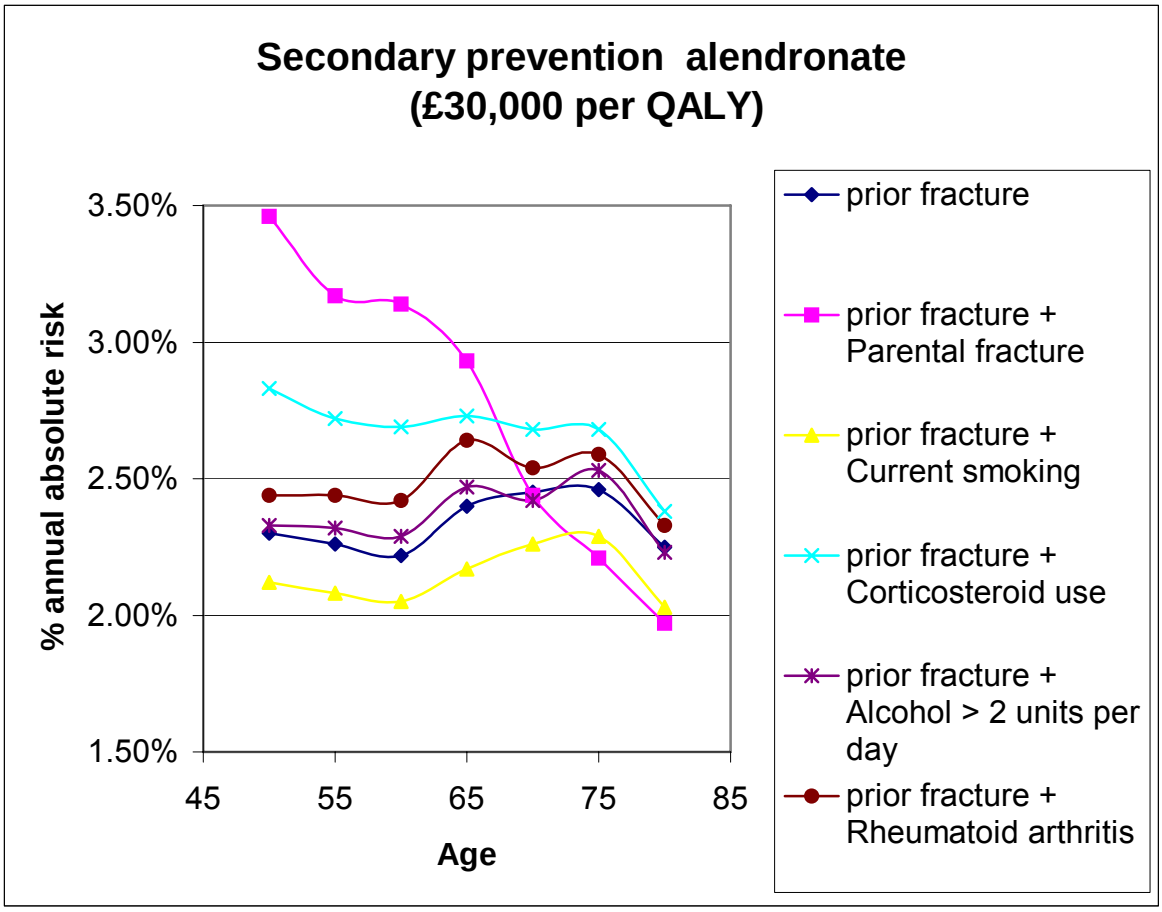
Data for women with previous fracture and other clinical risk factors, assuming maximum acceptable ICER £20,000 per QALY; data taken from Tables 34–40 in the strontium ranelate Assessment Report.



The impact of clinical risk factors on intervention thresholds is similar to those seen for primary prevention (Section 4.4). If corticosteroid use and rheumatoid arthritis contribute to absolute risk, cost effectiveness becomes slightly less favourable and therefore the intervention thresholds are increased slightly. When parental hip fracture contributes to absolute risk, the cost effectiveness is less favourable at ages younger than 70, but after that age becomes more favourable, compared with other risk factor combinations.

Figure 14 Intervention thresholds for alendronate

Data for women with previous fracture and other clinical risk factors, assuming a maximum acceptable ICER of £30,000 per QALY; data taken from Tables 34–40 in the Strontium ranelate Assessment Report.



5.4 Comparison of new modelling results with the existing guidance

The existing guidance for secondary prevention recommends treatment for certain risk groups characterised by T-score and age, and also includes some clinical risk factors in a qualitative way.

The current modelling differs from the previous modelling in two aspects with potential implications for the existing guidance.

