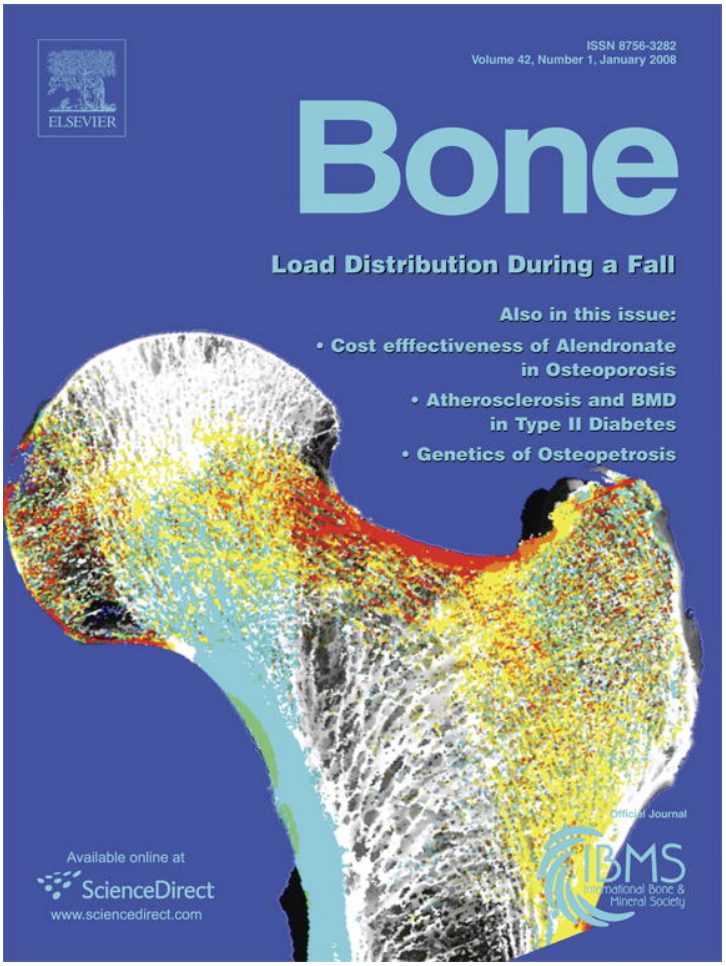

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Editorial

The cost-effectiveness of alendronate in the management of osteoporosis

Abstract

The National Institute for Health and Clinical Excellence (NICE) in the UK has recently issued health economic appraisals for the primary and secondary prevention of osteoporotic fracture that are more restrictive than previous guidelines for the management of osteoporosis despite a marked reduction of the cost of intervention. The aim of the present study was to examine the cost-effectiveness of the bisphosphonate, alendronate for the prevention and treatment of fractures associated with osteoporosis. A second aim was to investigate reasons for any disparities in cost-effectiveness between our findings and the NICE appraisals. We compared the effects of alendronate 70 mg weekly by mouth for 5 years with no treatment in postmenopausal women with clinical risk factors for fracture and computed the incremental cost-effectiveness ratio (ICER) using a lifetime simulation model based on Markov cohort methodology. A sensitivity analysis examined other common interventions.

Using a threshold of £30,000 and £20,000 per quality of life-year (QALY) gained to determine cost-effectiveness, alendronate was cost-effective for the primary prevention of fracture in women with osteoporosis irrespective of age as was treatment of women with a prior fragility fracture irrespective of BMD. Cost-effective scenarios were also found in women with strong risk factors for fracture with a bone mineral density value above the threshold for osteoporosis. The results were robust over reasonable assumptions in sensitivity analysis. We conclude that alendronate is a cost-effective agent for the prevention and treatment of fractures associated with osteoporosis. These findings, suitable for informing practice guidance, contrast with recent appraisals from 0NICE.

Keywords: Alendronate; Practice guidelines; NICE; Clinical risk factors; Fracture

Introduction

The clinical consequences of osteoporosis reside in the fractures that arise, particularly hip fracture which accounts for the major direct costs. In 1990, the number of osteoporotic fractures estimated in Europe was 2.7 million, with an estimated direct cost of €36 billion (£24.5 billion), of which €24.3 (£16.6) billion were accounted for by hip fracture. Costs are expected to rise to €76.8 (£52.4) billion by the year 2050 [1] because of the increasing numbers of the elderly.

Bisphosphonates are well established for the treatment of osteoporosis [2]. The bisphosphonate, alendronate, has been shown in randomised double blind trials to reduce the incidence of osteoporotic fractures, including hip and vertebral fractures [3]. In order to justify resource allocation, it is becoming increasingly important to determine the cost-effectiveness of intervention, and in 2005 the National Institute for Health and Clinical Excellence (NICE) in the UK published its appraisal for the secondary prevention of established osteoporosis (a bone mineral density (BMD) value 2.5 SD or more below the young healthy mean (i.e. a *T*-score of ≤ -2.5 SD) and a prior fragility fracture) [4]. A revised appraisal of the treatment and a new appraisal of prevention were issued by NICE for consultation in February 2007 [5,6]. Since the initial appraisal [4], alendronate has become available as a generic drug with a substantial reduction in price from around £300 a year to less than £90 a year. In the absence of other changes in the economic model, the price reduction would be expected to improve cost-effectiveness substantially. Paradoxically, the final appraisal determination (FAD) of secondary prevention shows little change in cost-effectiveness [7], and the FAD on primary prevention is surprisingly restrictive [8].

Guidance for the treatment and prevention of osteoporosis has been provided in the UK by the Royal College of Physicians (RCP) [9,10]. The RCP recommends that BMD testing be undertaken in postmenopausal women with strong risk factors for fracture and that treatment be considered where the *T*-score for BMD ≤ -2.5 SD. A less stringent *T*-score is recommended for glucocorticoid-induced osteoporosis [11] and treatment is also recommended for women with a prior fragility fracture without necessarily measuring BMD. Similar approaches to case finding have been recommended by the European Community and the International Osteoporosis Foundation [12,13]. In contrast the guidance of NICE does not recommend treatment of women under the age of 75 years with a prior fragility fracture unless the *T*-score for BMD is -2.5 SD or less.

The aim of the present study was to re-evaluate the cost-effectiveness of alendronate when targeted to postmenopausal

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women at high risk of fracture in order to inform the development of practice guidelines. The marked price reduction of alendronate, but without consequences on cost-effectiveness, might suggest that the NICE agenda is to seek to use cost-effectiveness modelling with ultra-conservative assumptions as a way of limiting access to medicines. A second aim was to investigate reasons for any disparities in cost-effectiveness between the findings of this study and the NICE appraisals.