1. The current model allows the aggregation of age, T-score and other clinical risk factors into absolute risk.

2. The current model was updated with more recent utility values, includes other osteoporotic fractures, and allows the consideration of clinical risk factors separately.

A comparison of the cost per QALY data derived from the modelling underpinning the existing guidance and the current modelling is shown in Table 17 for alendronate and teriparatide. The new modelling led to slightly more favourable cost per QALY data at age 60, and for the increased risk groups.

Table 17 Cost per additional QALY (£) for alendronate and teriparatide

Data for women with previous fracture, T-score –2.5 (April 2004 data from the April 2004 overview, Tables 6-2 and 12-2, SCENARIO 2; July 2005 data taken from Figures 8–15 in the Addendum Assessment Report).

Data	Age 50	Age 60	Age 70	Age 80
'Single risk'; % absolute risk	**1.7**	**2.3**	**3**	**4.2**
Alendronate – April 2004	32,937	36,595	12,191	Dominating
Alendronate – July 2005	>40,000	22,000	20,000	7,000
'Double risk'; % absolute risk	**3.4**	**4.6**	**6**	**8.4**
Alendronate – April 2004	14,501	15,149	1,595	Dominating
Alendronate – July 2005	6000	6000	4,000	Dominating
Teriparatide – April 2004	91,657	102,418	43,827	30,687
Teriparatide – July 2005 (RR for hip 0.50)	>50,000	>50,000	33,000	20,000
Teriparatide – July 2005 (RR for hip 1)	>50,000	>50,000	>50,000	45,000
'Quadruple risk'; % absolute risk	**6.8**	**9.2**	**12**	**16.8**
Teriparatide – April 2004	43,968	48,443	18,266	7,371
Teriparatide – July 2005 (RR for hip 0.50)	27,000	16,000	12,000	2,000
Teriparatide – July 2005 (RR for hip 1)	>50,000	>50,000	45,000	25,000

5.4.1 Bisphosphonates

The current recommendations for bisphosphonates can be compared with the conclusions that could be derived from the current modelling, based on the T-score/age matrix showing absolute risk. Table 18 highlights the groups of women for whom treatment has been recommended in the existing guidance. Table 19 highlights the groups of women to whom treatment with alendronate could be given cost effectively, according to the current modelling, assuming different willingness to pay thresholds. As can be seen from these tables, the current modelling leads to similar outcomes as the previous modelling, except that the current modelling also includes osteopenic elderly women with fractures who can be treated cost effectively.

Table 18 Illustration of existing guidance for bisphosphonates

Absolute annual risk of osteoporotic fracture (%) with the T-score/age combinations highlighted for which treatment with bisphosphonates has been recommended in the existing guidance (no other clinical risk factors).

	T-score (SD)												
Age band	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
50–54	12.0	7.1	4.4	3.0	2.2	1.7	1.4	1.1	1.0	0.9	0.8	0.8	0.7
55–59	10.2	6.5	4.3	3.0	2.3	1.8	1.4	1.2	1.0	0.9	0.9	0.8	0.8
60–64	9.3	6.2	4.3	3.1	2.3	1.8	1.5	1.2	1.0	0.9	0.9	0.8	0.7
65–69	9.7	6.8	5.0	3.7	2.9	2.3	1.8	1.5	1.3	1.2	1.1	1.0	0.9
70–74	11.0	8.2	6.2	4.8	3.8	3.0	2.4	2.1	1.8	1.6	1.5	1.3	1.2
75–79	12.6	9.6	7.4	5.7	4.5	3.6	2.9	2.5	2.1	1.9	1.7	1.5	1.3
80–84	14.5	11.1	8.6	6.7	5.3	4.1	3.4	2.9	2.5	2.1	1.8	1.6	1.4

Table 19 Illustration of current modelling for alendronate

Absolute annual risk of osteoporotic fracture (%) with the T-score/age combinations highlighted for which treatment with bisphosphonates could be given cost effectively according to the current modelling, assuming £30,000 per QALY highlighted in lighter grey, and £20,000 per QALY highlighted in dark grey (no other clinical risk factors).

	T-score (SD)												
Age band	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
50–54	12.0	7.1	4.4	3.0	2.2	1.7	1.4	1.1	1.0	0.9	0.8	0.8	0.7
55–59	10.2	6.5	4.3	3.0	2.3	1.8	1.4	1.2	1.0	0.9	0.9	0.8	0.8
60–64	9.3	6.2	4.3	3.1	2.3	1.8	1.5	1.2	1.0	0.9	0.9	0.8	0.7
65–69	9.7	6.8	5.0	3.7	2.9	2.3	1.8	1.5	1.3	1.2	1.1	1.0	0.9
70–74	11.0	8.2	6.2	4.8	3.8	3.0	2.4	2.1	1.8	1.6	1.5	1.3	1.2
75–79	12.6	9.6	7.4	5.7	4.5	3.6	2.9	2.5	2.1	1.9	1.7	1.5	1.3
80–84	14.5	11.1	8.6	6.7	5.3	4.1	3.4	2.9	2.5	2.1	1.8	1.6	1.4

5.4.2 Teriparatide

A similar comparison between the current recommendations for teriparatide and the conclusions that could be derived from the current modelling is illustrated in Table 20 and Table 21.