Methods

The cost-effectiveness of alendronate was compared to no intervention in a UK setting by simulating costs and outcomes in cohorts of postmenopausal women from the age of 50 years at different degrees of risk of an osteoporotic fracture. The study was performed taking a healthcare perspective that included only direct costs. Health effects were measured as quality adjusted life years gained (QALY's, i.e. taking into account quality of life as well as life years). The major results are presented as the incremental cost-effectiveness ratio (ICER). A threshold value of £30,000/QALY gained was taken as being cost-effective in line with previous appraisals for osteoporosis and other chronic disorders [3–6,14–17], although NICE used a threshold of £20,000 in the appraisal of primary prevention of osteoporotic fractures. We also examined the effect of the lower threshold. Costs and effects were discounted at 3.5% as recommended by NICE, though the NICE appraisals used discount rates of 6% for costs and 1.5% for benefits.

Simulation model

The simulation model was based on Markov cohort methodology. The model has been extensively used to evaluate the cost-effectiveness of treatments for osteoporosis and hormone replacement therapy in several countries, including the UK [18–25]. The model has also been used to compute intervention thresholds, predict fracture rates and mortality making it well validated and calibrated [26–29] and provides a reference model for the International Osteoporosis Foundation [30]. The cycle length was set to 1 year and all patients were followed until they died or reached the age of 100 years. One of the main reasons for modelling is to capture differences between the treatment alternatives no matter when in time they occur. Thus the time horizon should be of a duration that captures all relevant differences in the costs and effects between the treatment alternatives [31]. For osteoporosis, the lifetime horizon is the most appropriate and is the most frequently used in cost-effectiveness analyses of osteoporosis. A lifetime horizon is also consistent with the modelling of other chronic diseases [14,30,32], but contrasts with the NICE appraisal for osteoporosis and the subsequent FADs that took predominantly a 10-year perspective [5–8].

All patients began in the healthy state where each year they had a probability of a fracture of the hip, forearm, spine, or other site or dying. When a fracture occurred, the patient moved to the corresponding fracture health state (i.e. hip, vertebral, wrist or other fracture). The long-term consequences of hip and vertebral fractures were considered in separate health states. Wrist fracture and other osteoporotic fracture were assumed to have an impact on costs and morbidity only in the first year after fracture, and the patient was thus considered to have regained full health 1 year after the fracture. After a hip fracture, the patient was only at risk for another hip fracture or dying. After a vertebral fracture, the patient was at risk of sustaining a hip or a vertebral fracture or dying. This conservative simplification was adopted because there are few available data on the costs and effects of multiple fractures and, given the low probability of having a vertebral or a wrist fracture after a hip fracture, this discrepancy will have a minor impact on the ICER.

The data used to populate the model were based whenever possible on information from the UK and were the same as those used by NICE in their assessments, unless indicated otherwise.

Fracture risks

Fractures of the spine, rib, pelvis, humerus, forearm, hip and other femoral fractures, tibia and shoulder girdle were considered to be osteoporotic, since they are associated with low BMD and increase in incidence with age [33,34]. The incidence of fractures was taken from Singer et al. [35] except for rib and vertebral fractures, which are inconsistently reported in the UK [36]. The incidence of a clinical vertebral fracture was calculated by assuming that the ratio of clinical vertebral fracture to hip fracture would be similar in the UK compared to Sweden [3,16,37]. The same approach was used to assess the risk of rib fractures.

Age-specific fracture rates and mortality were assumed not to change over the lifetime of individuals. The assumption on mortality underestimates lifetime risk [38], but has little impact over the intervention period.

Effect of treatment

The effects of alendronate on fracture risk were taken from a meta-analysis conducted for the NICE appraisal [3]. The relative risk was 0.62 for hip fracture, 0.56 for vertebral fracture, 0.67 for forearm fracture and 0.81 for other non-vertebral fractures. These relative risks differ from those used by NICE in their FADs which were based on the pooled effects of risedronate and alendronate. Also, in the first appraisal of treatment, the impact of treatment was modelled on hip, clinical spine and forearm fractures, whereas subsequent appraisals included other osteoporotic fractures. We examined the effect of excluding these other fractures in sensitivity analysis.

Other interventions were examined in a sensitivity analysis. The relative risks of fracture with treatment are shown in Table 1 as given by NICE with the following exceptions. In the case of raloxifene, an effect of the agent on breast cancer was also incorporated (RR=0.38; 95% confidence interval=0.24–0.58) [39]. In a recent study, treatment with raloxifene was associated with an increased incidence of fatal stroke (RR=1.49; 95% confidence interval=1.00–2.24), but all cause mortality was not increased [40] and this risk was not modelled. For strontium ranelate, we used the assumptions of NICE, but modelled an additional scenario that included a post hoc analysis, accepted by the Committee of Human Medicinal Products of the European Medicines Evaluation Agency but not by NICE, showing a significant effect on hip fracture risk [41]. Oral ibandronate was also modelled, based on a study using 2.5 mg daily or an intermittent regimen of 20 mg on alternate days for 12 doses every 3 months [42], but was not appraised by NICE.

Table 1
Relative risk of fracture at the sites shown with 95% confidence intervals (CI) for different interventions

Intervention	Fracture site							
	Hip		Spine		Forearm		Other	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Alendronate	0.62	0.40–0.96	0.56	0.46–0.67	0.67	0.34–1.31	0.81	0.68–0.97
Etidronate	–	–	0.40	0.46–0.67	–	–	1.04	0.64–1.69
Ibandronate daily	–	–	0.38	0.25–0.59	–	–	–	–
Ibandronate intermittent	–	–	0.50	0.34–0.74	–	–	–	–
Raloxifene [a]	–	–	0.65	0.53–0.79	–	–	–	–
Risedronate	0.74	0.59–0.93	0.61	0.50–0.75	0.68	0.43–1.08	0.76	0.64–0.91
Strontium ranelate [b]	0.84	0.73–0.97	0.60	0.53–0.69	0.84	0.73–0.97	0.84	0.73–0.97
Strontium ranelate [c]	0.64	0.47–0.98	0.60	0.53–0.69	0.84	0.73–0.97	0.84	0.73–0.97

–, no data or no significant effect.
[a] Additional effects on breast cancer and stroke modelled.
[b] As assumed by NICE.
[c] Includes a post hoc analysis on hip fracture.

An intervention for 5 years was assumed. After stopping treatment, the risk reduction was assumed to reverse in a linear manner over a 5-year period. Recent studies suggest that this offset time may be conservative [43–46] and a 40% change in offset time was used in sensitivity analysis.

Side-effects were not included in the base case since neither randomised studies of efficacy nor studies of side-effects have shown significant differences between placebo and actively treated patients [47–50]. By contrast, perceived gastrointestinal side-effects are a frequent cause for stopping treatment [51]. The absence of side-effects, also assumed by NICE in the initial appraisal of treatment [4] was modified for the subsequent appraisals. In the latter appraisals, the prevalence and consequences of treatment, taken from non-randomised studies, assumed that there would be 23.5 additional GP consultations per 1000 patient months in the initial treatment period and 3.5 GP consultations subsequently, and the use of a proton pump inhibitor. Symptoms were assumed to persist for 1 month with a utility loss equivalent to a multiplier of 0.91 [51]. The frequency of side-effects was then multiplied ten-fold for an unknown reason. We included these assumptions in a sensitivity analysis.

The long-term persistence with bisphosphonates was set at 50% as used in the NICE appraisal. The remaining 50% were assumed to receive 3 months of drug treatment for no health gain [16], as adopted by NICE. These estimates were based largely on studies from North America, and estimates from the UK give higher values in the order of 80% when account is taken of switching medication [52–55]. A persistence rate of 70% was assumed for sensitivity analysis (base case +40%).

Clinical vignettes

The objective of using clinical scenarios was to test the case-finding strategy of the RCP. The strategy alerts the physician to osteoporosis in women with a strong risk factor for fracture. This provides a trigger to have a measurement of BMD, and treatment is considered in those women with a BMD value that lies in the range of osteoporosis. Treatment is, however, also recommended for women with a prior fragility fracture without necessarily measuring BMD. Whereas the RCP generally recommends treatment if the *T*-score is less than −2.5 SD, the present analysis computed the ICER with a range of *T*-scores. Since the development of the RCP guidelines, it has become apparent that the presence of several of the risk factors used to trigger a BMD test are associated with a fracture risk greater than can be accounted for by BMD [56]. Thus, the assessment of fracture risk in this analysis took account of the specific risk factor in addition to BMD and age.

The clinical risk factors selected for use in a case-finding strategy were based on a series of meta-analyses that identified clinical risk factors associated with an increase in fracture risk independently of age and BMD at the femoral neck. These included low body mass index (BMI; in part dependent on BMD) [57], a prior fragility fracture [58], a parental history of hip fracture [59], long-term use (e.g. for 3 months or more) of oral glucocorticoids [60], rheumatoid arthritis [60], current cigarette smoking [61] and high alcohol consumption (3 or more units/daily) [62]. The independent contribution of each of these risk factors to fracture risk has been determined from a series of meta-analyses of 9 population-based cohorts (190,000 patient years) from Europe, North America, Japan and Australia [63] and validated in a further 11 independent cohorts (1.2 million person-years) [64]. The contribution of these factors was used to provide clinical scenarios for modelling.

The weight of the various risk factors differs for hip fracture and other fracture outcomes and in the presence or absence of information on BMD. In the absence of a BMD test, BMI is an important predictor of fracture, but is almost entirely dependent on BMD [57]. Thus, for the purposes of modelling, BMI was set to a fixed value of 26 kg/m^2 — close to the average value for postmenopausal women.

In addition to rheumatoid arthritis, provision was made for the inclusion of other secondary causes of osteoporosis. The following secondary causes of osteoporosis have been consistently documented to be associated with a significant increase in fracture risk [65].

- Untreated hypogonadism in men and women, e.g. bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, androgen deprivation therapy for prostate cancer, hypopituitarism
- Inflammatory bowel disease, e.g. Crohn's disease and ulcerative colitis
- Prolonged immobility, e.g. spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, ankylosing spondylitis
- Organ transplantation
- Type I diabetes
- Thyroid disorders, e.g. untreated hyperthyroidism, over-treated hypothyroidism
- Chronic obstructive pulmonary disease

The dependence of the increased fracture risk on BMD is not known, so that (unlike rheumatoid arthritis) these additional secondary causes carried no weight in the presence of information on BMD.

The incidence of fracture was adjusted to reflect the risk in the target patient groups. The method of calculating fracture risk in the different patient groups relative to the population fracture risks based on BMD and prior fracture is described previously [66] and a similar approach was used for the other risk factors. Thus, the starting point was the fracture risk in the population with no clinical risk factors and with no BMD test. Since the risk factors are common, the starting risk is lower than the average population risk. Examples are provided in Table 2.

Costs

Costs of fracture were taken from Stevenson et al. [15] as used previously to determine cost-effectiveness of intervention in glucocorticoid-induced osteoporosis [17]. These differ somewhat from those used by NICE, which were based on Health Resource Group codes that are unrealistically low as judged by empirical data in the case of hip fracture, unavailable for vertebral fractures and inappropriate for forearm fractures in the elderly, since a substantial proportion of forearm fractures occur in young individuals[15]. Average in-patient and out-patient costs used in this analysis were £10,760 for hip fracture, £9236 for pelvic fracture, £13,771 for other femoral fractures, £1706 for vertebral fracture, £527 for forearm fracture, £147 for ribs and sternal fractures, £141 for scapular fractures, £1112 for humeral fractures and £3864 for fractures of the leg. These did not include any cost for home help. Costs were age-weighted [28] and included nursing home admissions after hip fracture that increased from 6.7% between the age of 50 and 59 years to 22.6% at the age of 90 years or more [67,68]. Nursing home costs were not included for fractures at other sites that might require admission to a nursing home.

The cost of medication was assumed to be £95 per annum (as given in the British National Formulary at the time of analysis, but now at less than half this cost). The costs for case finding were 3 min of GP time to administer the questionnaire on risk factors (£5.76), the cost of a BMD test at the femoral neck with dual energy X-ray absorptiometry (£35), and a 10 min consultation with a general practitioner to start treatment (£19.20). Conservatively, all patients treated were assumed to have a BMD test before treatment and 2-yearly thereafter. The unit cost is similar to that used in the NICE appraisal of treatment, but the total cost is lower than in the FAD for primary prevention, since the latter included the cost of systematic population-based screening.

Table 2
Hazard ratios (HR) for fracture and for death in women with no clinical risk factors without a BMD test and in women with no clinical risk factors and a BMD *T*-score of −2.5 SD

Age (years)	HR for osteoporotic fracture[a]		HR for hip fracture		HR for death	
	Without BMD	With BMD	Without BMD	With BMD	Without BMD	With BMD
50	0.78	1.21	0.5	4.08	0.78	0.94
55	0.79	1.21	0.51	2.78	0.79	0.94
60	0.81	1.18	0.52	1.88	0.8	0.93
65	0.83	1.15	0.53	1.31	0.81	0.93
70	0.85	1.09	0.54	0.95	0.82	0.92
75	0.86	1.03	0.55	0.71	0.84	0.92
80	0.88	0.95	0.56	0.55	0.85	0.91

[a] Fragility fractures other than hip fracture.

Mortality

The age-specific normal mortality rates for the general population in the UK were based on the years 2000–2002 [69]. These were adjusted in the model to take into account the mortality associated with the clinical risk factors and any outcome fracture. The NICE appraisals took account of the mortality associated with hip and vertebral fractures by assuming that approximately 30% of deaths are causally attributed to the fracture event [70–72]. The appraisals, however, did not take account of any mortality consequences associated with the presence or absence of other clinical risk factors.

Quality of life

The impact on quality of life the first year after a fracture (hip, vertebral and forearm) was based on empirical estimates [29]. The quality of life estimates for other fractures was based on expert opinion [73]. The quality of life in subsequent years after a hip fracture was assumed to be 91% of that of a healthy individual. Forearm fractures were estimated to have no quality of life reduction in the second and subsequent years. The quality of life in subsequent years after a vertebral fracture was reduced by 7.1% derived from empirical observations. In an international study when the clinical vertebral fracture may have occurred at a previously unknown time [74], the utility loss was 9%. These multipliers were used together with the population tariff values for the UK [75]. These values are similar to those used by NICE except for vertebral fracture where the utility multiplier in the first year was arbitrarily reduced by the appraisal committee by 27% from 0.626 to 0.792. The effect of this reduction was modelled in sensitivity analyses.

Results

The cost-effectiveness of alendronate directed to women at the threshold of osteoporosis is shown in Table 3. In women with osteoporosis (i.e. a femoral neck *T*-score equal to −2.5 SD) the ICER was stable up to the age of 60 years and, thereafter, decreased progressively with increasing age. Treatment was cost-effective at all ages, even assuming a willingness to pay of £20,000/QALY. Treatment was also cost-effective at all ages in women who had previously sustained a fragility fracture with a BMD set at the threshold of osteoporosis. Indeed, treatment was cost saving from the age of 75 years. A prior fragility fracture was a sufficiently strong risk factor that treatment was cost-effective even in women without other risk factors in whom BMD was not known (see Table 3).

The effect of different clinical risk factors at different *T*-scores for BMD is shown in Table 4. Prior fractures and a parental history of hip fracture were the strongest risk factors and treatment was cost-effective across all ages and *T*-scores. The use of glucocorticoids and the presence of rheumatoid arthritis had a lesser impact on cost-effectiveness, but across all ages and *T*-scores the ICER lay below a £30,000 threshold and below a £20,000 threshold of cost-effectiveness from the age of 70 years or with low *T*-scores. Current smoking and excessive alcohol intake were the weakest of the clinical risk factors and, cost-effectiveness was confined to the lower *T*-scores and higher ages using a £20,000 threshold.

For the strong risk factors, i.e. prior fracture and a parental history of hip fracture, treatment was cost-effective at all ages after the age of 50 years even in the absence of a BMD test (Fig. 1). For the other clinical risk factors the ICER lay above or slightly below the cost-effectiveness threshold at younger ages, but treatment was cost-effective from the age of 65 years for any single risk factor.

In the presence of more than one clinical risk factor the ICER depended on the weight of the clinical risk factor. In the absence of information on BMD, the combination of any two risk factors

Table 3
Cost-effectiveness of intervention with alendronate in women at the threshold of osteoporosis, with or without a prior fracture and in women with a previous fracture without BMD [a]

Age (years)	Cost (£000)/QALY gained		
	T-score = −2.5 no previous fracture	*T*-score = −2.5 + previous fracture	No BMD + previous fracture
50	14.7	6.7	14.6
55	16.2	7.3	14.1
60	14.3	7.3	11.6
65	7.0	2.9	5.0
70	3.7	0.8	2.1
75	3.0	c.s.	c.s.
80	c.s.	c.s.	c.s.

c.s. = cost saving.
[a] BMI set to 26 kg/m^2.

Table 4
Cost-effectiveness of intervention (cost (£000)/QALY gained) in women with clinical risk factors according to age and *T*-score for femoral neck BMD

Age (years)	*T*-score (SD)			
	0	−1	−2	−3
(a) Prior fracture				
50	18.1	15.7	9.9	3.2
60	18.4	15.6	10.5	2.6
70	9.0	6.5	3.2	c.s.
80	13.9	7.3	2.3	c.s.
(b) Family history				
50	16.3	14.7	11.1	5.9
60	15.7	14.0	10.4	5.9
70	9.0	6.0	1.8	c.s.
80	5.1	c.s.	c.s.	c.s.
(c) Glucocorticoids				
50	23.3	19.5	13.3	4.6
60	22.3	19.0	12.6	3.1
70	10.6	7.5	2.9	c.s.
80	15.0	6.4	c.s.	c.s.
(d) Rheumatoid arthritis				
50	21.1	22.6	15.4	6.2
60	25.1	21.1	14.4	6.3
70	11.5	8.4	4.4	c.s.
80	15.7	7.8	1.9	c.s.
(e) Alcohol >3 units daily				
50	28.5	24.3	16.2	6.0
60	27.1	22.7	15.0	6.1
70	12.6	8.9	4.4	c.s.
80	16.1	7.6	1.2	c.s.
(f) Current smoking				
50	37.6	31.7	19.9	6.6
60	37.7	31.1	19.5	6.7
70	18.5	13.1	5.6	c.s.
80	25.8	12.0	0.2	c.s.

c.s. = cost saving.

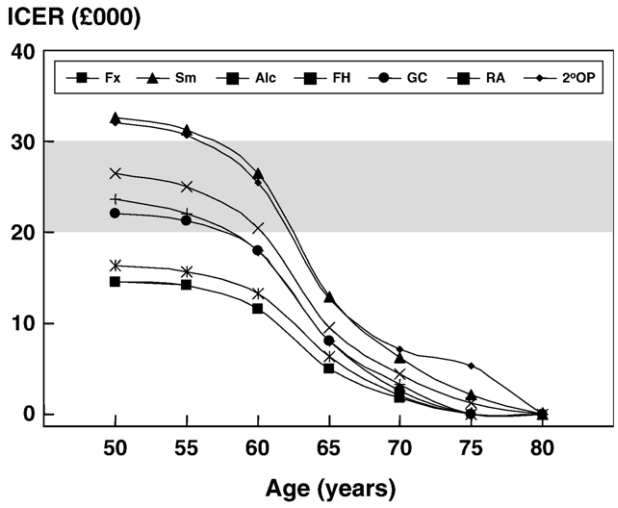

Fig. 1. Incremental cost-effectiveness ratio (ICER) in postmenopausal women treated with alendronate by age and the presence of clinical risk factors for fracture. Fx, prior fracture; Sm, smoking; Alc, alcohol intake 3 or more units daily; FH, family (parental) history of hip fracture; GC, long-term use of glucocorticoids; RA, rheumatoid arthritis; 2° OP, secondary causes of osteoporosis.

gave an ICER of less than £30,000 from the age of 50 years (Fig. 2) and below £20,000 from the age of 65 years.

A stochastic analysis using the distribution of treatment efficacy showed that the ICER fell below a threshold of £20,000 in all simulations of the base case (women aged 70 years). With a willingness to pay set at £10,000/QALY gained, treatment was cost-effective in 99% of simulations in patients with a prior fracture (with or without BMD) and in 96% of simulations for women with a BMD *T*-score = −2.5 SD (Fig. 3). With a prior fracture and no BMD test, treatment was cost saving in 9%, a proportion that rose to 35% for women with a prior fracture and a BMD *T*-score = −2.5 SD.

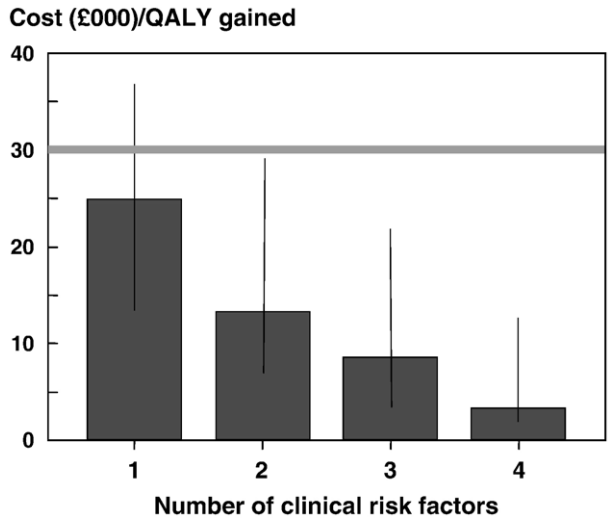

Fig. 2. Median cost-effectiveness (cost (£000)/QALY gained) of alendronate in postmenopausal women according to the number of clinical risk factors. The intervals show the range of cost-effectiveness which varies according to the weight of the clinical risk factors.

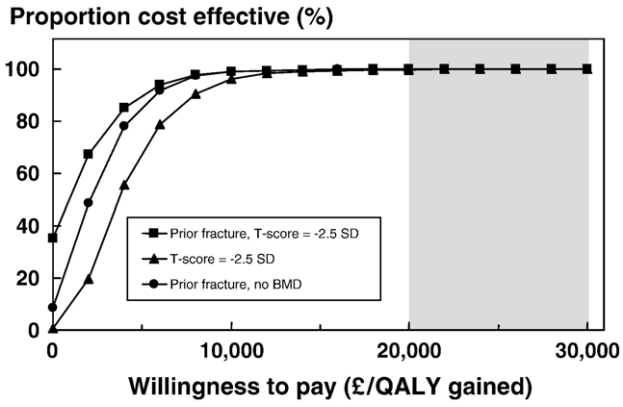

Fig. 3. Cost-effectiveness acceptability curves for alendronate in women aged 70 years. The shaded area encloses the two thresholds for cost-effectiveness.

Sensitivity analysis showed that changes in time horizon and assumptions concerning side-effects had marked effects on cost-effectiveness (Table 5). The ICERs were more than doubled when a 10-year rather than a lifetime horizon was used. When side-effects, as assumed by the systematic review for NICE, were included, this had a very modest effect on cost-effectiveness using the lifetime horizon, but had a slightly more marked adverse effect on cost-effectiveness with the shorter time horizon. When the frequency of side-effects was assumed to be ten-fold higher, the ICER increased, as expected, but in all the base case scenarios the ICER lay below a threshold of

Table 5
Sensitivity analysis of the cost-effectiveness of alendronate in women aged 70 years

	T-score = −2.5 SD		No BMD
	No prior fracture	Prior fracture	Prior fracture
Base case	3709	871	2130
10-year time horizon	10,950	4473	7421
Offset time +40% (7 years)	2659	0	1251
Offset time −40% (3 years)	4908	1896	3118
Treatment duration +40% (7 years)	3607	588	1961
Treatment duration −40% (3 years)	3294	740	1885
Non-adherence +40% (70%)	4914	1841	3135
Non-adherence −40% (30%)	3163	454	1698
Only hip, vertebral and wrist fracture included	5538	2324	3423
Higher utility for vertebral fracture	3768	888	2168
Nursing home admissions as NICE	4617	1903	2944
Side-effects			
Systematic review lifetime horizon	3780	904	2172
Systematic review 10-year time horizon	11,258	4604	7620
Frequency multiplied by 10 (lifetime)	4488	1222	2584
Frequency multiplied by 10 (10 years)	14,769	6001	9789
Intervention			
Alendronate	3714	867	2119
Etidronate	12,869	10,098	9093
Ibandronate daily	20,956	14,617	14,694
Ibandronate intermittent	31,154	21,587	21,745
Raloxifene	11,184	10,379	10,808
Raloxifene without breast cancer	34,011	23,544	23,755
Risedronate	18,271	12,659	13,853
Strontium ranelate	25,677	18,332	19,221
Strontium ranelate, post hoc analysis	18,628	13,077	13,673

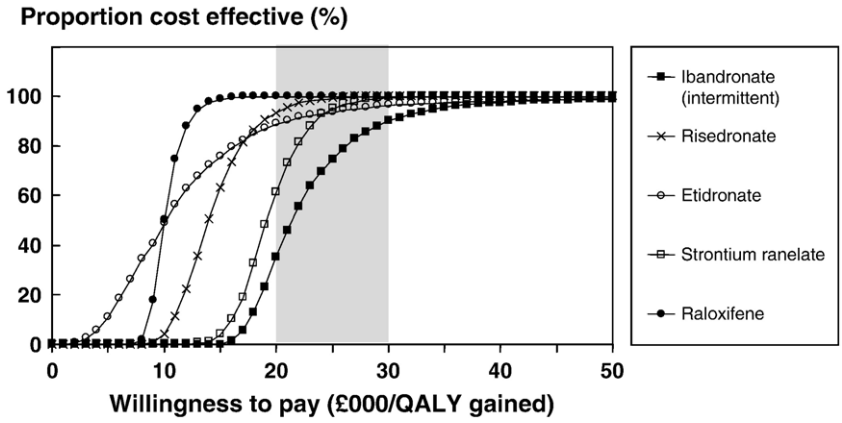

Fig. 4. Cost-effectiveness acceptability curves for raloxifene, strontium ranelate, etidronate, risedronate and ibandronate in women aged 70 years. The shaded area encloses the two thresholds for cost-effectiveness.

£20,000/QALY gained. Moderate effects on cost-effectiveness were observed with changes in the assumptions concerning offset time, adherence, effects of treatment only on hip, spine and vertebral fracture, utility weights for spine fracture and admission rates to nursing homes after hip fracture.

As expected, other treatments were less cost-effective than alendronate, but the ICER fell below a £30,000/QALY threshold for all treatments with the exception of intermittent ibandronate in women with a BMD *T*-score of −2.5 SD and no prior fracture. Indeed, with the exception of intermittent ibandronate, the ICER was below £20,000/QALY for all the base case scenarios. The exclusion of fractures other than those at the spine, hip and forearm had a modest effect to increase the ICER in the case of alendronate and risedronate (data not shown).

Cost-effectiveness acceptability curves showed no marked differences between agents (Fig. 4) in women aged 70 years, with a prior fracture and no BMD test. For ibandronate and strontium ranelate, the more conservative estimates of efficacy were used (see Table 2). At a willingness to pay of £30,000/QALY gained, treatment was cost-effective in 90% of simulations for ibandronate and in more than 96–100% of simulations for the other agents. At a threshold of £20,000/QALY gained the proportion that lay below this threshold was 35% for ibandronate, 61% for strontium ranelate, 89% for etidronate, 93% for risedronate and 100% for raloxifene. For ibandronate and strontium ranelate, where more than one efficacy scenario was modelled, the proportion of simulations that were cost-effective increased with greater efficacy assumed (Fig. 5). For daily ibandronate the proportions were 94% and 100% for thresholds of £20,000 and 30,000, respectively. For strontium ranelate the proportions were 94% and 100% for thresholds of £20,000 and £30,000, respectively when the post hoc analysis was included. As might be expected, the exclusion of breast cancer effects with raloxifene markedly impaired cost-effectiveness (proportions 14% and 86% respectively).

Discussion

The principal finding of the present study is that the treatment of osteoporosis and established osteoporosis with alendronate in postmenopausal women is highly cost-effective. The ICER decreased with increasing age because of the higher risk of fracture; but even at the age of 50 years, the average age of menopause, the ICER was less than £15,000 — well below a threshold of £20,000 or £30,000. The findings suggest that the

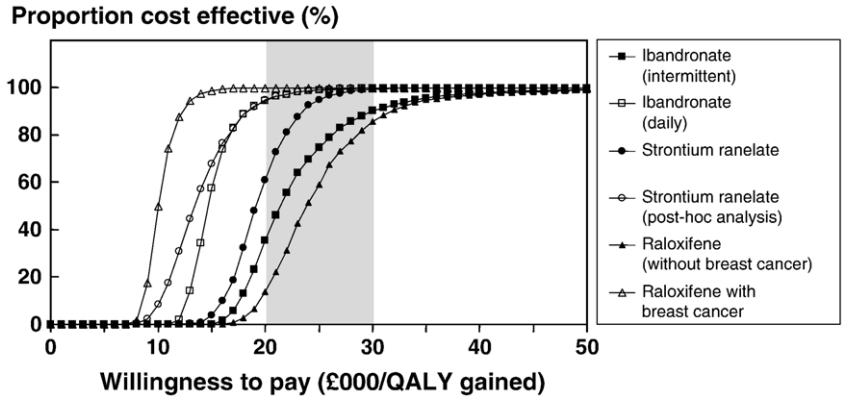

Fig. 5. Cost-effectiveness acceptability curves for raloxifene, strontium ranelate and ibandronate in women aged 70 years. Details of the scenarios modelled are given in Table 1. The shaded area encloses the two thresholds for cost-effectiveness.

current RCP guidelines are overly conservative in restricting treatment largely to women with a *T*-score of <-2.5 SD. In an extension of the RCP strategy, we were able to model the added fracture risk conferred by the presence of validated clinical risk factors and show that there are cost-effective scenarios to be found in women with low bone mass in whom BMD is higher than the threshold BMD for osteoporosis.

To date, treatment of osteoporosis has largely been determined by the level of BMD. Our findings that the presence of clinical risk factors and age modulate risk and therefore cost-effectiveness, reinforce the view that treatment should be directed on the basis of fracture probability, rather than on a BMD threshold [11,17,56,65,76,77]. The preferred metric is the probability of fracture, e.g. the ten-year fracture probability that integrates not only fracture hazards, but also competing death hazards. Thus, from a health economic perspective, an intervention threshold represents the fracture probability at which treatment becomes cost-effective. Intervention thresholds have previously been estimated for the UK [26,28], but are now redundant in the case of alendronate, given the very marked reduction in the cost of the drug.

For the purposes of this paper, we have not presented intervention thresholds for alendronate in terms of fracture probability for several reasons. The first was to enable comparison to the FADs arising from the NICE appraisals with the present study. Second, practising physicians are not yet familiar with the assessment of fracture probability, although algorithms will shortly be available to assess these in the UK [65]. Third, we wished to determine the manner in which the present analysis would modify the current guidance of the RCP.

Comparison with NICE

Our finding of good cost-effectiveness for the treatment of osteoporosis is not surprising, given that many treatments in osteoporosis or established osteoporosis, including alendronate, have been shown to be cost-effective in a UK setting [20,21,24,78] and that the price of alendronate has decreased to less than one third of its former price. Our findings, however, contrast markedly with those of NICE, which suggest that the reduction in price had little if any beneficial effect on cost-effectiveness. Moreover, the indications for treatment were much more stringent.

The lack of impact of the price reduction of alendronate on its cost-effectiveness in the technology appraisal of NICE is explained in part by a number of changes in the assumptions contained within the economic model. Examples of this include a decrease in the relative risk reduction for hip fracture for alendronate (0.51, 0.38 and 0.29 in successive appraisals on secondary prevention), achieved by pooling of data for risedronate and alendronate (despite separate cost-effectiveness analysis for these two drugs), reduction of the disutility value associated with vertebral fractures, and adopting a cost per QALY threshold for primary prevention of £20,000. New assumptions introduced into the model included costs and disutility associated with side-effects and non-adherence with treatment. Furthermore, the analyses assume that the efficacy of drugs on fractures is much less in patients with risk factors other than age, previous fracture and low BMD; this is adjusted by a correspondingly greater efficacy of drugs on fractures associated with age, low BMD and previous fracture. These assumptions fail to recognise the presence of risk factors other than age, low BMD and previous fracture in clinical trial populations; thus if intervention was indeed ineffective against fractures associated with risk factors other than age, BMD and fracture, this would be reflected in the relative risk reduction in the trial population.

Several of the assumptions of NICE were modelled in sensitivity analyses. Of these, the frequency of side-effects ascribed to alendronate was very sensitive. The relatively high incidence of gastrointestinal side-effects reported in post-marketing studies [79,80] but no excess risk in clinical trials may be partly due to a heightened awareness of the potential for gastrointestinal adverse events — a nocebo effect [81], and there is some clinical support for this view [48]. For these reasons we did not include gastrointestinal side-effects in the base case. Moreover, the continued administration of an agent with side-effects is counterintuitive to clinical practice when alternative treatments are available. Indeed, switching treatment is common [53,82,83]. When the assumptions of NICE were included in a sensitivity analysis, the cost-effectiveness ratio increased as expected, but the effect was modest except when the frequency of side-effects was assumed to be ten times higher than that derived from the systematic review commissioned by NICE [51].

A major difference between the present study and that of NICE is that the latter appraisal used a 10-year rather than a lifetime horizon. It is unusual to provide 10-year time horizons in chronic diseases and the standard and most appropriate approach is to model over remaining lifetimes [30,31] as recommended by NICE [32] and undertaken for example in the NICE appraisal of statins [14]. The 10-year horizon captures all the costs of treatment (identification of patients and cost of treatment), but loses a component of the benefit. For example, an individual who dies after 9 years is dead for life, and not for 1 year, as would be assumed with a 10-year horizon. Similar considerations pertain to other consequences of fracture. It might be argued that future uncertainties preclude long-term horizons, but uncertainties affect both treatment and untreated wings of study. The penalties for ignoring future costs and effectiveness have been previously shown in osteoporosis. Thus women at the threshold of osteoporosis (*T*-score $=-2.5$ SD) can be treated cost-effectively with risedronate from the age of 55 years when the time horizon extends over a lifetime. In contrast, when a 10-year horizon is used, cost-effectiveness was seen only from the age of 70 years [17]. The sensitivity analysis in the present study also indicates that modelling over a restrictive period markedly decreases cost-effectiveness. In women taking long-term glucocorticoids, treatment was cost-effective at the age of 50 years with a *T*-score of -1 SD (£9500/QALY). When a 10-year horizon was modelled, the ICER rose to £80,600/QALY, and fell to below £30,000/QALY only from the age of 70 years (data not shown).

A further limitation of a short fixed time horizon of 10 years is that potential benefits of changing assumptions in offset time cannot be effectively captured. Offset time is uncertain for the

bisphosphonates and, in early models, was assumed to be 5 years [84]. This was based on the knowledge that offset time was unlikely to be zero, and also unlikely to be infinity. Although the question has not been resolved completely, with the increasing duration of follow-ups, a 5-year offset now appears conservative for some of the bisphosphonates [43–46], oestrogens [85] and PTH [86].

Clinical risk factors

There are several considerations that determined the choice of clinical risk factors used for the assessment of fracture probability. The association of the risk factors with fracture was based on large meta-analyses of population-based prospective cohorts that used individual patient data, rather than summary statistics and were validated in independent cohorts (see Methods). This enabled the contribution of each risk factor to be quantified by age, BMD and BMI. The Osteoporosis Guideline Development Group (GDG) of NICE identified the same risk factors for fracture by systematic reviews, although not all were used by NICE in their technology appraisals. Thus inexpensive technologies (use of glucocorticoids and smoking) that improve the performance of case finding were ignored.

Aside from the availability of sufficient data, risk factors were chosen for their ease of use in the setting of primary care. A further consideration is that the risk factor should identify a risk that is amenable to the intervention intended. An example ad absurdum is the fracture risk associated with jumping from the tenth floor of a building. It seems unlikely that pre-dosing with alendronate would mitigate this risk. More realistically, liability to falls is a strong risk factor for fracture, but there is some uncertainty whether patients identified on the basis of such risk factors would respond to treatment with inhibitors of bone turnover [87]. The strongest level of evidence for the validity of the use of risk factors in this way is provided by randomised controlled trials that recruit patients on the basis of a candidate risk factor. Responsiveness to pharmacological intervention has been shown for patients selected on the basis of low BMD, prior fracture, or the use of oral glucocorticoids [88–91]. In the case of the other risk factors, no trials have recruited on the basis of their presence. Nor are they likely to in the future. However, analyses of randomised controlled trials indicate that the effects of treatment are not adversely (or beneficially) affected by the presence or absence of the other risk factors [86,89,91–94]. These considerations suggest that the risk factors chosen are appropriate.

Practice guidelines

Since the prevention of osteoporotic fractures is highly cost-effective, the question arises whether the strategy developed by the RCP should be modified. In the present analysis, we have used the same strategic approach in using a case-finding strategy where candidates for treatment are identified opportunistically by the presence of clinical risk factors and, where present, considered for a BMD test. We have not considered, therefore, the possible role for population-based screening, for example offering BMD tests to women at the age of 65 years as recommended in North America [95,96]. Trials of screening are currently in progress and may better inform the utility of this approach in the UK.

In contrast, the present study suggests that the threshold of risk at which intervention is worthwhile could be changed. The current RCP guidelines provide for the treatment of patients with a previous fracture without the need for a BMD test. Our cost-effectiveness analysis suggests that this can be justified from a health economic viewpoint, since the ICERs fell much below the £30,000 threshold or even a £20,000 threshold. Similar findings were evident in patients with a parental history of hip fracture. Thus, in the presence of these strong risk factors, treatment can be considered in postmenopausal women without recourse to testing with BMD.

For the other clinical risk factors, the ICERs exceeded a £20,000 threshold at younger ages, but the ICER decreased with age and, at the age of 65 years or more, was substantially less than £20,000. This suggests that women with the weaker clinical risk factors aged 65 years and above should be considered for treatment, but that women below this age should be referred for BMD testing. On the basis of our findings, treatment should be considered where the *T*-score for BMD at the femoral neck is −1 SD or lower for postmenopausal women with rheumatoid arthritis or committed to long-term oral glucocorticoids, and where the *T*-score for BMD at the femoral neck is −2 SD or lower for women with other secondary causes of osteoporosis, cigarette smokers or women that drink 3 units of alcohol or more daily. A possible management algorithm is shown in Fig. 6. As shown, treatment can be given cost-effectively in many patients without the need for a BMD test. It is a commonly held view that treatment should not be undertaken in women without recourse to a BMD test except in women with prior fragility fractures. The view arises because of a post hoc analysis showing reduced efficacy of alendronate in patients with *T*-scores that exceed −2.5 SD [97]. As noted above, several other studies have shown, however, little or no interaction of BMD on effectiveness of several agents, including the bisphosphonates [86,89,91–94]. Moreover, the clinical risk factors are not totally independent of BMD and, when clinical risk factors alone are used in women aged 70 years or more to select patients at high risk, BMD is approximately 1 SD lower in the high risk group compared with a low risk group [98]. A recent analysis has shown that the efficacy of the bisphosphonate clodronate is greater in patients with the higher fracture probabilities identified on the basis of clinical risk factors alone [99]. The adoption of BMD tests for all patients in a case-finding strategy would, however, not adversely affect our estimates of cost-effectiveness, since BMD testing was included in all scenarios. Rather, the avoidance of BMD testing would make treatment even more cost-effective.

A strength of the model is in the estimation of individual probabilities from fracture and death hazards based on age, BMD and clinical characteristics. The incremental information derived from the clinical risk factors increases the sensitivity of fracture prediction without loss of specificity [100] so that higher risk populations are selected [101]. It is important to note, however, that neither our analysis nor the management

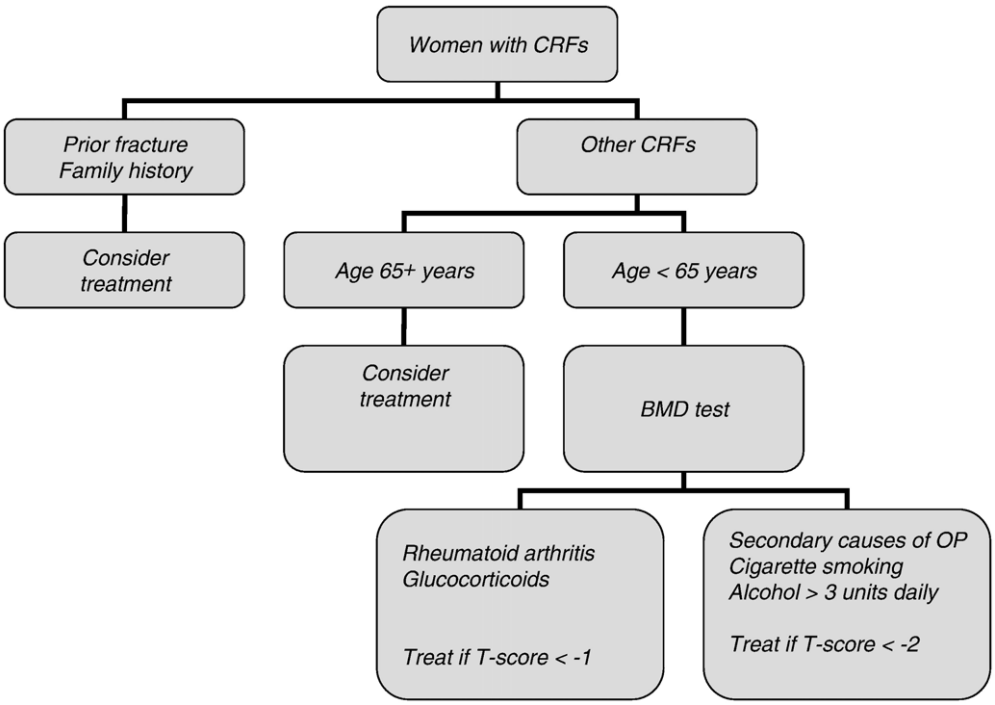

Fig. 6. Management algorithm for postmenopausal women.

algorithm takes account of dose-responses for several risk factors. For example, two prior fractures carry a much higher risk than a single prior fracture [102]. A prior clinical vertebral fracture carries a two-fold higher risk than a fracture of the appendicular skeleton or an asymptomatic vertebral fracture [103]. In such cases, therefore, treatment will be even more cost-effective. Dose-responses are also evident for smoking [61], alcohol intake [62,102], BMI [57] and glucocorticoid use [104]. Thus the gains in lower cost-effectiveness would be greater in patients taking higher than average doses of glucocorticoids and less in patients on lower than average doses. Moreover, the model is based on the ever-use of glucocorticoids, which may underestimate the fracture risk in women currently taking glucocorticoids. Whereas it is not practicable to model all such scenarios, these effects should be acknowledged, in order to give sufficient clinical flexibility in the interpretation of any guidance.

Interventions

The present study has focussed on the cost-effectiveness of alendronate 70 mg weekly, but examined some other interventions compared with no treatment in sensitivity analysis (etidronate, strontium ranelate, raloxifene, ibandronate, and risedronate). There is, however, no proven difference in efficacy between the majority of treatments [5,69] and head to head comparisons of interventions with fracture outcomes are not available. For these reasons, the value of an incremental analysis between the individual treatments is questionable, since any resulting hierarchy of treatments is dependent largely on price, but otherwise meaningless in clinical terms. In addition, the large number of untreated patients makes 'no treatment' a relevant comparator. Notwithstanding, this study supports the view that alendronate can be considered as a first line intervention. The view arises, not because of apparent differences in efficacy between treatments, but because of cost. The cost-effectiveness of alendronate was much greater than that of etidronate, strontium, raloxifene, ibandronate and risedronate in sensitivity analysis. Nevertheless, cost-effective scenarios were found for treatments other than alendronate, providing credible alternative options for patients unable to take alendronate. There are differences, however, in the spectrum of proven efficacy of these alternatives across different fracture sites that will determine their suitability for in the clinical management of individuals. In contrast to the recommendation of NICE, our analysis indicates that raloxifene can be a cost-effective option for primary prevention as well as for secondary prevention of fractures. This provides consistency across prevention in women with and without prior fractures. The omission of raloxifene for primary prevention in the NICE appraisal ignores the strong evidence base for its significant extraskeletal benefit and unnecessarily restricts patient choice. It is perverse that side-effects are ignored by NICE for raloxifene, yet emphasised for alendronate.

Conclusion

Alendronate provides a cost-effective treatment for the prevention of fractures in postmenopausal women when targeted to women at high fracture risk. The use of clinical risk factors to aid in fracture risk assessment identifies new high risk populations that can be treated cost-effectively.

Acknowledgments and competing interests

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JAK, FB, CC, JEC, BJ and PS act as advisors to and have received funding from many pharmaceutical companies involved in marketing products for treatment of osteoporosis. JA, CC, JC, DP and PS are members of the NICE Osteoporosis Guideline Development Group (GDG).

JAK was asked by NICE to leave the GDG in 2006 for competing interests declared to NICE in 2002.

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