Accepting the current modelling would lead to the inclusion of women aged 50–64 with very low BMD (T-scores < –4.5) and women aged 80 and over with a T-score of –3.5, as they can be treated cost effectively. However, women aged 65–74 with a T-score of –4 are no longer cost effective to treat with teriparatide.

Table 20 Illustration of existing guidance for teriparatide

Absolute annual risk of osteoporotic fracture (%) with the T-score/age combinations highlighted for which treatment with teriparatide has been recommended in the existing guidance (no other clinical risk factors).

	T-score (SD)								
Age band	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**
50–54	12.0	7.1	4.4	3.0	2.2	1.7	1.4	1.1	1.0
55–59	10.2	6.5	4.3	3.0	2.3	1.8	1.4	1.2	1.0
60–64	9.3	6.2	4.3	3.1	2.3	1.8	1.5	1.2	1.0
65–69	9.7	6.8	5.0	3.7	2.9	2.3	1.8	1.5	1.3
70–74	11.0	8.2	6.2	4.8	3.8	3.0	2.4	2.1	1.8
75–79	12.6	9.6	7.4	5.7	4.5	3.6	2.9	2.5	2.1
80–84	14.5	11.1	8.6	6.7	5.3	4.1	3.4	2.9	2.5

Table 21 Illustration of current modelling for teriparatide

Absolute annual risk of osteoporotic fracture (%) with the T-score/age combinations highlighted for which treatment with teriparatide can be given cost effectively according to the current modelling, assuming £30,000 per QALY highlighted (no other clinical risk factors, including an effect on hip fracture).

	T-score (SD)								
Age band	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**
50–54	12.0	7.1	4.4	3.0	2.2	1.7	1.4	1.1	1.0
55–59	10.2	6.5	4.3	3.0	2.3	1.8	1.4	1.2	1.0
60–64	9.3	6.2	4.3	3.1	2.3	1.8	1.5	1.2	1.0
65–69	9.7	6.8	5.0	3.7	2.9	2.3	1.8	1.5	1.3
70–74	11.0	8.2	6.2	4.8	3.8	3.0	2.4	2.1	1.8
75–79	12.6	9.6	7.4	5.7	4.5	3.6	2.9	2.5	2.1
80–84	14.5	11.1	8.6	6.7	5.3	4.1	3.4	2.9	2.5

5.5 Comparison of Assessment Group model and the strontium ranelate submission

The submission for strontium ranelate contained two economic models. In both models, strontium ranelate was compared with no treatment. These two models differ in several aspects from the Assessment Group model, some of which favour the intervention in the Assessment Group model, some of which favour the intervention in the submission model. A detailed critique of the submission models can be found in the Strontium ranelate Assessment Report, Appendix 7, pages 130-138.

The first submission model was based on the individual patient methodology that had been developed by ScHARR and was used for the original appraisal. Analysis

was confined to those with a prior fracture. The analysis resulted in a mean cost-effectiveness ratio under £30,000 for women older than 75 with a previous fracture, and for women aged 65–75 with an additional risk factor that doubles risk (Table 22). These results are very similar to the results from the Assessment Group model (Table 22).

The second submission model was developed by Stockholm Health Economics (described in Section 4.6 of this overview). The results are more favourable than the Assessment Group model (Table 22), which could be due to the higher cost for hip fracture assumed, the longer time horizon and the shorter treatment time used in this submission model.

Table 22 Cost per QALY (£) (95% CI) for strontium ranelate compared to no treatment from the submission models and from the AG model

Data for the AG model derived from Figure 6 in the Strontium ranelate Assessment Report, page 66.

Model	Age	Women with previous fracture T-score < -2.5 *(absolute risk)*	Women with previous fracture and doubled risk T-scores of -2.5 (*absolute risk*)
Submission 1	65–75	[redacted] CIC	[redacted] CIC
Submission 1	75+	[redacted] CIC	[redacted] CIC
Submission 2	65	13,470	–
Submission 2	70	6,341	–
Assessment Report	65	> 35,000 *(2.3%)*	20,000 *(4.6%)*
Assessment Report	70	33,000 *(3%)*	14,000 *(6%)*
Assessment Report	75	27,000 (3.6%)	10,000 *(7.2%)*

6 Issues for consideration

- Should bisphosphonates be considered as a class or should the drugs be differentiated?
- How should the breast cancer benefit from raloxifene be considered, given that the cost effectiveness becomes less favourable with increasing risk of fracture when the breast cancer effect is included?
- Which estimate of the reduction in risk of hip fracture should be assumed for strontium ranelate: (1) midpoint RR pooled across the entire study population; (2) no effect (as not statistically significant); or (3) midpoint RR for women aged 74 and over?
- Although the WHO algorithm is not available to practitioners in the UK at the moment, the Assessment Group has developed an approach for identifying women who can be treated cost effectively. Is such a simplified approach acceptable?

- Can absolute risk thresholds be used in the recommendations?

- In primary prevention, the analyses show that there are osteoporotic women below the age of 70 who could be treated cost effectively. However, it is not cost effective to systematically risk assess these individuals, that is, to apply the identification approaches explored in the Assessment Report to younger postmenopausal women, due to the lower percentage of high-risk women in this age group. Does this pose an equity issue?

- Should special consideration be given to women aged 50–69 who are seen by clinicians because they are prescribed corticosteroids? Could this be used as a flag for assessing their fracture risk?

7 Authors

Elisabeth George, Health Technology Analyst
Meindert Boysen, Health Technology Analyst
Kate Burslem, Health Technology Analyst
Janet Robertson, Technical Advisor
NICE Appraisal Team
August 2005

Appendix A. Sources of evidence considered in the preparation of the overview

1. *The Clinical Effectiveness and Cost Effectiveness of Prevention and Treatment of Osteoporosis*. Assessment report by Dr Matt Stevenson, ScHARR, University of Sheffield, February 2003.
2. DSU report by Dr Matt Stevenson, Dr Myfanwy Lloyd Jones, Ms Sarah Davis and Ms Catherine Beverly; ScHARR, March 2005.
3. Prescribing data from the Prescription Pricing Authority website.
4. Cost-effectiveness data from the submissions received in 2002 from the Alliance for Better Bone Health (that is, Aventis UK and Proctor and Gamble), Eli Lilly, Merck Sharp and Dohme, and Proctor and Gamble.
5. Submission received in 2005 from Servier on strontium ranelate.
6. Assessment Report for strontium ranelate by Dr Matt Stevenson, Dr Myfanwy Lloyd Jones and Ms Sarah Davis, July 2005.
7. Addendum to the DSU report by Dr Matt Stevenson and Ms Sarah Davis, July 2005.
8. References for compliance:

Prowse et al. (2005) *Rheumatology* 44 (Suppl. 1):135.
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Appendix B. Outline of existing NICE guidance for secondary prevention

In January 2005, NICE recommended the following treatment options for the prevention of fractures in postmenopausal women who have already experienced a fracture (secondary prevention).

- Bisphosphonates (alendronate, etidronate and risedronate):
  - in women aged 65 and older; in women aged between 65 and 74 the presence of osteoporosis (a T-score of –2.5 or below) should be confirmed by DXA scanning
  - in postmenopausal women younger than 65, if they have a very low BMD, that is a T-score of approximately –3 or below, or if they have confirmed osteoporosis plus at least one additional age-independent risk factor: low body mass index (< 19 kg/m^2); family history of maternal hip fracture before the age of 75; untreated premature menopause; certain medical disorders independently associated with bone loss (such as chronic inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism or coeliac disease); conditions associated with prolonged immobility.
- Raloxifene:
  - in women who cannot take bisphosphonates because these are contraindicated, who are physically unable to comply with the special recommendations for use of bisphosphonates, or who are intolerant of bisphosphonates
  - in women who have had an unsatisfactory response to bisphosphonates.
- Teriparatide:
  - in women aged 65 and older who have had an unsatisfactory response or intolerance to bisphosphonates, and:
    - who have an extremely low BMD (with a T-score of approximately –4 or below), or
    - who have a very low BMD (with a T-score of approximately –3 or below) plus multiple fractures (that is, more than two) plus at least one additional age-independent risk factor: low body mass index (< 19 kg/m^2); family history of maternal hip fracture before the age of 75; untreated premature menopause; conditions associated with prolonged immobility.

Unsatisfactory response was defined as occurring when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is also evidence of a decline in BMD below her pretreatment baseline. Intolerance of bisphosphonates was defined as oesophageal ulceration, erosion or stricture, or severe lower gastrointestinal symptoms, any of which warrants discontinuation of treatment with a bisphosphonate. It was also recommended that in their choice of bisphosphonate, clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients.