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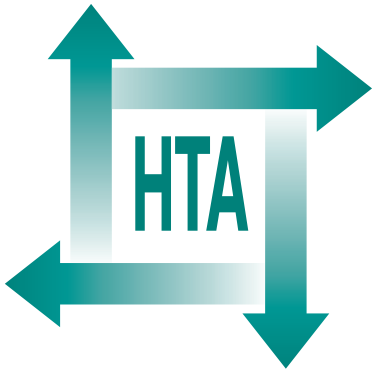

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Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis

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The research reported in this monograph was commissioned by the HTA Programme as project number 01/06/02. The contractual start date was in April 2002. The draft report began editorial review in November 2004 and was accepted for publication in May 2006. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis

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Objectives: To determine whether strategies can be devised for the assessment and treatment of glucocorticoid-induced osteoporosis (GIO).
Data sources: Electronic databases were searched up to October 2002.
Review methods: A systematic review of interventions was undertaken of all randomised controlled trials in which fracture was measured as an outcome. Effectiveness was compared with effectiveness in postmenopausal osteoporosis. The risk of osteoporotic fractures at any given *T*-score for bone mineral density (BMD) was determined from published meta-analyses of the relationship between BMD and fracture risk. The risk of an osteoporotic fracture in the presence of a prior osteoporotic fracture was computed from a published meta-analysis of the relationship between the prior occurrence of fracture of each type and the risk of a future fracture of each type. The additional risk due to exposure to glucocorticoids was determined by meta-analysis of prospectively studied population-based cohorts. The consequences of fracture on mortality were assessed for each fracture type. Costs and utilities were determined for osteoporosis in the UK by updating systematic reviews of the literature. A model was prepared that comprised an individual patient-based approach that simulated whether or not events occurred in each subsequent year for each patient. Effectiveness was populated from a systematic review of interventions in GIO and postmenopausal osteoporosis. Treatments were given for 5 years using a 5-year offset time (in this context, offset time is the duration for which an effect on fracture persists after the treatment stops). The analytic framework was set at 10 years. Because of the many uncertainties, extensive sensitivity analysis was undertaken.
Results: Evidence of anti-fracture efficacy was confined to a minority of agents used in the management of GIO. Only risedronate (a bisphosphonate) and calcidiol (vitamin D) were shown to have significant effects on vertebral fracture risk, but neither had significant effects on non-vertebral fracture risk. In further meta-analyses, the effects of bisphosphonates in GIO were compared with effects combining all available data for bisphosphonates in GIO and in postmenopausal osteoporosis. Since calcidiol is not licensed for use in the UK, cost-effectiveness analysis was confined to risedronate and to a pooled bisphosphonate effect. Analysis of cost-effectiveness of risedronate using the empirical data in GIO showed better cost-effectiveness with increasing age, but at no age did cost-effectiveness ratios fall below the threshold value of £30,000 per quality-adjusted life-year gained. When account was taken of BMD, cost-effectiveness was confined to less than 10% of patients with very low *T*-scores for BMD. Assuming that bisphosphonate efficacy on fracture risk was comparable to that observed with bisphosphonates in postmenopausal osteoporosis, cost-effectiveness was shown in patients with a prior fracture. In patients with no prior fracture, cost-effectiveness was observed in individuals aged 75 years or more. In younger patients without a prior fracture, cost-effective scenarios were found contingent upon a *T*-score for BMD that was 2.0 SD or less.
Conclusions: Cost-effective scenarios for risedronate in the management of GIO were identified, but only at the extremes of age and *T*-score, such that less than 10% of patients aged 50 years or more would be eligible for treatment. Greater cost-effectiveness was observed assuming that the effects of bisphosphonate in GIO were similar to those observed in postmenopausal osteoporosis, an assumption tested by meta-analysis. An assessment algorithm is proposed based on age, the presence of a prior fragility fracture and BMD tests in individuals aged 50 years or more with no fracture. The conclusions derived are conservative, mainly because of

the assumptions that were made in the absence of sufficient data. Thus, conclusions that treatment scenarios are cost-effective are reasonably secure. By contrast, scenarios shown not to be cost-effective are less secure. As information in these areas becomes available, the implications for cost-effectiveness of interventions should be reappraised. Health economic assessment based on probability of fracture is an important area for further research. Other areas for further research arise from gaps in empirical knowledge on utilities and side-effects that are amenable to primary research. Further secondary research is recommended to evaluate more closely the impact of all vertebral fractures (rather than clinically overt vertebral fractures) on cost-effectiveness and methods of monitoring treatment.

Contents

List of abbreviations

BMD	bone mineral density
BNF	British National Formulary
CaMos	Canadian Multicentre Osteoporosis Study
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
DOES	Dubbo Osteoporosis Epidemiology Study
DXA	dual energy X-ray absorptiometry
EPOS	European Prospective Osteoporosis Study
EQ-5D	EuroQol-5 instrument
EVOS	European Vertebral Osteoporosis Study
FDA	Food and Drug Administration
GI	gastrointestinal
GIO	glucocorticoid-induced osteoporosis
GPRD	General Practice Research Database
HCHS	Hospital and Community Health Services
HES	Hospital Episode Statistics
hPTH	human parathyroid hormone
HRT	hormone replacement therapy
HUI	Health Utility Index
LOS	length of stay
NICE	National Institute for Health and Clinical Excellence
NOF	National Osteoporosis Foundation (USA)
NSAID	non-steroidal anti-inflammatory drug
PTH	parathyroid hormone
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
SD	standard deviation
SERM	selective estrogen receptor modulator
SHEMO	Sheffield Health Economic Model for Osteoporosis
SLE	systemic lupus erythematosus
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background and aims

Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a subsequent increase in bone fragility and susceptibility to fracture. Aside from postmenopausal osteoporosis, the most common secondary cause of osteoporosis is that due to the long-term use of oral glucocorticoids.

The most serious clinical consequence of osteoporosis is hip fracture, which increases in incidence exponentially with age and incurs high morbidity, mortality and healthcare expenditure. Other common fractures occur at the spine, forearm and shoulder, but the osteoporotic skeleton is liable to fracture at many sites.

Glucocorticoids are widely used in medicine and long-term use is characterised by a significant increase in fracture risk. Approximately 250,000 men and women take long-term glucocorticoids in the UK, but few are treated for skeletal disease.

The mechanism for increased fracture risk is multifactorial and includes loss of bone tissue mass, disturbances in skeletal architecture, myopathy and the underlying disorders for which glucocorticoids are prescribed.

There are various agents available for the treatment of osteoporosis, and several are licensed for use in the prevention and treatment of glucocorticoid-induced osteoporosis (GIO). The evidence for their efficacy is examined and their cost-effectiveness is modelled in a case-finding strategy.

Methods

Therapeutic intervention

A systematic review was undertaken of all randomised controlled trials in which fracture was measured as an outcome. The interventions reviewed were bisphosphonates, vitamin D, 1α-hydroxylated derivatives of vitamin D, calcitonin, calcium, oestrogens, oestrogen-like agents, anabolic steroids, fluoride salts, thiazide diuretics, raloxifene, testosterone and parathyroid hormone. Effectiveness was compared with effectiveness in postmenopausal osteoporosis.

Epidemiology, costs and utilities

The annual risk of osteoporotic fracture was characterised for men and women from the UK. For the purpose of this report, fractures of the femur, pelvis, spine, distal forearm, tibia and fibula, clavicle, scapula and sternum and humerus were designated as being osteoporotic. The most common fractures (hip, spine, forearm and proximal humerus) account for approximately 70% of osteoporotic fractures and more than 70% of the morbidity.

The risk of osteoporotic fractures at any given *T*-score for bone mineral density (BMD) was determined from published meta-analyses of the relationship between BMD and fracture risk. The risk of an osteoporotic fracture in the presence of a prior osteoporotic fracture was computed from a published meta-analysis of the relationship between the prior occurrence of fracture of each type and the risk of a future fracture of each type. The additional risk due to exposure to glucocorticoids was determined by meta-analysis of prospectively studied population-based cohorts.

The consequences of fracture on mortality were assessed for each fracture type.

Costs and utilities were determined for osteoporosis in the UK by updating systematic reviews of the literature.

Health economics model

The model used comprised an individual patient-based approach that simulated whether or not events occurred in each subsequent year for each patient.

Transition states included fracture states (e.g. hip, wrist, vertebral and proximal humerus), death from hip fracture, nursing home admission due to hip fracture and death from other causes.

The model simulated cohorts at fixed ages (50–80 years at 5-year intervals) and fixed *T*-scores for BMD. The proportion of the population with

different fracture types was simulated from the known distribution of these fractures at different ages.

Effectiveness was populated from a systematic review of interventions in GIO and postmenopausal osteoporosis. Treatments were given for 5 years using a 5-year offset time (in this context, offset time is the duration for which an effect on fracture persists after the treatment stops). The analytic framework was set at 10 years. Because of the many uncertainties, extensive sensitivity analysis was undertaken.

Results

The results of the systematic review of RCTs indicated that the bisphosphonate risedronate and calcidiol reduced the incidence of vertebral fracture. The risk of non-vertebral fractures, including hip fracture, was not significantly decreased.

For several agents, failure to demonstrate efficacy, particularly for hip fracture, was largely due to the lack of appropriate RCTs. When data were pooled, the combined effects of all bisphosphonates on vertebral and non-vertebral fracture incidence were comparable to that observed in postmenopausal osteoporosis.

Previous glucocorticoid use was associated with a significantly increased risk of any osteoporotic fracture and hip fracture when adjusted for BMD. For osteoporotic fracture, the range of relative risk with age was 2.63–1.71 and for hip fracture 4.42–2.48 (i.e. decreasing with age). No significant difference in risk was seen between men and women. The risk was independent of prior fracture. In the three cohorts that documented current glucocorticoid use, BMD was significantly reduced at the femoral neck, but fracture risk was still only partly explained by BMD.

Analysis of cost-effectiveness was undertaken for risedronate using the empirical data in glucocorticoid-induced osteoporosis. Further analysis of bisphosphonate used data on efficacy that assumed that their effects were comparable to those shown for bisphosphonates in postmenopausal osteoporosis. The results at each age were presented as a central estimate of cost per quality-adjusted life-year (QALY) gained compared with no treatment. Costs were discounted at 6% and QALYs at 1.5% in base-case scenarios. The estimate was bounded by a 95% confidence interval representing the range of cost–utility that was incurred by 95% of the combinations of relative risks for efficacy.

When risedronate was assumed to have efficacy on vertebral fracture alone, without effects on appendicular fractures, cost-effectiveness ratios fell with age, but at no age did treatment become cost-effective at the average *T*-score for women at each age. When account was taken of BMD, cost-effectiveness was confined to less than 10% of individuals with very low *T*-scores.

Further analysis with bisphosphonate showed cost-effective scenarios in patients with a prior fracture. In patients without a prior fracture, cost-effectiveness was observed in the elderly (aged 75 years or more) and in others with low *T*-scores for BMD.

In sensitivity analysis, important determinants of cost-effectiveness included age and cost of intervention. Cost-effectiveness ratios were sensitive to changes in discount rates for benefits and changes in the assumption concerning offset of effect (offset time). Cost-effectiveness improved markedly by selecting patients according to BMD.

The results were not markedly affected by the threshold used for cost-effectiveness, poor compliance, varying the assumptions about mortality after hip fracture or differences in discount rates. The inclusion of costs of added years of life (direct costs only) had little effect. By contrast, the inclusion of all vertebral fractures (in addition to clinically overt fractures) had a marked effect on improving cost-effectiveness, as did the avoidance of BMD and associated medical supervision. Cost-effectiveness was also sensitive to offset time, duration of treatment and the time horizon used.

Several patient assessment algorithms were tested. The current guidance of the Bone and Tooth Society was unsatisfactory, since the age threshold at which treatment was recommended (age 65 years or more) did not provide cost-effective intervention. Moreover, the use of a *T*-score threshold of –1.5 standard deviation (SD) in patients without a prior fracture was cost-ineffective.

The following strategy was considered appropriate in patients receiving long-term glucocorticoids. Patients with a prior fragility fracture would be eligible for treatment, as would individuals aged 75 years or more, irrespective of BMD. At other ages, patients without prior fractures would be

eligible for treatment contingent upon a BMD threshold, with a *T*-score of –2.0 SD or less.

The strategy would demand BMD testing in 73.4% of patients and render 47% eligible for treatment.

In patients taking higher than average doses of glucocorticoids, less stringent *T*-score cut-offs may be appropriate because of the higher fracture risks using the higher doses of glucocorticoids.

Conclusions

Cost-effective scenarios for risedronate in the management of GIO were identified, but only at the extremes of age and *T*-score, such that less than 10% of the population of patients aged 50 years or more would be eligible for treatment.

Greater cost-effectiveness was observed assuming that the effects of bisphosphonate in GIO were similar to those observed in postmenopausal osteoporosis, an assumption tested by meta-analysis.

An assessment algorithm is proposed based on age, the presence of a prior fragility fracture and BMD tests in individuals aged 50 years or more with no fracture.

The conclusions we derive are conservative, mainly because of the assumptions that were made in the absence of sufficient data. The conservative assumptions include:

1. Not all vertebral fractures are included.
2. The risk of re-fracture in the few years after a fracture is likely to be underestimated. It should be noted, however, that, if short-term risks are underestimated, then long-term fracture risks will be overestimated.
3. Long-term effects of osteoporotic fractures on utilities are ignored.
4. The costs of BMD tests and medical supervision are included for all patients.
5. Only average doses of glucocorticoids are modelled, but the risk of fractures is increased in a dose-dependent manner.
6. A relatively short time horizon (10 years).

Thus, conclusions that treatment scenarios are cost-effective are reasonably secure. By contrast, for the reasons outlined above, scenarios shown not to be cost-effective are less secure. As information in these areas becomes available, the implications for cost-effectiveness of interventions should be reappraised. In the meantime, account needs to be taken of these factors in applying these analyses to practice guidance.

Recommendations for research

Intervention thresholds differ substantially from diagnostic thresholds, and should be based on the absolute fracture probability that depends not only on the *T*-score but also on other independent risk factors. Health economic assessment based on probability of fracture is an important area for further research.

Other areas for further research arise from gaps in our empirical knowledge on utilities and side-effects which are amenable to primary research. We also recommend that further secondary research be undertaken to evaluate more closely the impact of all vertebral fractures (rather than clinically overt vertebral fractures) on cost-effectiveness and methods of monitoring treatment.

Chapter 1
Introduction

The internationally agreed definition of osteoporosis is.[1]

> "A systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture."

The clinical consequences of osteoporosis are the fractures that arise. Common sites include vertebral compression fractures, fractures of the distal radius and the proximal femur and fractures of the proximal humerus. Osteoporotic fractures occurring at the spine, forearm and humerus are associated with significant morbidity, but the most serious consequences arise in patients following hip fracture, which is associated with a significant increase in mortality, particularly in the elderly.

At the age of 50 years, the remaining lifetime probability of hip fracture in the UK has been estimated as 4.8% in men and 14.0% in women.[2] The probability of fracture varies according to age and bone mineral density (BMD). Although osteoporosis is defined in terms of BMD, age captures an aspect of risk over and above that provided by BMD. For the same BMD there is a greater than two-fold difference in fracture probability between the ages of 50 and 80 years (*Table 1*).[3] Other known risk factors such as prior fracture and family history contribute to fracture risk independently of BMD, but do not eliminate the important effect of age.

The major cause of osteoporosis is that arising in women after the menopause, so-called postmenopausal osteoporosis. Fracture rates, however, also increase with age in men, although the incidence of osteoporotic fracture is approximately half of that found in women. Over and above the osteoporosis associated with ageing, there are several additional secondary causes of osteoporosis, of which the most important is glucocorticoid-induced osteoporosis (GIO).[4–6]

The exogenous use of glucocorticoids and adrenocorticotrophin has been recognised as a risk factor for osteoporosis and fractures since the 1940s. Many prospective and epidemiological studies have shown that glucocorticoids decrease bone mass and thereby increase the risk of fractures, particularly fractures of the ribs, spine and forearm. Fractures have occurred in 30–50% of hospital series, usually with high doses of glucocorticoids.[7–9] The first population-based study of limb fractures was by Hooyman and colleagues,[10] who reported that the risks of hip, distal forearm and proximal humeral fractures were approximately doubled in a group of patients with rheumatoid arthritis exposed to glucocorticoids when compared with patients with

TABLE 1 *10-year probability of fracture (at hip, forearm, spine or hip) according to age and sex in the average population from Sweden, at the threshold of osteoporosis (T-score = –2.5 SD) and the population with osteoporosis (T-score = <–2.5 SD)*[3]

Age (years)	Average		At threshold of osteoporosis		*T*-score <–2.5 SD	
	M	F	M	F	M	F
50	3.3	6.0	7.7	11.3	9.2	13.9
55	3.9	7.8	8.6	13.4	10.4	16.8
60	4.9	10.6	9.5	16.2	11.6	20.5
65	5.9	14.3	10.4	19.3	13.0	24.9
70	7.6	18.9	13.1	22.8	16.2	29.8
75	10.4	22.9	17.5	24.5	21.5	32.6
80	13.1	26.5	18.7	25.6	23.2	34.4
85	13.1	27.0	16.7	23.8	21.4	33.1

Reproduced from Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. *Osteoporos Int* 2001;**12**;989–95, *Tables 1–3*.

TABLE 2 *Relative risk of fracture at the sites shown amongst patients taking glucocorticosteroids*[14]

	GPRD		Meta-analysis	
Outcome	**RR**	**95% CI**	**RR**	**95% CI**
Any fracture	1.33	1.29 to 1.38	1.91	1.68 to 2.15
Hip fracture	1.61	1.47 to 1.76	2.01	1.74 to 2.29
Vertebral fracture	2.60	2.31 to 2.92	2.86	2.56 to 3.16
Forearm fracture	1.09	1.01 to 1.17	1.13	0.66 to 1.59

Reproduced from van Staa TP, Leufkens HGM, Cooper C. *Osteoporos Int* 2002;**13**:777–87, *Table 1*, p. 778.

rheumatoid arthritis alone. A subsequent British case–control study confirmed that the use of glucocorticoids approximately doubled the risk of hip fracture.[11] In a general practice setting, approximately 20% of patients on long-term treatment with glucocorticoids had previously sustained a fragility fracture.[12]

The most detailed analysis in the UK of the relationship between glucocorticoid use and fracture risk was a retrospective cohort study comparing 244,235 oral glucocorticoid users and an equal number of age- and sex-matched controls.[13] The relative risk (RR) of any non-vertebral fracture was 1.33 [95% confidence interval (CI) 1.29 to 1.38], that of a hip fracture was 1.61 (95% CI 1.47 to 1.76), that of a forearm fracture was 1.09 (95% CI 1.01 to 1.17) and that of a vertebral fracture was 2.60 (95% CI 2.31 to 2.92). These estimates of fracture risk are comparable to those determined by meta-analysis of studies reporting fracture outcomes in individuals taking 5 mg or more of prednisolone[14] (*Table 2*). Comparable figures are derived from the USA.[15]

Fracture risk is particularly high following transplantation, and risk ratios of 5–40 have been reported depending on age, sex and type of transplant.[16–18] Increases in fracture risk are also found in children, particularly those taking high doses of steroids. A site particularly vulnerable to fracture was the humerus. In children taking four or more courses of oral glucocorticoids, the risk was doubled (odds ratio 2.17; 95% CI 1.01 to 4.67). It is not clear how far this is directly related to the use of glucocorticoids or to the underlying disease.[19]

Use of glucocorticoids

GIO is the leading cause of secondary osteoporosis because of the widespread use of these agents in medicine. Several studies have described the use of glucocorticoids in the UK.[6,13,20–22] A recent study using the General Practice Research Database (GPRD) identified 1.6 million oral glucocorticoid prescriptions over a 10-year period.[13] The prevalence of oral glucocorticoid use was similar between men and women and was 0.9% of the total adult population, but increased with age. The prevalence of current utilisation was 0.2% at the age of 20–29 years, rising to 2.5% between the ages of 70 and 79 years. Of the three dose categories studied, the intermediate dose (2.5–7.5 mg prednisolone or equivalent daily) was the most frequently used (0.4% of the adult population). The prevalence of a higher dose therapy (more than 7.5 mg daily) was 0.3% and that of lower dose treatment (<2.5 mg daily) was 0.1%. These estimates accord with those found in the Trent Region of the UK.[22] In this study of eight large general practices with a catchment population of nearly 66,000 individuals, current continuous use of glucocorticoids was defined as individuals taking glucocorticoids for at least 3 months. This was documented in 0.5% of the population, and in 1.4% of the population aged 55 years or more. In a meta-analysis of 42,000 men and women drawn from prospective population-based adult cohorts from around the world, the prevalence of ever-use of long-term glucocorticoids was 3% at the age of 30 years and rose almost linearly with age to 5.2% at the age of 80 years (*Table 3*).[23]

Pattern of use

The most frequent indication for the use of oral glucocorticoids in general practice is respiratory disease, followed by musculo-skeletal and cutaneous diseases.[13] Although most patients received glucocorticoids for a short period, treatment for longer than 6 months was observed in 22% of patients and treatment for more than 5 years in 4.3%. The utilisation pattern is similar

TABLE 3 *Prevalence of ever use of oral glucocorticosteroids (%) in men and women*[23]

Age (years)	Men and women	Men	Women
30	3.0	1.8	3.5
40	3.3	2.1	3.9
50	3.7	2.6	4.3
60	4.1	3.0	4.7
70	4.6	3.5	5.1
80	5.2	4.2	5.6
90	5.8	4.9	6.2

Reproduced from Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Melton LJ III, *et al*. *J Bone Miner Res* 2004;**19**:893–9.

between men and women but differs by age. Elderly patients take oral glucocorticoids for longer than younger patients. Glucocorticoid therapy taken for over 2 years was documented in approximately 20% of men and women aged 70 years or more, compared with 2.5% of men and women aged less than 30 years. With respect to the long-term use of glucocorticoids, the most common underlying disorder was rheumatoid arthritis (23%), followed by polymyalgia rheumatica (22%) and asthma or chronic obstructive pulmonary disease (19%). The mean dose of prednisolone was 8 mg daily with a median duration of 3 years. Some 7.3% of patients had received oral glucocorticoids for over 10 years and 2.6% for over 20 years.[22]

Size of the problem

These epidemiological data from the GPRD suggest that the current population taking glucocorticoids in the UK might be as large as 350,000 individuals.[13] In this particular study, 58% of patients had more than one prescription, suggesting that long-term use occurred in 0.5% of the adult population, giving an estimate of 240,000 individuals at risk of developing glucocorticoid-induced fractures. If the figures from Walsh and colleagues[22] are representative of the UK, they suggest that 250,000 men and women are taking long-term glucocorticoids. By contrast, the use of bone active medication is extremely low amongst users of oral glucocorticoids.[13,24] In the study from the GPRD,[13] approximately 5% received hormone replacement therapy and 1.8% had received bisphosphonates during the period of follow-up. In the survey of Walsh and colleagues,[22] only 14% of patients taking oral glucocorticoids had received any drug treatment in the past 4 years for osteoporosis – a figure not markedly different from that in the general population. These data suggest that most glucocorticoid-treated individuals have not been treated for skeletal disease, although uptake of treatment is markedly affected by the availability and access to testing for BMD.[12]

Dose dependency

It has been difficult to demonstrate clear dose–response effects because of the heterogeneity of skeletal response to glucocorticoids and the small samples studied. The most extensive data available to date, undertaken within the general practice research framework, indicate dose responsivity in that the risks of a fracture are higher, the higher is the dose of glucocorticoids. With a standardised daily dose of prednisolone of <2.5 mg, hip fracture risk was 0.99 (95% CI 0.82–1.20), rising to 2.27 (95% CI 1.94–2.66) at doses of 7.5 mg or greater. Dose responses were also observed for vertebral fracture[20] (*Table 4*). These findings indicate that doses hitherto regarded as of little importance to osteoporosis carry a substantial risk. The guidelines for osteoporosis produced by the Royal College of Physicians[25] gave a daily dose of 7.5 mg or more of prednisolone as the threshold at which one should

TABLE 4 *Relative risk of fracture (95% CI) in patients according to daily dose of glucocorticosteroids*[20]

	Daily dose of prednisolone or equivalent		
	Low (<2.5 mg)	Intermediate (2.5–7.5 mg)	High (>7.5 mg)
Any non-vertebral fracture	1.17 (1.10 to 1.25)	1.36 (1.28 to 1.43)	1.64 (1.54 to 1.76)
Forearm	1.10 (0.96 to 1.25)	1.04 (0.93 to 1.17)	1.19 (1.02 to 1.39)
Hip	0.99 (0.82 to 1.20)	1.77 (1.55 to 2.02)	2.27 (1.94 to 2.66)
Spine	1.55 (1.20 to 2.01)	2.59 (2.16 to 3.10)	5.18 (4.25 to 6.31)

Reproduced from van Staa T, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. *J Bone Miner Res* 2000;**15**:993–1000, *Table 3*, p. 996.

be concerned about fracture risk, whereas more recent studies clearly indicate a substantial risk in individuals taking between 2.5 and 7.5 mg daily, a risk that was significantly higher than individuals taking a low dose (2.5 mg daily or less) for non-vertebral fracture, hip fracture or vertebral fracture.[20] This has resulted in more recent guidelines recommending that the threshold dose should be less than 7.5 mg daily or that there should be no threshold dose.[5] It is notable that a minority of individuals taking glucocorticoids are on doses of 2.5 mg daily or less (21%).[20]

Within the general practice framework, risk was clearly related to dose, but less securely related to duration of exposure. In a recent meta-analysis and a large study from the USA, both dose and duration of exposure were found to be important determinants of risk.[14,15]

Inhaled glucocorticoids have been demonstrated to have effects on skeletal markers of bone metabolism and on BMD,[26–30] but the effects have been variable and the significance for fracture risk uncertain. In the GPRD, the risk of fracture in individuals taking inhaled glucocorticoids, but not taking systemic glucocorticoids, was increased. The RR of non-vertebral fracture was 1.15 (95% CI 1.10 to 1.20), for hip fracture 1.22 (95% CI 1.04 to 1.43) and for spine fracture 1.51 (95% CI 1.22 to 1.85). Although the risk was increased, the risk was similarly increased in patients taking bronchodilators without the use of glucocorticoids.[31,32] Such data support the view that the major risk of fractures lies in patients given oral or intravenous glucocorticoids.

The susceptibility to bone loss may not be the same for all disorders for which glucocorticoids are used. Some studies have shown that younger patients are most at risk.[33] Patients with end-stage chronic renal failure appear to be relatively resistant to high doses of glucocorticoids,[9] whereas transplant receipts are highly susceptible, perhaps in part due to other prescribed indications that adversely affect skeletal metabolism. Within each disease category, genetic variants of the enzyme 11β-hydroxysteroid dehydrogenase may modulate responsiveness to glucocorticoids and thus the risk of osteoporosis.[34,35]

Pathogenesis

The manner in which glucocorticoids induce bone loss is complex and incompletely understood[9,36,37] (*Figure 1*), in part because there are no suitable animal models. A major effect on the skeleton is a decrease in bone formation and unchanged or enhanced bone resorption.[38] Glucocorticoids are thought to affect directly the differentiation, activity and lifespan of osteoblasts and osteocytes.[39–41] They inhibit expression of genes important for bone formation including collagen A1, transforming growth factor β, fibronectin and insulin-like growth factor-1.[42]

The reason for increased bone resorption is unclear, but might include immobilisation, intestinal malabsorption of calcium and gonadal hormone deficiency. The mechanism for measured bone resorption has not been fully established, but includes increased production of receptor activator of NFkB ligand (RANKL) in association with reduced production of osteoprotegerin (OPG), resulting in increased osteoclast recruitment and osteoclast survival.[41] Histomorphometric analysis of biopsies from glucocorticoid-treated individuals has shown a reduction in bone formation at the cellular and tissue level, resulting in reduced bone volume and trabecular thickness[43–45] and a decrease in the number of viable osteocytes.[46] The decrease in bone formation is greater than that noted in postmenopausal osteoporosis. There is some evidence that glucocorticoids cause thinning of trabecular elements, in contrast to postmenopausal osteoporosis, where loss of trabeculae is more characteristic.[47] Higher doses of glucocorticoids are also associated with an increase in bone turnover and resorption, leading to greater bone loss and disruption of cancellous bone architecture.[34,48,49]

Glucocorticoids also affect many other target tissues that in turn may have an impact on skeletal metabolism. These include reduced intestinal calcium absorption and increased renal excretion.[50–52] Low serum testosterone levels have also been reported in glucocorticoid-treated men, and are believed to be due to direct effects on testosterone production and indirect effects mediated via the suppression of gonadotrophin hormone secretion.[53,54]

Despite the complex pathophysiology, the ultimate effect on bone is similar in many respects to postmenopausal osteoporosis. There is an imbalance between the amount of bone resorbed and that formed during each bone remodelling sequence and, in patients who are relatively immobilised, bone turnover is also increased. The evidence for a causal association between glucocorticoid use and increased bone turnover is, however, not complete[9] and may be

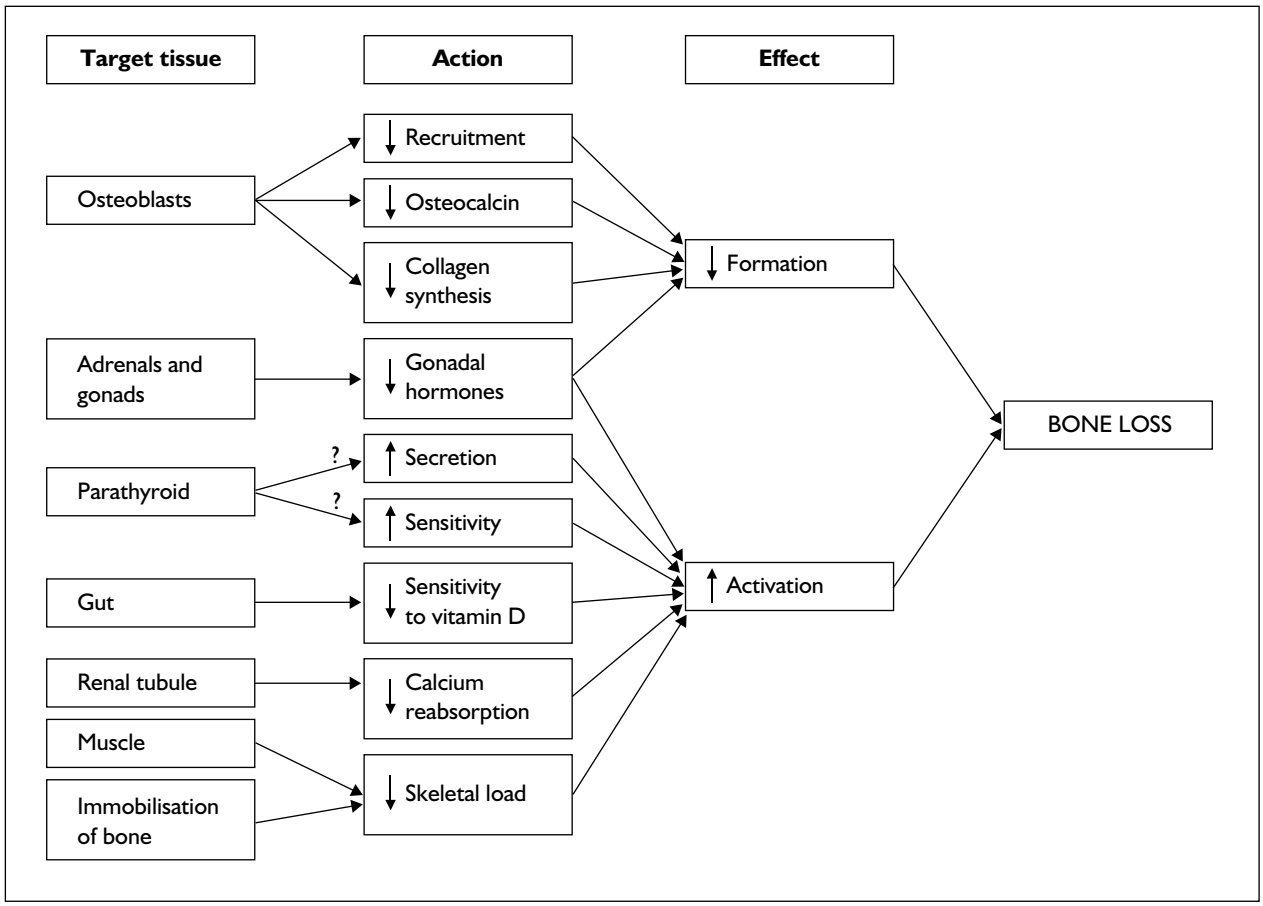

FIGURE 1 *Scheme to illustrate some effects of excess glucocorticoids on skeletal metabolism. Effects on target tissues induce loss of bone by decreasing bone formation or by increasing the activation frequency with which bone is remodelled (an increase in bone turnover). Reproduced from Kanis JA.* Textbook of osteoporosis, *Oxford: Blackwell Science; 1996, Figure 5.7, p. 162.*

due to immobilisation rather than a direct effect of steroids.

As is the case with postmenopausal osteoporosis, many studies have documented the losses of bone following glucocorticoid use at all sites accessible to measurements.[14,55] In a meta-analysis of 66 studies with BMD estimates in 2891 patients, bone loss at the spine and the hip was 11% greater than that expected for age and sex and 12% greater at the forearm.[14] Several investigators have suggested that bone loss may occur preferentially at axial rather than appendicular sites.[56–60] This may only reflect the proportion of cancellous bone at the site of measurement and the duration of follow-up, since losses at these sites of cancellous bone are expected to be greater in the short-term than losses at cortical sites. This view is consistent with observations that long-term exposure decreases bone mass at all sites but, as expected with most forms of osteoporosis, vertebral fractures occur sooner in the course of the diseases than hip fractures.[61] Glucocorticoid therapy results in rapid loss of BMD, which is greatest in the first year of therapy and may be as high as 30% in the first 6 months.[62,63] There is some evidence that these effects are partially reversible on the cessation of glucocorticoid therapy.[20,58]

In addition, the disorders for which glucocorticoids are given are associated with their own co-morbidity and consequent immobilisation, both of which may increase the risk of osteoporosis and fracture.[10] In the present analysis (see Chapter 4), individuals with rheumatoid arthritis had an increased risk of fracture when adjusted for use of glucocorticoids and BMD.

The risk of fracture following use of glucocorticoids may not be related only to loss of bone tissue and the underlying disorder for which they are prescribed. It is of interest that the risk appears to increase rapidly on exposure to glucocorticoids and to wane rapidly when treatment is stopped.[14,20] Risks, however, remain increased after stopping treatment.[64] Such rapid changes in risk are

unlikely to be related to changes in BMD, but suggest the importance of other non-skeletal factors, possibly related to the underlying disorder or, more likely, to other effects of glucocorticoids.

Treatment and treatment thresholds

A wide variety of pharmacological interventions has been shown to decrease bone loss in GIO.[5,65,66] Until recently, effects on fracture risk have not been well studied. Treatments proposed include bisphosphonates, hormone replacement therapy (HRT), vitamin D (cholecalciferol or calciferol) and calcium, calcitriol, calcidiol, alfacalcidol, calcitonin, fluoride, testosterone and anabolic steroids. Current practice guidelines recommend that preventive measures should be started when BMD reaches a critical threshold at the hip or lumbar spine. Recommended intervention thresholds include a BMD that lies 1 standard deviation (SD) below the value for young healthy women,[67] 1.5 SD,[5,65] 1.7 SD or 2.5 SD below the value for young healthy women.[25,68–71] The choice for these different thresholds is arbitrary. Also, the clinical significance of different *T*-scores (the BMD in SDs below the average value in the young healthy female population) differs according to age.[72] Indeed, there is an approximately 3-fold range in hip fracture risk that is accounted for by changes in BMD with age in postmenopausal women, whereas there is a 10-fold range in hip fracture risk amongst postmenopausal women with age after adjustment for BMD.

The reason for the different thresholds that have been used is the notion that fractures occur at a higher BMD than in age-related or postmenopausal osteoporosis,[73,74] although this has not been a universal observation.[75] It has been noted[5] that fracture rates in the placebo group of randomised studies are higher in the case of glucocorticoid-treated patients despite a higher BMD.[76–79] Definitive evidence for a difference in the relationship between BMD and fracture risk is best derived from prospectively studied cohorts drawn randomly from the general population. A meta-analysis of prospectively studied cohorts is contained within the body of this report (see Chapter 4).

Against this background, there is a need to rationalise strategies for the assessment and treatment of GIO. There is also a need for management strategies to be placed in an appropriate health economic perspective. The majority of economic studies in osteoporosis have been focused on the menopause and the use of HRT, and until recently few studies were focused on other treatment modalities in postmenopausal osteoporosis.[80–90] Limited analyses are available for the use of non-HRT interventions,[80,89–95] some of which are placed in a UK setting. No analyses are available for strategies in GIO. Since there are now many agents available for the treatment of the disorder, clear guidelines are required to provide a rational basis for their use in the community.

The specific aims of this report were to determine whether strategies can be devised for the assessment and treatment of GIO.

Chapter 2

Therapeutic intervention in glucocorticoid-induced osteoporosis

In approaching a systematic review of trials of efficacy for application to health economic models, there are two strategies. The first is to review randomised controlled trials (RCTs) that examine fracture risk. This has the advantage of incorporating outcomes of clinical significance. The major disadvantage is that there is a relative paucity of trials that examine fracture as the primary outcome compared with studies on BMD. This is partly because regulatory authorities world-wide accept studies of BMD as criteria for efficacy for prevention of osteoporosis.[96–98] Moreover, registrations in GIO have been granted following registration for postmenopausal osteoporosis on the basis that treatment-induced changes in the two disorders are comparable. The problem is compounded because, even in postmenopausal osteoporosis, there is little information on the effect of interventions on non-vertebral fracture. The argument runs that, since osteoporosis is a systemic disease and treatments induce systemic effects, an agent that decreases vertebral fracture risk will do so also at other sites vulnerable to osteoporosis.

The second option is, therefore, to review studies of prevention of bone loss and to infer anti-fracture efficacy from the known relationship between BMD and fracture. This is an approach used in early pharmacoeconomic evaluations.[88,99] Although the relationship between BMD and fracture risk is well established in untreated cohorts, the relationship between a change in BMD and change in fracture risk is less secure.[97,100,101] Indeed, recent RCT data indicate that treatment-induced changes in BMD may underestimate anti-fracture efficacy, i.e. the decrease in fracture rate is greater than that which can be explained on the basis of the measurement of BMD alone.[97,102]

The approach that we have taken is the more direct but more limited approach, namely to examine and model fracture outcomes based on RCT evidence from a systematic review of the literature. Because of the few trials that report fracture as a primary outcome, we also included studies where fracture is reported as a secondary outcome or safety measure.

In view of the paucity of information on fracture outcomes, it is important to recognise that a lack of demonstrated anti-fracture efficacy is not evidence of lack of efficacy, only that the appropriate studies have not been conducted. In this context, efficacy may be inferred indirectly from RCTs that examine treatment-induced changes in BMD, albeit with a lower level of evidence. The effects of interventions in GIO on BMD have recently been systematically reviewed.[5] Whereas our primary focus is on studies of fracture outcome, we also include, where appropriate, information on treatment-induced changes in BMD in this systematic review.

Methodology

A systematic review was undertaken to compare the effectiveness of pharmacological interventions in preventing osteoporotic fractures in patients exposed to long-term use of oral glucocorticoids. Details of the methodology are given in Appendix 1.

The emphasis of the review is on pharmacological interventions. Most fractures arise following a fall and a potential intervention strategy would be the prevention of falls or mitigating the impact of falls with the use of hip protectors. No data are available for such strategies in GIO, and the experience in postmenopausal osteoporosis is disappointing. A meta-analysis of seven trials which included an exercise intervention study in the elderly indicated a 10% reduction in fall frequency.[103] No study to date, however, has shown a significant reduction in fracture rate.[104] A component of the beneficial effects of vitamin D may be mediated by a decrease in falls and, in a recent meta-analysis, the use of vitamin D decreased the risk of falls by 22% (95% CI 8 to 36%) compared with patients taking placebo or calcium alone.[105] The minimisation of skeletal trauma following falls has been inconsistently achieved by the use of hip protectors[106,107] and adequate compliance with these devices has been a problem.[108]

Inclusion criteria

We included studies in which patients had been treated with glucocorticoids irrespective of BMD at the start of the study. Studies were included which reported any of the following types of intervention:

- bisphosphonates
- vitamin D with and without calcium
- derivatives of vitamin D (including calcidiol and calcitriol)
- calcitonin
- pharmacological doses of calcium
- oestrogens (opposed and unopposed)
- oestrogen-like molecules
- anabolic steroids
- fluoride salts
- thiazide diuretics
- selective estrogen receptor modulators (SERMs)
- testosterone
- parathyroid hormone.

Only RCTs were included. Trials were accepted as RCTs if the authors described the allocation of subjects to treatment groups as either randomised or double-blind. All studies were included which reported on vertebral or non-vertebral fracture.

Exclusion criteria

No studies were excluded on the basis of language.

Published studies were included with a cut-off date of October 2002 (including those only available as abstracts). As unpublished studies are more likely than published studies to demonstrate small or absent treatment effects, it is recognised that this approach is likely to overestimate the true effects of treatment. It was not possible, however, to seek out unpublished studies in the time available.

Literature search

Searches were undertaken of the electronic databases listed in Appendices 2 and 3. Each database was searched as far back as possible. No language restrictions were used. Update searches were carried out on MEDLINE, EMBASE and the Cochrane Library in October 2002.

A combination of free-text and thesaurus terms were used. General 'population' search terms (e.g. osteoporosis, bone density, diseases, fracture) were used to identify all potentially relevant studies. 'Intervention' terms were not used in the main searches since it was felt that these might restrict the results and cause possibly relevant articles to be missed. The strategy developed by the Cochrane Collaboration to identify RCTs was used to limit the searches to RCTs.

The search strategies for MEDLINE are listed in Appendix 4. Search strategies from other databases are available from the authors.

The reference lists of relevant studies identified through the electronic searches were checked. Citation searches on the same references were carried out using the Science Citation Index. Reference lists of published reviews were also checked.

In principle, the references identified by the literature searches were sifted in two stages, being screened for relevance first by title and then by abstract. However, as it was not possible to identify all relevant studies with fracture outcomes from titles alone, the title sifting stage was used essentially to reject studies which were clearly irrelevant. Following this, the abstracts of all studies which used the relevant interventions in the relevant populations were screened (for studies which did not provide abstracts, the full studies were screened).

Search results

Electronic searching yielded 12,375 potentially relevant articles, 48 of which related to 44 trials that fulfilled the inclusion criteria for this review. An additional relevant trial was identified from a citation. Details of the sifting process and yields are given in Appendices 1 and 5. A total of 45 individual RCTs met the review inclusion criteria and are listed in Appendix 7, followed by a list of studies that were excluded, and reasons for this (Appendix 8). Data from included studies were extracted by a single reviewer, using a predefined data extraction form.

Studies which met the entry criteria were eligible for inclusion in the meta-analyses, provided that they reported fracture incidence as the number of patients sustaining fractures. Studies which reported only numbers of fractures or fracture rates (i.e. numbers of fractures per hundred or thousand patient years) were not included in the meta-analyses unless it was possible to obtain from the authors unpublished information on the numbers of subjects who sustained fractures. Their inclusion would have violated the basic statistical assumption that the occurrence of one event does not increase the likelihood of a subsequent event[109] since, once a subject has suffered an osteoporotic fracture, the risk of a subsequent fracture increases.[110–112] In practice, the bias may be small since the number of individuals sustaining multiple vertebral fractures is small.

Since the end-point of interest was fracture, it seemed appropriate (Meunier[113]) to include open-label studies. Especially in relation to the identification of radiographic vertebral fractures, the most commonly used fracture end-point, it is more important that the outcome assessor be blinded to treatment allocation than that the patient or healthcare provider be so blinded.

Meta-analysis was carried out using Review Manager.[114]

Quality assessment

A quality assessment was undertaken of all trials which met the inclusion criteria using the tool developed by Gillespie and colleagues.[115] This tool was selected because it was intended specifically for the assessment of randomised or quasi-randomised trials of interventions designed to prevent fractures associated with osteoporosis. Details are provided in Appendix 6.

Definitions of the various levels of randomisation and concealment of randomisation derived from Prendiville and colleagues[116] were incorporated in the tool (see Appendix 6).

Evidence from clinical trials

Each of the eligible studies is summarised in Appendix 9. A summary of the studies together is given in Appendix 1. The therapeutic agents included the bisphosphonates, etidronate, alendronate and risedronate, all of which are licensed for use in GIO in the UK. In addition, fluoride salts, thiazide diuretics, raloxifene, parathyroid hormone, vitamin D and derivatives, calcitonin, calcium, oestrogen, testosterone and the anabolic steroids that are used in postmenopausal osteoporosis or in specialist centres were included.

Studies that compared an active intervention with placebo or no treatment are discussed first, by intervention. This is followed by a discussion of those studies that compared two or more active interventions. However, evidence relating to side-effects and continuance from the studies which compared active interventions are given in Appendix 1.

In addition, other studies that did not report fracture outcomes are reviewed briefly since, as mentioned, the approval of agents in GIO has been largely on the basis of changes in BMD rather than on fracture outcomes. Where appropriate, key studies are given that document changes in BMD, drawn from a recent systematic review.[5]

Alendronate

The only study which met the inclusion criteria[64] reported the pooled results of a US and a multinational RCT of near-identical design which compared various doses of oral alendronate with placebo. A total of 447 men and women, either newly exposed to glucocorticoids (34%) or established on glucocorticoids for more than 4 months (66%), were studied initially over a 48-week period. The mean BMD of the lumbar spine increased by 2.1 and 2.95% in the groups that received 5 or 10 mg of alendronate, respectively, and decreased by 0.4% in the placebo group.

Fracture data relating to the 83 patients who were randomly allocated to 2.5 mg of alendronate were not reported, and only pooled data were presented from the 5- and 10-mg groups. Using the US Food and Drug Administration (FDA) criteria for an incident vertebral fracture (a decrease of >20% and >4 mm between baseline and follow-up in anterior, middle or posterior vertebral body height), the estimate of relative risk at 48 weeks was 0.6 (95% CI 0.19 to 1.94). Marginal significance ($p = 0.05$) was reported with the semi-quantitative method for analysing incident vertebral fractures, when analysis was confined only to postmenopausal women in the study.[64] Such an analysis is inappropriate since randomisation was not stratified by gender and menopausal status.

A subsequent 12-month follow-up of 208 subjects at selected centres showed continued effectiveness in the second year, at least in terms of BMD. In this study extension, patients originally allocated to 2.5 mg of alendronate were switched blindly to 10 mg daily.[117] The study reported a significant decrease in the risk of vertebral fracture at 24 months (RR 0.1; 95% CI 0.01 to 0.90), but this cannot be accepted uncritically. Only 208 of the original 560 subjects took part in the extension study, so that the original randomisation was weakened. In particular, patients who had suffered incident vertebral fractures during the original treatment period were disproportionately under-represented in the extension study. Although the analysis of 2 years was said to be by intention-to-treat, overall, the 2-year data were only represented in relation to those patients who completed the 12-month follow-up (45% of the pooled alendronate group and 37% of the placebo

group). We have therefore taken the estimate at 1 year as the most appropriate estimate of efficacy.

With respect to non-vertebral fractures, the incidence at 48 weeks was said to be identical at 4.4% in both placebo and combined alendronate groups, although the exact numbers and sites of fracture in the two groups were not given.

Side-effects and continuance are described in Appendix 1. Continuance in the study ranged between 84 and 87%, but is of the order of 70% on post-market surveillance.[118–121]

Clodronate

There have been several RCTs that have examined the effects of clodronate in glucocorticoid-treated individuals.[122–124] Only one study has reported fracture outcomes in an RCT in patients who had undergone renal transplantation.[124] A dose of 800 mg daily was compared with 200 IU daily of intranasal calcitonin and with no treatment. Both clodronate and calcitonin were taken cyclically with 14 days of treatment followed by 75 treatment-free days.

No incident vertebral fractures were reported in any group, and two non-vertebral fractures occurred, one in the calcitonin arm and the other in the placebo arm (clodronate versus calcitonin; RR 0.35; 95% CI 0.02 to 8.80; clodronate versus placebo; RR 0.33; 95% CI 0.01 to 7.58). No patient discontinued treatment. Compliance was not reported.

A study published after the cut-off date showed a reduction in the incidence of vertebral fracture (RR 0.25; 95% CI 0.15 to 0.91) in patients treated with intramuscular clodronate, 100 mg weekly.[125]

Etidronate

The cyclical use of etidronate on BMD has been examined in a large number of studies. The regimen of etidronate for 2 weeks in each 3 months was initially shown to be effective in a small single-blind primary prevention study in 20 elderly women with giant cell arteritis. A significant increase in lumbar spine BMD (mean 1.4%) was seen over 12 months in women randomised to receive etidronate, whereas in untreated controls lumbar spine BMD fell by 4.9%.[126] Similar small randomised open-label[127,128] or double-blind[129,130] primary prevention studies, principally in patients with rheumatic diseases, showed essentially similar results. Significant treatment benefits on BMD at the spine and/or hip were also shown in patients established on glucocorticoid therapy.[130–134] Further studies have shown treatment-induced effects at the lumbar spine, but not at the proximal femur.[135,136]

Two studies of cyclical etidronate therapy in patients undergoing organ transplantation showed significant decreases in BMD at the spine and proximal femur.[137,138] In patients receiving long-term glucocorticoid therapy for transplantation, a significant treatment effect on lumbar spine has been reported, but no effect on the proximal femur.[139,140]

The systematic review identified 12 RCTs with reported fracture outcomes. Three of these compared etidronate with active treatments (calcidiol, calcitonin, calcitriol and alphacalcidol).[137,138,141] The remainder compared etidronate with placebo[128–130,132,133,135,139,140,142] or no treatment.[128,132,142]

As reported, the quality of these studies was variable and only one study provided evidence of adequately masked randomisation,[139] and only three stated that the fracture outcome assessors were blinded to study allocation.[128,133,140] In one study, 'randomisation' was undertaken by alternate allocation.[137]

All the comparisons with active treatment were carried out in transplant recipients. None of the studies were adequately powered for fracture end-points and in none of the studies were significant effects on vertebral or non-vertebral fracture observed (for details see *Table 67*, Appendix 1).

Ten studies provided information relating to the incidence of vertebral fracture in comparison with placebo or untreated control groups. All but one study[140] yielded point estimates which favoured etidronate, but none were statistically significant. When data were pooled for meta-analysis from studies in which etidronate treatment was started within 100 days of the use of high-dose glucocorticoids (i.e. prevention studies), the estimate of RR was 0.59 (95% CI 0.27 to 1.32) (*Figure 2*). In studies where patients had received glucocorticoids for at least 3 months, the estimate of RR was 0.48 (95% CI 0.14 to 1.64). When a study in which normal BMD was an inclusion criterion[140] was removed, the RR was 0.32 (95% CI 0.06 to 1.64). When data from both prevention and treatment studies were pooled, the effect was computed at an RR of 0.55 (95% CI 0.28 to 1.08).

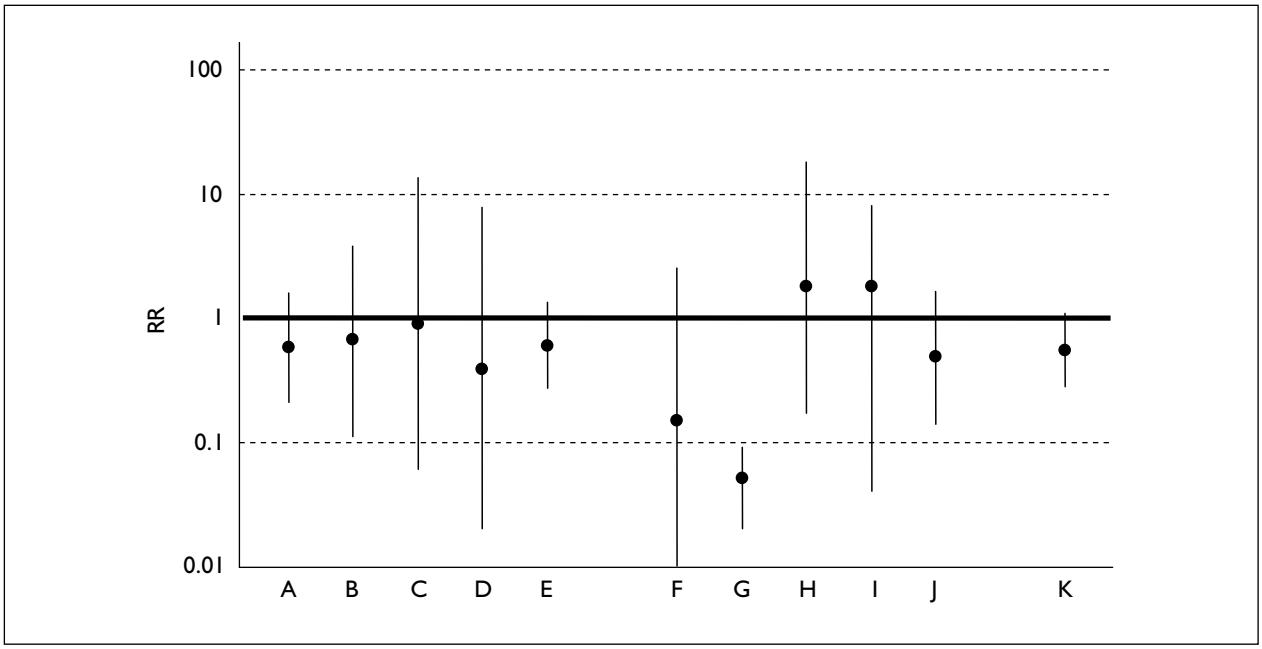

FIGURE 2 *Meta-analysis of the effects of etidronate on vertebral fracture risk (RR ± 95% CI). A, B, C and D are studies of prevention[129,130,133,135] and are combined in E. F, G, H and I are studies of treatment[132,139,140,142] summarised in J. K combines studies of prevention and treatment.*

Three studies reported non-vertebral fractures.[129,135,139] Pooling the data from the two assessable studies gave an RR of 0.38 (95% CI 0.10 to 1.38).

Ibandronate

Only one relevant RCT was identified,[143] which compared bolus injections of ibandronate with no treatment in men and women who were transplant recipients. In this study of 72 patients, two vertebral fractures and two non-vertebral fractures occurred with equal numbers in both wings of the study.

Pamidronate

A variety of studies have examined the effects of the bisphosphonate pamidronate on BMD. The doses used were not standardised. Significant treatment benefits on metacarpal cortical area and vertebral BMD were reported by Reid and colleagues[144] with oral pamidronate 150 mg daily. Using intermittent intravenous administration of pamidronate (90 mg followed by 30 mg at 3-monthly intervals), significant benefits over the control group were shown in BMD at the lumbar spine and the hip.[145] In a similar study over 1 year, the benefits of pamidronate were similar with a single infusion of 90 mg compared with the same dose followed by 30 mg at 3-monthly intervals.[146] In a three-way study of cyclical etidronate, pamidronate 30 mg given at 3-monthly intervals and calcitonin, significant increases were observed with etidronate and calcitonin.[147]

Similarly, in patients undergoing organ transplantation, significant effects of pamidronate have also been reported on BMD. Bianda and colleagues[148] showed significant attenuation of bone loss at 1 year in heart transplant recipients, but the benefit was no longer apparent after 18 months of treatment. In a study of patients with cystic fibrosis undergoing lung transplantation, 30 mg of pamidronate intravenously at 3-monthly intervals resulted in large gains in spine and femoral BMD after 2 years.[149] Fan and colleagues[150] showed preservation of bone mass at the spine and hip in those treated with intravenous pamidronate 0.5 mg/kg at the time of renal transplantation and 1 month later, whereas the control group showed significant bone loss at both sites.

With respect to fracture outcomes, four relevant RCTs were identified by the systematic review.[146,148,149,151] One[148] compared pamidronate with calcitriol plus intranasal calcitonin in patients who had undergone cardiac transplantation. Another[151] studied the effects of pretransplant infusion of pamidronate on patients undergoing liver transplant. A third[149] compared 3-monthly intravenous infusions of pamidronate with no treatment in patients with cystic fibrosis who had received lung transplants 1–12 months previously. The fourth study[146] compared an initial intravenous infusion of pamidronate with or without subsequent 3-monthly infusions, with no

treatment in patients at the time of starting high doses of prednisolone.

All four studies appeared to be open label and none provided evidence of appropriately concealed randomisation. One study[148] 'randomised' by alternate allocation and another[146] used a method of allocation which would make fully blinded randomisation impossible. Only one study[151] stated that fracture assessors were blinded to treatment allocation.

In the study comparing pamidronate with calcitriol plus intranasal calcitonin,[148] one vertebral fracture occurred in the comparator wing and none in the pamidronate wing (RR 0.2; 95% CI 0.01 to 6.50). No non-vertebral fractures occurred.

In the three studies which compared pamidronate with no treatment, vertebral fractures did not occur in one study.[146] In the remaining two studies, more fractures occurred in the pamidronate wing, but there was no statistical difference between pamidronate and no treatment. The studies were not pooled because of the differences in patient groups and treatment regimens.

With respect to non-vertebral fractures, none occurred in the study of Boutsen and colleagues.[146] In the study of Aris and colleagues,[149] three of 16 patients sustained fractures in the pamidronate wing and six of 18 sustained fractures in the control wing (RR 0.56; 95% CI 0.17 to 1.89). In the study by Ninkovic and colleagues,[151] one fracture was reported amongst 37 pamidronate-treated patients, whereas in controls one non-vertebral fracture occurred in 43 patients (RR 1.16; 95% CI 0.08 to 17.94).

Risedronate

Three RCTs were identified which compared risedronate with placebo.[152–154] All trials reported outcomes that included BMD and fracture.

In an RCT in which patients receiving long-term glucocorticoids for rheumatoid arthritis were randomised to treatment with 2.5 mg risedronate daily, 15 mg cyclical risedronate (daily for 2 weeks every 12 weeks) or placebo for nearly 2 years, BMD was maintained at the lumbar spine (mean +1.4%) and trochanter (mean +0.4%) in the 2.5-mg daily risedronate group, whereas significant bone loss occurred in the placebo group at the lumbar spine (–1.6%) and trochanter (–4.0%).[152] At the femoral neck, there was a non-significant bone loss in the 2.5-mg daily risedronate group (mean –1.0%), whereas in the placebo group, bone mass decreased significantly (mean –3.6%). The difference between placebo and 2.5-mg daily risedronate group was significant in the lumbar spine and trochanter only. No significant treatment benefit was demonstrated in the group treated with cyclical risedronate. Vertebral fractures were reported in three of 33 placebo-treated patients, two of 30 patients receiving cyclical risedronate and seven of 31 patients receiving risedronate daily. The RR of daily risedronate versus placebo was 2.48 (95% CI 0.70 to 8.76) and that of cyclical risedronate versus placebo was 0.73 (95% CI 0.13 to 4.09).

Two separate RCTs have been reported in which 2.5 and 5 mg of risedronate daily were compared with placebo for a 12-month period.[153,154] The lumbar spine BMD fell significantly (mean –2.8%) in the placebo group, and losses were prevented with both doses of risedronate. In the study of primary prevention[153] significant differences were seen between risedronate 5 mg daily and placebo at the lumbar spine (mean +3.8%), femoral neck (mean +4.1%) and femoral trochanter (mean +4.6%). Similar benefits were seen in the secondary prevention study in patients who had been taking glucocorticoids for more than 6 months at baseline.[154] BMD increased significantly at the lumbar spine (+2.9%), femoral neck (+1.8%), and femoral trochanter (+2.4%) in the 5-mg risedronate group. These changes were significant when compared with the placebo group, where BMD did not change at these sites.

In the primary prevention study,[153] both active treatment wings showed a reduction in vertebral fracture risk (RR 0.64 for the 2.5-mg dose and 0.33 for the 5-mg dose), but in no instance was this significant. Comparable results were observed in the secondary prevention study[154] in that the RR was decreased (0.33 for each of the active treatment wings compared with placebo), but this reduction was not statistically significant. In a published *post hoc* analysis in which both these studies were combined, there was a significant reduction in vertebral fracture rates in the 5-mg treatment group (5.4%) compared with the placebo group (16.2%).[78]

In the present meta-analysis, the pooled effect of a 2.5-mg dose[152–154] on vertebral fracture was not statistically significant (RR 0.81; 95% CI 0.26 to 2.55). Pooling of the 5-mg dose showed a significant decrease in vertebral fracture risk (RR 0.33; 95% CI 0.14 to 0.80). When outcomes in men were compared with those in women, there was no apparent difference in the point estimate,

although in neither instance was the 5-mg dose effect significant (Appendix 1). When the 2.5- and 5-mg daily doses were pooled in men, a significant effect on vertebral fracture frequency was observed (RR 0.22, 95% CI 0.06 to 0.76).[155]

Two studies[153,154] reported the number of patients sustaining non-vertebral fractures. The pooled estimate of the two studies showed no effect of the 2.5-mg dose (RR 1.13; 95% CI 0.49 to 2.61) or of the 5-mg dose (RR 1.07; 95% CI 0.46 to 2.47).

Raloxifene

No studies were identified.

Parathyroid hormone

One RCT was identified which compared the effects of parathyroid hormone peptide 1–34 (teriparatide) in 51 postmenopausal women with chronic inflammatory diseases treated with oestrogen and glucocorticoids.[156–158] Women already on HRT were randomised to treatment with teriparatide 400 IU daily subcutaneously or to no treatment. Significant increases in spine BMD were seen at 12 months (mean 11%) compared with the control group. No significant benefit was seen for BMD at the hip. The treatment benefit on BMD was sustained for 1 year when treatment with teriparatide was stopped and patients received HRT alone.[158]

One of 18 patients sustained fractures in the control group, whereas none occurred in 26 patients in the teriparatide group. The decrease in vertebral fracture risk (0.23) was not significant (95% CI 0.01 to 5.45). Also, there was no significant effect on non-vertebral fracture risk (RR 0.82; 95% CI 0.13 to 5.39).

Calcium

There have been several studies of the effects of calcium supplementation on bone mass with variable results. An early study showed a reduction in bone loss from the metacarpals with the use of microcrystalline hydroxyapatite compound.[159] Other studies have shown no effect of treatment with daily doses of 1200 mg of calcium or greater on BMD.[160,161] One study reported fracture outcomes, but has been excluded since it was not fully randomised.[161]

Vitamin D

Several studies have examined the effects of parent vitamin D on BMD in patients on long-term glucocorticoid therapy for various medical conditions in combination with calcium supplements. No effect on BMD was reported with the use of 4000 IU of vitamin D on alternate days at the lumbar spine or femoral neck[162] and no effect of 50,000 IU of vitamin D given weekly at the lumbar spine.[163] Similarly, no effect of 250 IU of vitamin D_3 daily was reported in a small study of 17 patients assessing BMD at the lumbar spine at 12 months.[164] A single study reported that treatment with 1 g of calcium and 500 IU of vitamin D daily was associated with a significant reduction in bone loss from the lumbar spine in 66 patients on long-term glucocorticoid therapy for rheumatoid arthritis.[165]

One RCT[166] was identified by the systematic review which studied the use of vitamin D for the treatment of glucocorticoid-induced osteoporosis and reported fracture data. This was a comparator trial with alfacalcidol. There was no significant difference between vertebral and non-vertebral fracture rates between the two wings (RR 1.74 and 1.43, respectively, in favour of alfacalcidol). A further RCT[163] compared vitamin D 50,000 IU weekly plus calcium with placebo. No significant effect on vertebral fracture risk was found (RR 0.62; 95% CI 0.16 to 2.37). No non-vertebral fractures were reported.

Alfacalcidol

There is a wealth of data concerning the effects of alfacalcidol on BMD, but data on fracture outcomes are scarce and confined to five studies identified in the systematic review.

In a study of 145 men and women recently started on glucocorticoids for various medical disorders, a 1-year treatment with alfacalcidol 1 μg daily significantly prevented bone loss at the lumbar spine.[167] In another trial, in 41 women recently started on glucocorticoids, alfacalcidol 0.25–1 μg daily prevented bone loss from the lumbar spine, hip and radius over a 3-year interval.[168] Clinical fractures (sites unspecified) occurred in one of 21 patients given alfacalcidol and two of 20 patients given calcium (RR 0.48; 95% CI 0.05 to 4.85).

In a study of established glucocorticoid-induced osteoporosis in 85 patients, alfacalcidol 1 μg daily was compared with vitamin D 1000 IU daily for 3 years.[166] There was a significant increase in lumbar spine BMD with alfacalcidol (mean +2.0%), but no significant change in femoral neck BMD. No change at either site was seen with vitamin D and calcium. Fewer vertebral and non-vertebral fractures were observed in the alfacalcidol group (RR 0.57 and 0.70, respectively), but in neither instance was this statistically significant.

In a study of 212 transplant recipients and 42 patients with rheumatoid arthritis on glucocorticoid treatment with alfacalcidol 0.5–1 μg daily had a beneficial effect over 2 years on bone loss from the lumbar spine.[169] In a further study of premenopausal women receiving glucocorticoids for collagen disorders, the addition of trichlormethazide to alfacalcidol prevented the development of hypercalciuria observed in women treated with alfacalcidol alone and was also associated with a significant increase in metacarpal index at 24 months.[170] In this study, three vertebral fractures occurred in 14 patients treated with alfacalcidol and none of 11 patients receiving the combination (RR 5.60; 95% CI 0.32 to 98.21). In a further study that compared alfacalcidol with etidronate,[137] three symptomatic vertebral fractures were observed in 19 patients given etidronate, whereas none were reported in 22 patients given alfacalcidol (RR 0.12; 95% CI 0.01 to 2.26).

Of the five RCT's which reported fracture outcomes, only one study[170] compared alfacalcidol with no treatment. Three of 14 patients treated with alfacalcidol sustained a fracture and two of 13 patients in the control group (RR 1.39; 95% CI 0.28 to 7.05). No non-vertebral fractures were reported.

Calcitriol

In a study of 23 patients on glucocorticoids for rheumatoid arthritis, no effect of calcitriol (0.25–1 μg daily) on forearm BMD was observed.[171] One study compared calcitriol, with or without calcitonin, in 103 men and women who had recently started glucocorticoid therapy for a variety of medical conditions.[172] This study found that calcitriol 0.5–1 μg daily significantly decreased bone loss from the lumbar spine over 12 months, but had no effect on bone loss from the hip. Calcitriol, either alone or in combination with calcitonin, did not have a statistically significant effect on vertebral fracture risk relative to placebo (RR 0.43; 95% CI 0.04 to 4.47; and RR 1.00; 95% CI 0.15 to 6.63, respectively). One non-vertebral fracture occurred in the group given calcitriol alone and one in the control group (RR 0.85; 95% CI 0.06 to 13.04).

In a study of 65 patients undergoing cardiac or lung transplantation, calcitriol 0.5–0.75 μg together with calcium daily significantly reduced bone loss from the proximal femur compared with treatment with calcium alone.[173] By contrast, in a similar group of patients only partial protection was observed with calcitriol 0.5 μg daily,[138] but etidronate was used as a comparator. No patient given calcitriol developed clinical vertebral fractures, whereas three occurred in the comparator wing (RR 0.14; 95% CI 0.01 to 2.48). More non-vertebral fractures occurred in the calcitriol treated wing (RR 4.77; 95% CI 0.24 to 93.68). In a study of 101 patients on long-term glucocorticoids after cardiac transplantation, no effect of calcitriol 0.25 μg daily was observed on bone loss from the lumbar spine.[174] In the first year, no fractures occurred in 47 placebo-treated patients and two occurred in 54 calcitriol–treated patients (RR 4.36; 95% CI 0.21 to 88.67).

In a study of 56 premenopausal women on glucocorticoids for systemic lupus erythematosis, there was a significant increase (mean +2.1%) in lumbar spine BMD with calcitriol 0.5 μg and calcium 1200 mg daily compared with placebo, but no significant effects were noted on forearm or hip BMD.[160] In a 2-year randomised open study, BMD at the lumbar spine and femoral neck decreased by 1 and 0.7%, respectively, in glucocorticoid-treated patients receiving calcitriol 0.25 μg twice daily, whereas those treated with cyclical etidronate and vitamin D showed corresponding mean changes of +1.1 and +0.6%.[175]

Overall, five RCTs were identified by the systematic review which compared calcitriol with another intervention and reported fracture outcomes (see *Table 87*, Appendix 1). No significant difference was observed between interventions. With regard to comparisons with placebo or no treatment, three studies were identified that reported fracture outcomes.[172–174,176] In none of the studies was there a significant reduction in vertebral fracture frequency. The information was not pooled due to the heterogeneity of studies and their low quality and inadequate reporting. However, it seemed appropriate to pool data for the first and second years of the two studies by Stempfle and colleagues[174,176] which yielded RR in year 1 of 1.73 (95% CI 0.23 to 12.89) and in year 2 of 0.87 (95% CI 0.06 to 13.54).

Four studies reported non-vertebral fractures, none of which yielded statistically significant results.

Calcidiol

Several studies have suggested that 25-hydroxyvitamin D (calcidiol) is effective in preventing glucocorticoid induced bone loss. In a 12-month study of patients given 35 μg calcidiol daily, bone loss at the distal radius was prevented in patients recently started on glucocorticoids for polymyalgia rheumatica.[177] In a further study,[178] 40 μg of calcidiol and 3 g of calcium daily were

compared with placebo in 77 patients starting glucocorticoids at the time of renal transplantation. Over the 12-month study, bone loss observed in untreated patients in the spine and hip was prevented by calcidiol and calcium. Inquiry to the author indicated that 19 of 41 patients given calcidiol sustained a vertebral fracture whereas 30 of 36 patients in the placebo wing developed vertebral fractures (RR 0.56; 95% CI 0.39 to 0.80).

Calcidiol has also been compared with calcitonin and with etidronate.[141] Fewer fractures occurred in the calcidiol group compared with calcitonin (RR 0.11; 95% CI 0.01 to 1.88) and with etidronate (RR 0.15; 95% CI 0.01 to 2.71).

Calcitonin

Studies of the effects of intranasal subcutaneous calcitonin on glucocorticoid induced bone loss have produced conflicting results. Five studies performed in patients undergoing organ transplantation failed to show a significant treatment benefit on BMD.[124,141,161,179] In a further study,[180] liver transplant recipients treated with calcitonin or cyclical etidronate showed a significant increase in lumbar spine BMD after 1 year of treatment (6.4 and 8.2%, respectively), but there was no control group.

In several studies performed in other patient groups, a significant treatment benefit has been demonstrated in lumbar spine BMD compared with controls,[73,181,182] but no effect on spinal BMD was demonstrated in three other studies,[147,183–185] although in one study[185] a significant gain in proximal femoral BMD was demonstrated. In two of the studies in which significant effects on spinal BMD were demonstrated compared with placebo, bone loss was not completely prevented by calcitonin.[181,185]

With regard to fracture outcomes, an active comparator study[141] showed no advantage on vertebral fracture risk compared with either calcidiol or etidronate. In those studies where calcitonin was compared with placebo or controls, the effects of intervention were variable and five studies presented data suitable for meta-analysis (see Appendix 1). Pooling of the data from the evaluable studies which compared calcitonin with either placebo or no treatment did not produce a statistically significant result (RR 0.59; 95% CI 0.2 to 1.73).

Five studies reported non-vertebral fractures, although none produced a statistically significant result.[179,182,184,186,187] In two of these studies no fractures were reported in either group. A pooled estimate of the remaining three studies showed no significant effect (RR 0.99; 95% CI 0.23 to 4.21).

Hormone replacement therapy

There have been few studies of the use of HRT in glucocorticoid-induced osteoporosis. A randomised trial[188] examined the effects of transdermal oestradiol with norethisterone compared with calcium in a group of postmenopausal women with rheumatoid arthritis. Forty-two women were treated with glucocorticoids and in this group the mean increase in lumbar and femoral BMD was 3.75 and 1.62%, respectively, compared with increases of 0.85 and 1.12% in the calcium-treated patients. The difference between groups was significant at the spine at 24 months. In a further randomised study,[189] the effects of tibolone 2.5 mg daily were studied in 37 postmenopausal women with rheumatoid arthritis. After 24 months of treatment, significant increases were observed in spine BMD (4%) and at the total hip (4.2%). No fracture outcomes were reported in either of these studies.

In a further study,[190] 28 young hypogonadal women with systemic lupus erythematosis treated with long-term glucocorticoid therapy were randomised to receive HRT or calcitriol. After 2 years of treatment, lumbar BMD increased by 2.0% in the HRT group and decreased by 1.74% in the calcitriol group, which was significant. A significant treatment benefit was also observed for the total radius, but no difference in BMD was noted at the femoral neck. No fractures occurred throughout the study. The effects of HRT and calcitriol have been compared in a group of women with glucocorticoid-induced osteoporosis,[191] with an increase in BMD assessed by quantitative computed tomography at an unspecified site. Treatment-induced changes were greater in women receiving HRT, but the difference was not significant.

Fluoride

The effects of sodium fluoride on glucocorticoid-induced bone loss have been investigated in a number of randomised trials in patients requiring glucocorticoids for various indications.[192-198] In most of these studies sodium fluoride was given alone, but in two studies it was used in combination with cyclical etidronate[196] or calcidiol.[194] Marked increases in spine BMD were noted, but no significant effects were demonstrated at the femoral neck or forearm.

Five RCTs were identified in the systematic review which studied fluoride in patients receiving glucocorticoid therapy and which reported

TABLE 5 *Summary of estimates of efficacy obtained from the systematic review*

	Vertebral fracture		Non-vertebral fracture	
Agent	**RR**	**95% CI**	**RR**	**95% CI**
Bisphosphonates				
Alendronate	0.60	0.19 to 1.94[b]	1.00	–[b]
Clodronate	–		0.33	0.01 to 7.58[a]
Etidronate	0.57	0.27 to 1.21	0.26	0.03 to 2.14
Ibandronate	1.00	0.07 to 15.38[a]	1.00	0.07 to 15.38[a]
Pamidronate	3.38	0.39 to 29.29[a]	0.56	0.17 to 1.89[a]
Risedronate	0.33	0.14 to 0.80	1.97	0.15 to 2.47
Vitamin D and derivatives				
Vitamin D + calcium	0.62	0.16 to 2.37	–	
Calcidiol	0.56	0.39 to 0.80[a]		
Alfacalcidol	1.39	0.28 to 7.09	–	
Calcitriol	0.43	0.04 to 4.47[b,c]	0.85	0.06 to 13.04
Other				
Calcitonin	0.59	0.20 to 1.73	0.99	0.23 to 4.21
PTH	0.23	0.01 to 5.45	0.82	0.13 to 5.39
Fluoride	4.37	0.23 to 83.63	4.17	0.50 to 34.61[b]
Thiazides	0.23	0.01 to 4.40		

[a] In transplant recipients.
[b] Estimate at 1 year.
[c] RR 4.37 (0.23–12.89) in transplant recipients.

fracture outcomes.[195-199] Three of these studies compared fluoride with placebo or no treatment, none of which reported adequately masked randomisation or stated that the assessors of fracture outcome were blinded to treatment allocation. In only one of these studies[195] was vertebral fracture risk assessable (RR 4.37; 95% CI 0.23 to 83.63). Of those studies reporting non-vertebral fracture risk, analysis was possible in only one study.[196] This showed an increase in risk in fluoride-treated patients at year 1 and at year 2 (RR 4.17 and 1.04, respectively).

Thiazide diuretics

Only one RCT[170] reported fracture outcomes in a study of alfacalcidol with or without the thiazide diuretic trichloromethazide. No fractures occurred in the group treated with thiazides together with alfacalcidol compared with alfacalcidol, whereas two fractures occurred in 13 individuals untreated and three in 14 individuals given alfacalcidol alone. These differences were not significant.

Anabolic steroids

No RCTs were identified that reported a fracture outcome.

Conclusions

A summary of the therapeutic agents where assessment of RR was possible is summarised in *Table 5*. With one exception, no single study demonstrated a significant effect of treatment on vertebral fracture outcomes. The exception was calcidiol when given to renal transplant recipients. The pooled estimate additionally indicated that with risedronate at a dose of 5 mg daily in patients receiving glucocorticoid therapy for reasons other than organ transplantation a significant treatment-induced effect was observed. An effect of etidronate on vertebral fractures was of borderline significance. No intervention was shown to decrease the risk of non-vertebral fractures significantly.

Chapter 3

Synthesis of data and modelling strategy

In the previous chapter, the evidence for the efficacy of a wide range of interventions was reviewed, based on the literature available for RCTs. The quality of the search strategies used with the electronic databases was such that few trials were identified by other means, such as by handsearching or from reference lists. It therefore seems likely that few published studies have been missed. No trials were excluded because of language restrictions for agents that are available in the UK.

Quality of evidence

As published, most of the trials had potential methodological weaknesses.

Efficacy of intervention

As noted above, there was some heterogeneity between studies in terms of study populations, the underlying disorders, interventions and capture of primary end-points, including the definition of incident vertebral fracture. There were insufficient data to test formally for heterogeneity.

Bone mineral density

Most studies on GIO have examined the effects of interventions on BMD, the majority of which are reviewed in this report.[5] Grades of recommendation in the prevention of glucocorticoid-induced bone loss, based on conventional levels of evidence (*Table 6*) are shown in *Table 7*. The gradings refer solely to the level of evidence of efficiency, regardless of effect size. Agents that have shown evidence of efficacy in postmenopausal osteoporosis appear to have effects similar to those described in GIO.

As is the case for antifracture efficacy, the most robust data come from the bisphosphonates. A meta-analysis of RCTs examined the effects of bisphosphonates as the percentage change in BMD in the treatment group minus the percentage change in the placebo group. The combined effects were weighted for trial size using a random effects model.[200] At 1 year, the difference in lumbar BMD was 4.3% (95% CI 2.7 to 5.9%) with a more modest effect at the femoral neck (effect size 2.1%; 95% CI 0.01 to 4.3).

Vertebral fracture

The data reviewed above suggest that the bisphosphonate risedronate and calcidiol reduce the risk of vertebral fracture in patients with GIO. There was no evidence that vitamin D derivatives, oestrogen, oestrogen-like molecules, anabolic steroids or other agents reviewed reduced this risk. A study published after our cut-off date also showed that the bisphosphonate clodronate reduced the incidence of vertebral fracture (RR 0.25; 95% CI 0.15 to 0.91).[125]

TABLE 6 *Guideline strength: levels of evidence and grades of recommendation*[5]

Level of evidence	Type of evidence	Grade of recommendation
Ia	Meta-analysis of RCTs	A
Ib	At least one RCT	A
IIa	At least one well-designed, controlled study without randomisation	B
IIb	At least one well-designed quasi-experimental study	B
III	At least one well-designed, non-experimental descriptive study (e.g. comparative studies, correlation studies, case studies)	B
IV	From expert committee reports/opinions and/or clinical experience of authorities	C

Reproduced from Bone and Tooth Society. Guidelines Writing Group. *Glucocorticoid-induced osteoporosis. Guidelines for prevention and treatment*. London: Royal College of Physicians; 2002, *Table 3*, p. 20.

TABLE 7 *Effect of interventions on the prevention/reduction of glucocorticoid-induced bone loss and vertebral fracture: grade of recommendations*[5]

Intervention	Spine BMD	Proximal femur BMD	Vertebral fracture
Alendronate	A	A	A[a]
Alfacalcidol	A	A[b]	NAE
Calcitonin	A[b]	A[b]	NAE
Calcitriol	A[b]	A[b]	NAE
Calcium	ND	ND	NAE
Calcium + vitamin D	A[b]	A	NAE
Clodronate	A	A	NAE[c]
Cyclic etidronate	A	A	A[a]
Fluoride	A	ND	NAE
HRT (including tibolone)	A	A	NAE
Pamidronate	A	A	NAE
PTH	A	A	NAE
Raloxifene	No data	No data	No data
Risedronate	A	A	A[a]
Testosterone	A	NAE	NAE

NAE, not adequately assessed; ND, not detected.
[a] Not a primary end-point.
[b] Data inconsistent.
[c] Subsequently shown to reduce fracture risk.[125]
Reproduced from Bone and Tooth Society. Guidelines Writing Group. *Glucocorticoid-induced osteoporosis. Guidelines for prevention and treatment*. London: Royal College of Physicians; 2002, *Table 4*, p. 20.

It was not possible to determine whether efficacy differed in patients with or without prevalent vertebral fractures at trial entry. This is an important issue since differences would have implications for the assumptions used for health economics modelling. Information is available for bisphosphonates, fluoride and SERMs in post-menopausal osteoporosis.[80] For none of these treatments was there a significant difference when patients were stratified according to the presence or absence of prevalent vertebral fractures.

A further heterogeneity of potential importance is the criterion used to define incident vertebral fractures. It is well recognised that the less stringent criteria increase the apparent incidence of vertebral fracture – but at the expense of a high false-positive rate. For example, if in biological reality 10 fractures occurred in the placebo arm and five in the treatment arm, this would give an RR reduction of 50%. If the same trial was contaminated with false-positives (for example, three in each arm), the apparent efficacy would fall to 38%. In this review, the criteria used to define vertebral fracture varied between studies. In some, a minimum reduction of 15% in vertebral height was required, in some 20% and in others the definition used was not specified. It has been demonstrated that the use of a 20–25% definition rather than a lower figure such as 15% will increase the statistical power of a study by reducing the number of false-positives. In a previous review, it was shown that studies which used a 20% definition produced results more favourable to the intervention than those which used a 15% definition.[80] It was not possible in the present review to examine efficacy according to such criteria, due to the paucity of the available information.

Non-vertebral fracture

No intervention was demonstrated by the meta-analyses reported above to reduce the risk of non-vertebral fracture. No agent appeared to confer protection against hip fracture.

Side-effects

The various interventions reviewed here varied in their associated effects, both adverse and, in some cases, beneficial. They are reviewed in Appendix 1. The adverse effects most commonly found in association with the different interventions are set out in *Table 8*. It is important to recognise that a systematic review of side-effects has not been undertaken and only those studies eligible for the meta-analysis have been reviewed. Some of the interventions studied also have associated effects that are beneficial. For example, calcitonin and

TABLE 8 *Adverse effects most commonly reported in the reviewed studies*

Intervention	Adverse effect
Alendronate	Upper gastrointestinal complaints
Clodronate	Lower gastrointestinal complaints
Etidronate	Mild upper gastrointestinal complaints
Ibandronate	Bone pain, flatulence
Pamidronate	Acute phase reaction, occular side-effects
Risedronate	Upper gastrointestinal symptoms
Parathyroid hormone	Headache
Vitamin D	None
Calcium plus vitamin D	Hypercalciuria
Vitamin D derivatives	Hypercalciuria; hypercalcaemia
Calcitonin	Hot flushes, gastrointestinal complaints and minor local nasal disorders (intranasal)
Calcium	Gastrointestinal symptoms
Fluoride	Lower extremity pain, bone lesions and incomplete fractures; osteomalacia; gastrointestinal complaints

nandrolone have been associated with reductions in the intensity of osteoporotic pain and with improved mobility. In one study, fluoride also appeared to be associated with a significant reduction in back pain.[80] Although the bisphosphonates may reduce bone pain in the context of neoplastic bone disease,[201] there is no evidence that they improve quality of life in osteoporosis above that due to the prevention of fractures.

Continuance

For each intervention there was considerable variation between studies in terms of the number of patients treated with the active intervention and those who completed the protocol. This information is given in Appendix 1 and summarised for each intervention in *Table 9*. Compliance, in terms of the number of individuals who continued to take the medication and the proportion of medication which they had taken, was reported specifically in few studies. Hence the information provided is too heterogeneous to summarise further, other than to note that continuance appears to be particularly low because of attrition due to deaths and patients stopping treatment with glucocorticoids. Nevertheless, it is to be expected that continuance and compliance with medication would be higher in the context of an RCT than in real life. For example, in studies of postmenopausal osteoporosis, 80–90% of women taking bisphosphonates complete the various trials, whereas studies of post-marketing surveillance in postmenopausal osteoporosis have reported considerably lower compliance in patients of the order of 70% after 1 year.[118–121]

TABLE 9 *Continuance (percentage of patients completing protocol) as reported by the studies reviewed*

Intervention	Continuance (%)
Alendronate	57–87
Clodronate	97
Etidronate	38–100
Ibandronate	90
Pamidronate	Not assessable
Risedronate	75–78
Parathyroid hormone	80–90
Vitamin D	>80
Calcium plus vitamin D	37
Vitamin D derivatives	58–90
Calcitonin	>80
Calcium	71
Oestrogen	Not assessable
Oestrogen-like molecules	Not assessable
Fluoride	73–92
Thiazides	No information

Discussion

Evidence of efficacy has been identified in this review for few of the interventions studied: risedronate and calcidiol for vertebral fracture and none for non-vertebral fracture. However, failure to demonstrate the efficacy of the remaining interventions may reflect the small size and short duration, and also the inappropriate reporting of fracture outcomes of the studies that were suitable for meta-analysis. A further reason for failure to demonstrate efficacy may include the heterogeneity of patient groups in their underlying disease, dose and duration of exposure to glucocorticoids and the timing of intervention for bone disease.

A principal reason for the paucity of information available relates to the regulations for approval of agents in osteoporosis. The standard development route for new agents is to demonstrate efficacy in established postmenopausal osteoporosis.[96–98] The most commonly studied end-point is vertebral fracture, so that information on hip fracture risk with some exceptions is much less than for vertebral fracture. Against this background, the Committee for Human Medicinal Products (CHMP) and the FDA have approved licences for GIO where studies have demonstrated equivalent effects of the intervention on BMD in the two forms of osteoporosis. The argument runs that the pathophysiology of the diseases is sufficiently similar that responses in BMD are adequate surrogates for antifracture efficacy in GIO.

The most extensively studied class of agent testing in GIO has been the bisphosphonates, although the data are, for the reasons given, less complete than in postmenopausal osteoporosis. In the latter disorder we have previously come to the conclusion that there was little evidence for differences in efficacy between the bisphosphonates studied.[80] Those studied most thoroughly in postmenopausal osteoporosis include alendronate, risedronate and etidronate. Because trials of fracture efficacy are unlikely to be undertaken, and because these three agents are licensed for use in GIO, we pooled the information available. The combined analysis of risedronate, etidronate and alendronate showed a significant reduction in vertebral fracture (RR 0.46; 95% CI 0.28 to 0.77; *Figure 3*; *Table 10*).[64,129,130,132,133,139,140,142,153,154] The point estimates of the three bisphosphonates tested are comparable.

An identical meta-analysis of the available information with these agents in postmenopausal osteoporosis was undertaken and gave comparable effects (RR 0.57; 95% CI 0.50 to 0.66; *Figure 4*; *Table 11*), but with tighter confidence estimates since the sample size in postmenopausal osteoporosis was very much greater (n = 9681) than in GIO (n = 987).[76,77,202–209] As in the case of GIO, the point estimate for each bisphosphonate was similar. Moreover, there was no heterogeneity between studies as judged by the I^2 statistic.[210]

For non-vertebral fractures, the pooled data for bisphosphonates showed no significant effect (RR 0.77; 95% CI 0.39 to 1.51; *Table 12*).[135,139,153,154] The point estimate was, however, comparable to that obtained in postmenopausal osteoporosis (RR 0.81; 95% CI 0.73 to 0.90; *Table 13*).[76,77,202–204,206,207,209,211–213]

As for vertebral fracture, there was no significant heterogeneity between studies. Note that the estimates for efficacy in GIO are based on a total 500 patients for non-vertebral fracture. By contrast, estimates in postmenopausal osteoporosis are derived from 14,551 patients.

With regard to hip fracture outcomes, only two studies are available for GIO. In one study,[139] one hip fracture occurred amongst 18 patients treated with risedronate and in two of 19 patients given placebo (RR 0.53; 95% CI 0.05 to 5.33). In the

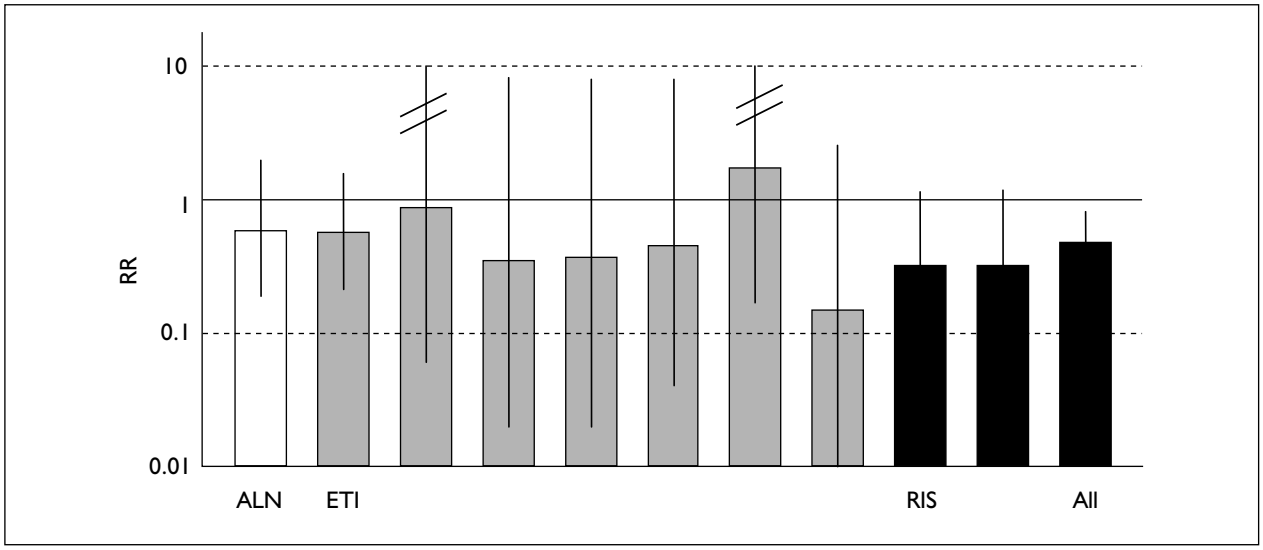

FIGURE 3 *Effects of bisphosphonates (RR ± 95% CI) on vertebral fracture risk in corticosteroid-induced osteoporosis. ALN, alendronate; ETI, etidronate; RIS, risedronate. All describes the combined effect (RR 0.46; 95% CI 0.29 to 0.77).*

TABLE 10 *Summary of effects (RR ± 95% CI) of bisphosphonates on vertebral fracture risk in corticosteroid-induced osteoporosis*

Agent	Study	Sample size		Weight (%)	RR	95% CI
		Treatment	Control			
Alendronate	Saag, 1998[64]	266	134	15.1	0.60	0.19 to 1.94
Etidronate	Worth, 1994[142]	14	19	8.7	0.15	0.01 to 2.55
	Adachi, 1997[133]	57	65	21.1	0.57	0.21 to 1.57
	Geusens, 1998[139]	18	19	3.3	0.35	0.02 to 8.09
	Pitt, 1998[140]	26	23	2.4	1.77	0.17 to 18.26
	Cortet, 1999[129]	44	39	2.4	0.89	0.06 to 3.70
	Jenkins, 1999[130]	6	7	3.2	0.38	0.02 to 7.93
	Jinnouchi, 2000[132]	16	9	2.9	0.56	0.04 to 7.95
	Subtotal[a]	181	181	44.0	0.54	0.26 to 1.11
Risedronate	Cohen, 1999[153]	53	52	20.6	0.33	0.09 to 1.14
	Reid, 2000[154]	60	60	20.4	0.33	0.09 to 1.17
	Subtotal[a]	113	112	40.9	0.33	0.14 to 0.80
Bisphosphonate	Total[a]	560	427	100.0	0.46	0.28 to 0.77

[a] Fixed-effects model; $I^2 = 0\%$.

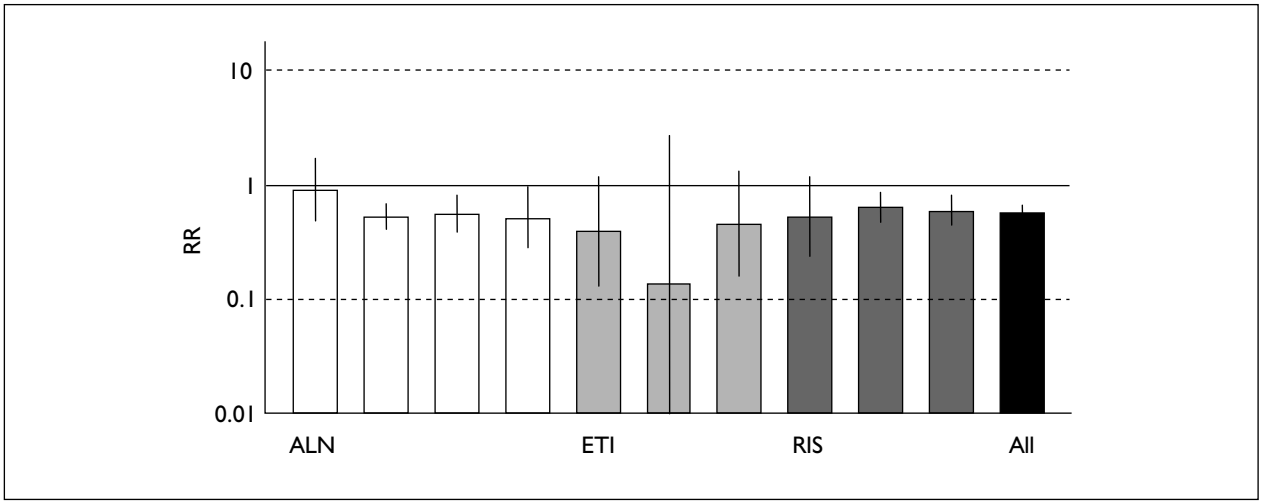

FIGURE 4 *Effects of bisphosphonates on vertebral fracture risk (95% CI) in postmenopausal osteoporosis. ALN, alendronate; ETI, etidronate; RIS, risedronate. All describes the combined effect (RR 0.57; 95% CI 0.50 to 0.66).*

other study, also with risedronate,[153] one hip fracture occurred in each arm amongst 76 patients given risedronate and 77 patients given placebo. The combined effect gave an RR 0.69 (95% CI 0.12 to 3.97). In postmenopausal women, the combined effect of bisphosphonates on hip fracture risk was comparable, with an RR 0.61 (95% CI 0.47 to 0.81)[76,77,79,202,204,207] (*Table 14*).

The analysis, summarised in *Figure 5* suggests that there is no evidence to support a hypothesis that the effects of bisphosphonates on fracture outcomes differ in GIO from postmenopausal osteoporosis. Thus, from a health economic perspective, the following general approach was taken. First, cost-effectiveness was examined for agents showing efficacy in the meta-analysis for GIO alone. Since calcidiol is not available in the UK, this left risedronate (5 mg daily). For this purpose, the relative risk reduction (RRR) for vertebral fracture was 67% (95% CI 20 to 86%). No effect on non-vertebral fractures was assumed.

Second, for the purposes of examining case finding strategies we assumed that the wider experience in postmenopausal osteoporosis was applicable to GIO. Thus, for vertebral fracture we assumed an RRR of 43% (95% CI 34 to 50%) for

TABLE 11 *Summary of effects (RR ± 95% CI) of bisphosphonates on vertebral fracture risk in postmenopausal osteoporosis*

Agent	Study	Sample size		Weight (%)	RR	95% CI
		Treatment	Control			
Alendronate	Liberman, 1995[202]	526	355	5.4	0.52	0.28 to 0.97
	FIT, 1998[a,203]	2057	2077	16.0	0.56	0.39 to 0.80
	FIT, 1996[b,204]	981	965	30.1	0.53	0.41 to 0.69
	Dursun, 2001[205]	38	40	2.8	0.90	0.48 to 1.69
	Subtotal[c]	3602	3437	54.3	0.56	0.46 to 0.67
Etidronate	Watts, 1990[206]	98	91	2.1	0.46	0.16 to 1.31
	Lyritis, 1997[207]	39	35	2.0	0.40	0.13 to 1.18
	Montessori, 1997[208]	39	39	0.7	0.14	0.01 to 2.68
	Subtotal[c]	176	165	4.8	0.39	0.19 to 0.80
Risedronate	Harris, 1999[76]	696	679	19.4	0.64	0.47 to 0.97
	Fogelman, 2000[209]	112	125	3.3	0.53	0.24 to 1.17
	Reginster, 2000[77]	344	346	18.3	0.60	0.44 to 0.81
	Subtotal[c]	1152	1149	40.9	0.61	0.50 to 0.75
Bisphosphonate	Total[c]	4930	4751	100.0	0.57	0.50 to 0.66

[a] Non-fracture arm.
[b] Fracture arm.
[c] Fixed-effects model; $I^2 = 0\%$.

TABLE 12 *Summary of effects (RR ± 95% CI) of bisphosphonates on non-vertebral fracture in corticosteroid-induced osteoporosis*

Agent	Study	Sample size		Weight (%)	RR	95% CI
		Treatment	Control			
Etidronate	Geusens, 1998[139]	18	19	21.6	0.26	0.03 to 2.14
	Roux, 1998[135]	59	58	22.3	0.49	0.09 to 2.58
	Subtotal[a]	77	77	43.9	0.38	0.10 to 1.38
Risedronate[b]	Cohen, 1989[153]	76	77	22.0	0.76	0.18 to 3.28
	Reid, 2000[154]	99	94	34.1	1.27	0.46 to 3.51
	Subtotal[a]	175	171	56.1	1.07	0.47 to 2.45
	Total[a]	252	248	100.0	0.77	0.39 to 1.51

[a] Fixed-effects model.
[b] Risedronate 5 mg daily; $I^2 = 0\%$.

vertebral fracture, 19% (95% CI 10 to 27%) for non-vertebral fractures (i.e. humerus and forearm) and 39% (95% CI 19 to 53%) for hip fracture.

Treatment assumptions

In this review, it was assumed that the end-point estimate of efficacy derived from RCTs would apply to the 5-year treatment interval to be used for health economics modelling. As discussed elsewhere, a longer time frame would provide a less secure basis since, for some treatments, transients in efficacy are found at least in postmenopausal osteoporosis.[80] A key assumption relating to the long-term effectiveness of an intervention is the duration for which an effect persists after stopping treatment – a concept that has been termed offset time.[214]

A great deal of uncertainty surrounds the offset of therapeutic effect once treatment has stopped. Relatively rapid offset of effects on BMD has been observed with calcium and calcitonins. Such data suggest that no further gains can be expected from treatments that have been stopped 3 years earlier. In the case of the bisphosphonates, the offset of effect has not been fully characterised but is long. The cessation of treatment is associated with an increase in skeletal markers of resorption and formation, but bone loss does not appear to occur immediately. In one study, average losses

TABLE 13 *Summary of effects of bisphosphonates on non-vertebral fracture risk (RR ± 95% CI) in postmenopausal osteoporosis*

Agent	Study	Sample size		Weight (%)	RR	95% CI
		Treatment	Control			
Alendronate	Liberman, 1995[202]	597	379	6.9	0.75	0.50 to 1.14
	FIT, 1998[a,203]	2214	2210	43.8	0.89	0.76 to 1.04
	Pols, 1999[211]	950	958	5.5	0.52	0.30 to 0.89
	FIT, 1996[b,204]	1022	1005	22.3	0.81	0.65 to 1.01
	Subtotal[c]	4783	4560	78.5	0.83	0.83 to 0.93
Etidronate	Storm, 1990[212]	33	33	0.9	0.83	0.28 to 2.46
	Watts, 1990[206]	105	104	2.4	1.24	0.68 to 2.25
	Lyritis, 1997[207]	50	50	0.8	0.60	0.15 to 2.38
	Wimalawansa, 1998[213]	17	19	0.1	1.06	0.07 to 15.62
	Subtotal[a]	205	205	4.2	1.03	0.64 to 1.66
Risedronate	Harris, 1999[76]	812	815	7.8	0.64	0.42 to 0.97
	Fogelman, 2000[209]	177	180	1.9	0.55	0.22 to 1.34
	Reginster, 2000[77]	406	406	7.6	0.71	0.47 to 1.06
	Subtotal[d]	1395	1401	17.3	0.66	0.50 to 0.87
Bisphosphonate	Total[d]	6383	6166	100.0	0.81	0.73 to 0.90

[a] Non-fracture arm.
[b] Fracture arm.
[c] Fixed-effects model, moderate heterogeneity; $I^2 = 23\%$.
[d] Fixed-effects model; $I^2 = 0\%$.

TABLE 14 *Summary of effects of bisphosphonates on hip fracture risk (RR ± 95% CI) in postmenopausal women*

Agent	Study	Sample size		Weight (%)	RR	95% CI
		Treatment	Control			
Alendronate	Liberman, 1995[202]	597	397	2.9	0.22	0.02 to 2.12
	FIT, 1996[a,204]	1022	1005	18.0	0.49	0.24 to 1.01
	Subtotal[b]	1619	1402	21.0	0.45	0.23 to 0.90
Etidronate	Lyritis, 1997[207]	50	50	1.6	0.50	0.05 to 5.34
Risedronate	Harris, 1998[76]	812	815	12.2	0.80	0.38 to 1.70
	Reginster, 2000[77]	406	406	15.5	0.74	0.37 to 1.45
	McClung, 2001[79]	3624	1821	49.8	0.60	0.41 to 0.89
	Subtotal[b]	4842	3042	77.4	0.66	0.49 to 0.90
Bisphosphonate	Total[b]	6511	4494	100.0	0.61	0.47 to 0.81

[a] Fracture arm.
[b] Fixed-effects model; $I^2 = 0\%$.

over 3 years, after stopping treatment with alendronate for 3 years, were comparable to those in placebo-treated patients, but the time course of change was not reported. A very sustained effect of bisphosphonates on BMD was observed following a short course of alendronate in the treatment of osteoporosis.[215] Studies of the use of pamidronate and alendronate have suggested, however, that bone loss may eventually resume.[215–219] Similar findings have been reported for risedronate.[220] The most detailed study followed women for up to 7 years after stopping alendronate.[221] Although bone loss occurred after stopping treatment, the rate of loss was similar to that observed in placebo-treated patients, so that the treatment-induced gains in BMD were sustained throughout the observation period.

The question arises of whether sustained effects on BMD would have sustained effects on fracture risk reduction. The question cannot be answered with certainty since the relevant RCTs have not been undertaken. However, fracture rates appear not to increase when alendronate is stopped.[219]

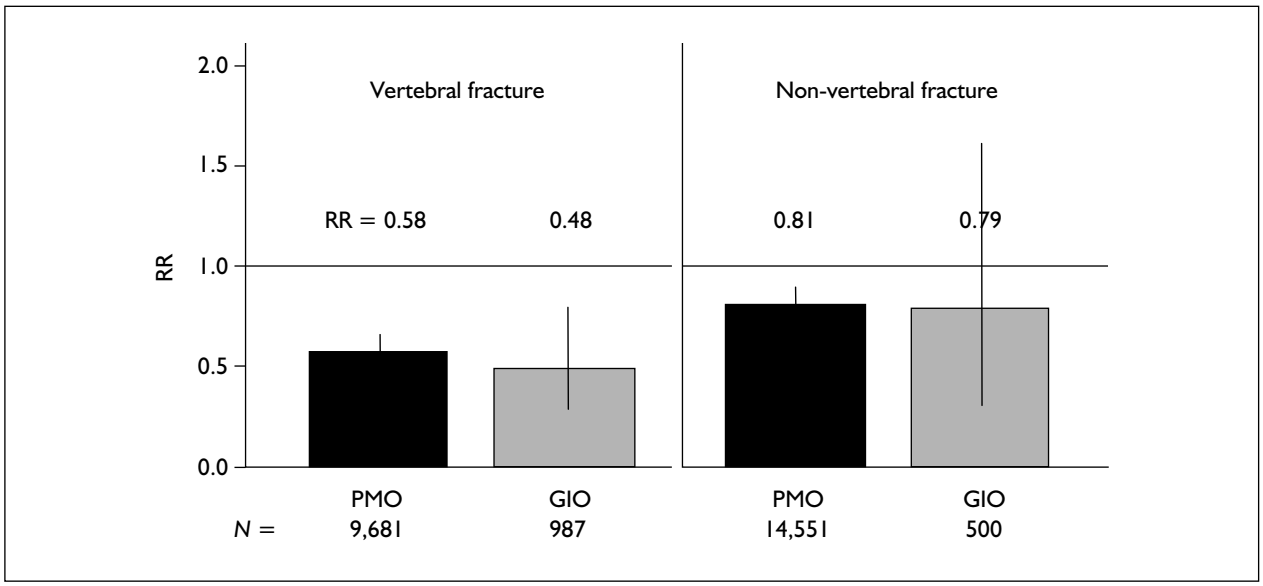

FIGURE 5 *Summary of effects of bisphosphonates (RR ± 95% CI) on vertebral fracture, non-vertebral fracture and hip fracture in postmenopausal osteoporosis (PMO) and glucocorticoid-induced osteoporosis (GIO)*

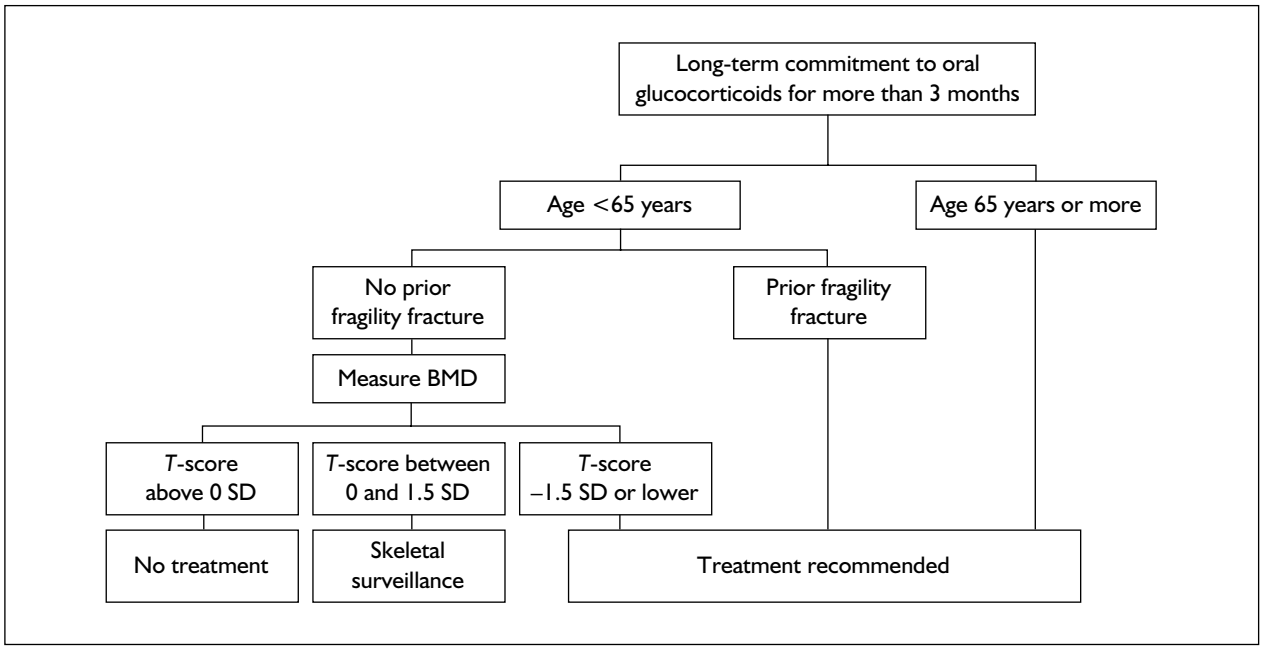

FIGURE 6 *Management algorithm for men and women committed to long-term glucocorticoid treatment. Adapted from Bone and Tooth Society, National Osteoporosis Society and Royal College of Physicians. Glucocorticoid-induced osteoporosis. A concise guide to prevention and treatment. London: Royal College of Physicians; 2002.*

Continued antifracture efficacy is observed when parathyroid hormone (PTH) is stopped, at least for several years[222], and for considerably longer with HRT.[223] The available evidence suggests that these agents have a slow offset of effect, not only on BMD, but also on fracture risk. There is a marked impact of different assumptions concerning offset time on cost-effectiveness.[214] In the present study, an offset time of 5 years has conservatively been assumed. An increased offset time of 10 years was examined in a sensitivity analysis.

Treatment strategies

Guidelines for the management of GIO have been published recently in the UK.[5,224] The management algorithm is shown in abbreviated form in *Figure 6*.[224] The starting point is the eligibility for case-finding, which is a patient either committed to long-term glucocorticoids

or who has been exposed to long-term glucocorticoid treatment for more than 3 months. No distinction is made between men and women, but a branch point is at the age of 65 years. At or above this age, the risk of fractures is considered to be sufficiently high that treatment with skeletally active agents is appropriate.

Below the age of 65 years, treatment is appropriate with a history of a prior fragility fracture. In the absence of a prior fracture, a BMD test is recommended and active intervention is recommended where the *T*-score is –1.5 SD or lower. We have used this as a base-case scenario for a management strategy.

Chapter 4

Epidemiology, costs and utilities

In addition to information on efficacy, side-effects and compliance associated with interventions, economic evaluation requires information on additional components that include

- the incidence of osteoporotic fractures
- the prevalence of established osteoporosis
- the risk of fracture associated with osteoporosis
- the risk of fracture associated with a prior fracture
- the independent risk associated with glucocorticoid treatment
- the mortality associated with osteoporosis and fracture
- the interactions between osteoporosis and other health states
- the direct and indirect costs of osteoporotic fractures
- costs of treatment and monitoring
- utilities for osteoporotic fractures with which to quality-adjust years of life saved.

Wherever possible, the data used to populate the health economics model were derived from a UK information base. This chapter reviews the sources of data. Limitations and the assumptions that derive from them are reviewed in detail elsewhere[80] but are summarised below. The uncertainties that are inherent in the estimates provide a rationale for subsequent sensitivity analysis.

Fracture

Osteoporotic fractures

The choice of fractures to include is not straightforward since there is no consensus view to clarify which fracture is due to osteoporosis. Definitions based on high-energy trauma[225] or with reductions in BMD[226] are imperfect. An alternative approach is to quantify, by expert opinion, the proportion of fractures at each site as due to osteoporosis, an approach used in Switzerland[227] and the USA[228,229] to characterise the burden of disease, but is also arbitrary and based on as many assumptions.

An indirect arbiter of an osteoporotic fracture is the finding of a strong association between the fracture and the risk of classical osteoporotic fractures at other sites. Vertebral fractures, for example, are a very strong risk factor for subsequent hip and vertebral fracture.[111,230–232]

The fracture sites that we included were based on their known association with low BMD. In addition, fractures that showed no increase in incidence with age were excluded.[233] Fractures classified as 'osteoporotic' comprised fractures of the spine, rib, pelvis, humerus, forearm, femur, tibia and fibula (except in men), and clavicle, scapula and sternum. Fractures of the skull, face, hands, patella, finger, feet, toes and ankle were therefore not included. The distribution of osteoporotic fractures in adults from Sweden is shown in *Table 15*.[233]

Fracture risks

The fracture risks used in this report are derived where possible from the UK. There have been several recent surveys reporting fracture rates in the UK.[234–239] For hip, forearm and proximal humeral fracture rates, we used the data from Singer and colleagues,[236] based on a population in Edinburgh (*Table 16*). This was preferred to the data of Johansen and colleagues[237] in Cardiff, since there were more fractures analysed (15,293 versus 6467). Hip fracture rates were smoothed assuming an exponential increase in incidence with age. Hip fracture rates of the series from Singer and colleagues were mid-way between the estimate of Johansen and colleagues and the GPRD,[234] but were broadly comparable. Similarly, for forearm and shoulder fractures, fracture rates in Singer and colleagues[236] lay mid-way between those of Johansen and colleagues[237] and the GPRD.[234] Overall, the differences in risk between these series were less than the ranges found within other countries.[241]

Vertebral fracture may be defined in several ways. Morphometric fractures describe radiographic deformities identified on radiographs as due to fracture. These may be symptomatic or clinically silent. Several studies indicate that the ratio of clinical to morphometric fractures is approximately 20% in women and 40% in men.[242,243] In the context of this report, we have preferred to estimate the incidence of clinically diagnosed

TABLE 15 *Proportion (%) of osteoporotic fractures at different sites in men and women by age*[233]

Fracture type	Age range (years)							
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89
Men								
Vertebra	21.9	9.1	20.3	12.1	19.9	20.7	12.6	12.3
Ribs	36.3	57.6	35.8	39.5	34.1	26.9	41.3	31.0
Pelvis	1.3	1.2	1.9	1.6	2.0	2.7	2.4	3.0
Humeral shaft	2.5	0.8	1.8	1.6	2.8	2.0	1.0	1.7
Proximal humerus	7.3	2.4	5.4	4.6	8.2	6.0	3.2	5.1
Clavicle, scapula, sternum	13.0	10.7	8.0	10.8	7.9	8.7	8.9	8.8
Hip	4.7	5.2	12.0	13.7	19.8	31.4	25.9	33.3
Other femoral	1.7	1.4	2.1	2.1	1.7	1.7	1.2	1.3
Tibia and fibula[a]	–	–	–	–	–	–	–	–
Distal forearm	11.3	11.6	12.6	14.1	3.6	5.9	3.5	3.3
Women								
Vertebra	15.1	12.7	19.2	16.4	20.0	17.3	12.7	11.3
Ribs	11.8	13.0	10.6	12.7	11.1	14.0	15.3	21.9
Pelvis	0.8	1.3	1.8	1.8	3.2	3.2	4.8	4.8
Humeral shaft	3.8	3.4	2.7	4.4	3.3	3.3	2.1	2.6
Proximal humerus	11.6	10.2	8.0	13.2	9.9	9.8	6.4	7.7
Clavicle, scapula, sternum	7.2	7.8	2.7	5.4	3.1	5.6	4.5	2.4
Hip	3.8	7.3	11.4	14.5	21.0	26.3	36.8	35.6
Other femoral	1.0	1.4	2.3	1.9	2.3	2.3	2.6	2.8
Tibia and fibula	5.6	6.3	5.6	3.7	2.7	2.3	1.6	1.4
Distal forearm	39.1	36.6	35.9	25.9	23.2	16.0	13.2	9.5

[a] Tibial fractures not classified as osteoporotic in men.
Reproduced from Kanis JA, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A. *Osteoporos Int* 2002;**12**;417–24, *Table 3*.

TABLE 16 *Fracture incidence (%) by age and gender at the sites shown*[a,236,240]

Age (years)	Hip fracture		Vertebral fracture		Wrist fracture		Proximal humerus	
	Men	Women	Men	Women	Men	Women	Men	Women
50–54	0.022	0.030	0.059	0.079	0.104	0.255	0.033	0.058
55–59	0.039	0.057	0.113	0.163	0.060	0.374	0.052	0.085
60–65	0.069	0.107	0.105	0.163	0.061	0.467	0.055	0.136
65–69	0.121	0.201	0.171	0.284	0.063	0.573	0.076	0.126
70–74	0.213	0.379	0.299	0.533	0.161	0.699	0.120	0.246
75–79	0.374	0.713	0.317	0.605	0.094	0.697	0.047	0.306
80–84	0.657	1.344	0.345	0.706	0.175	0.749	0.123	0.372
85–89	1.115	2.532	0.514	1.128	0.138	1.001	0.166	0.362
90–94	2.003	4.770	0.812	1.908	0.320	0.919	0.000	0.391

[a] Data computed from Singer and colleagues, 1998,[236] *Table 3*, p. 247, except for vertebral fracture. Vertebral fracture data computed from Kanis and colleagues, 2000.[240]

vertebral fracture, since the patients involved are those most likely to be identified for treatment. The incidence of clinically identified fractures has been studied in the UK within the GPRD.[234] The incidence is, however, very low and it is likely that the majority of fractures were not coded.[244] Indeed, reported rates of vertebral fracture vary by more than 10-fold in general practice in the UK.[245] The ratio of clinical fractures identified in the GPRD to those identified by morphometry in the UK is unrealistically low compared with other countries,[246] which supports the view that the GPRD database has markedly under-reported clinical vertebral fracture.

For these reasons, we imputed vertebral fracture rates from data available from Malmö in Sweden that represent the incidences of hip and vertebral

TABLE 17 *Increase in incidence (%) of hip, forearm and proximal humerus fractures to incorporate fractures at other sites*

Age (years)	Hip fracture	Proximal humerus fracture	Forearm fracture
50–54	27	112	79
55–59	20	69	40
60–64	22	37	24
65–69	19	44	35
70–74	28	41	52
75–79	17	35	77
80–85	22	21	106

fractures that come to clinical attention.[240]
It was assumed that the ratio of the incidence of vertebral fracture and hip fractures in Malmö would be comparable to the ratio of vertebral fracture incidence in the UK (unknown) and hip fracture incidence in the UK (Edinburgh). The rates are shown in *Table 16*.

It is important to note that morphometrically diagnosed fractures that do not come to clinical attention also give rise to morbidity and are associated with a high risk of future fractures. For this reason, we also examined cost-effectiveness using the morphometrically derived incidence rates in a sensitivity analysis assuming from our calculations that 22% of morphometric deformities come to clinical attention in women.[243] In men, approximately 42% of vertebral deformities come to clinical attention,[243] and this latter figure was used in a sensitivity analysis.

For fractures of the ribs, clavicle, scapula, sternum, tibia and fibula we used the same approach as that for vertebral fracture and assumed, therefore, for each age and sex, that the ratio of the index fracture to hip fracture was similar in the UK to that found in Sweden. Fractures at other sites used data from the UK.[236,237] For the purposes of modelling, we incorporated pelvic fractures and other femoral fractures with hip fracture and the incidence of 'hip fracture' was uplifted as shown in *Table 17*. A similar adjustment was made for proximal humerus fractures to accommodate the incidence of fractures of the humeral shaft, tibia and fibula. Finally, forearm fracture rates were uplifted to accommodate fractures of the ribs, sternum and scapula.

There are several other uncertainties concerning the risks that we use. There is concern that regional estimates may not be representative of the UK. A greater problem is the use of these estimates for modelling future events. The concern arises for several reasons:

1. We assume that over 10 years (the time frame used in the base case), the risk of fracture will not change in the population. The increase in the age- and sex-specific incidence in hip fracture appears to have flattened in the UK,[247] but if age-specific rates decrease in the future, the impact of treatments on fracture burden will be overestimated. Secular trends for other fractures are not documented in the UK, but age- and sex-specific incidence appears to be increasing in some countries including those in Europe.[248]
2. It is also assumed that the mortality hazard does not change over 10 years. On the other hand, mortality has continued to decrease and is likely to do so in the future.[249] Failure to take account of these trends will underestimate the impact of treatments on the numbers of fractures saved.
3. The fracture rates used are drawn from population samples over a limited period (1 year). Fracture rates given will include individuals with a first fracture and a minority who have previously sustained a fracture at the same site. Hence, the risk of first fracture is overestimated. The overestimate is greater in the elderly than in the young.[240]

There are, therefore, factors that variously overestimate and underestimate fracture risk. For the purposes of this report, we have not considered these further since the cancelling sources of error are likely to provide a more reasonable estimate than corrections based on untestable assumptions.

BMD and fracture risk

Gradients of risk

A number of prospective studies have examined the risk of fracture as a function of BMD. In general, the lower the BMD, the greater is the risk of fracture. The increase in fracture risk is approximately doubled for each SD decrease in BMD. Thus, an individual with a BMD value 1 SD lower than average BMD for a given age has about a two-fold higher fracture risk than an individual with an average BMD for that age. The gradient of risk, however, varies according to the site of assessment and the technique used. A meta-analysis of absorptiometric techniques showed that the gradient of risk depended on both the site of measurement and the technique.[250] For example,

TABLE 18 *Relative risk (with 95% CI) of fracture in women for a 1 SD decrease in BMD (absorptiometry) below the age-adjusted mean*[250]

Site of measurement	Forearm fracture	Hip fracture	Vertebral fracture	All fractures
Distal radius	1.7 (1.4 to 2.0)	1.8 (1.4 to 2.2)	1.7 (1.4 to 2.1)	1.4 (1.3 to 1.6)
Femoral neck	1.4 (1.4 to 1.6)	2.6 (2.0 to 3.5)	1.8 (1.1 to 2.7)	1.6 (1.4 to 1.8)
Lumbar spine	1.5 (1.3 to 1.8)	1.6 (1.2 to 2.2)	2.3 (1.9 to 2.8)	1.5 (1.4 to 1.7)

Reproduced from Marshall D, Johnell O, Wedel H. *BMJ* 1996;**312**;1254–6.

BMD measurements by dual-energy X-ray absorptiometry (DXA) to predict hip fracture were better when measurements were made at the hip rather than at the spine or forearm (*Table 18*). An individual with a *T*-score of –3 SD at the hip would have a 2.6^3 or greater than 15-fold higher risk than an individual with a *T*-score of 0 SD. By contrast, the same *T*-score at the spine would yield a much lower risk estimate – approximately 4-fold increased (1.6^3). Similarly, spine measurements predict spine fractures more accurately than measurements made at other sites.

The gradient of risk is highest for hip fracture prediction from measurements at the hip. Also, measurements at the hip predict all fractures in addition to measurements at other sites. For this reason, the proximal femur is the preferred and recommended site for diagnostic use,[251] and is the site that we have assumed would be used for diagnostic purposes. For humeral fractures, no data are available and we assumed the gradient of risk with which all fractures were predicted (1.6/SD). There is little difference in predictive power between measurements made at the femoral neck or the region of total hip, but the data are limited.[252] For the purposes of this report, we have chosen the femoral neck since a UK reference range was available[253] and meta-analyses of predictive value of BMD have been based on estimates made at the femoral neck.[250,254]

The computation of risk from gradients of fracture risk per SD of BMD assumes that gradients are similar at all ages and between sexes and that the risk ratio does not attenuate with time – at least over a 10-year interval used for modelling. A recent meta-analysis of population-based cohorts indicated that there was very little attenuation of the gradient of risk with time since assessment and no difference in the gradient of risk between men and women.[254] The same meta-analysis indicated, however, that the gradient of risk for hip fracture for BMD at the hip is higher at younger ages than in the elderly (*Table 19*). By contrast, the gradient of risk for other fracture outcomes was stable with age. Hence, if a fixed gradient of risk is used for all ages, the risk of hip fracture would be underestimated at the age of 50 years and overestimated in the very elderly, and this age-dependent feature is incorporated in the model.

TABLE 19 *Gradient of hip fracture risk per SD decrease in BMD at the proximal femur by age in men and women combined*[254]

Age (years)	RR/SD	95% CI
50	3.68	2.61 to 5.19
55	3.35	2.51 to 4.47
60	3.07	2.42 to 3.89
65	2.89	2.39 to 3.50
70	2.78	2.38 to 3.23
75	2.58	2.30 to 2.90
80	2.28	2.09 to 2.50
85	1.92	1.76 to 2.10

Reproduced from Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, *et al*. *J Bone Miner Res* 2005;**20**:1185–94, *Table 4*, p. 1190.

The gradient of risk is also dependent on the initial BMD and the gradient of risk for osteoporotic fractures other than for hip fracture is higher with lower values for hip BMD, but the effect is not marked.

Fracture risk according to BMD

The approach that we used was first to examine the relationship between *Z*-score (the deviation in units of SD of a BMD value from the mean value in individuals of the same age and sex) and *T*-score at different ages using conversion factors derived from the UK population[253] from which to compute fracture risk at any given *T*-score. The average *T*-score for women between the ages of 50 and 54 years is 0.66 SD. This decreases with age to –0.92, –1.17, –1.43, –1.69, –1.94, –2.20 and –2.43 in 5-year age intervals, respectively. Knowing the gradient of risk of fracture from BMD, the fracture

TABLE 20 *Fracture risk (%) in men and women with an average value for BMD (Z-score = 0)*

Age range (years)	Hip fracture	Vertebral fracture	Wrist fracture	Proximal humerus
Men				
50–54	0.02	0.06	0.10	0.03
55–59	0.03	0.11	0.06	0.05
60–64	0.05	0.09	0.06	0.05
65–69	0.09	0.15	0.06	0.07
70–74	0.16	0.27	0.15	0.11
75–79	0.26	0.27	0.09	0.04
80–84	0.51	0.29	0.16	0.11
85–89	0.91	0.42	0.12	0.14
Women				
50–54	0.02	0.07	0.25	0.06
55–59	0.04	0.14	0.35	0.08
60–64	0.06	0.13	0.41	0.11
65–69	0.10	0.20	0.40	0.10
70–74	0.17	0.34	0.51	0.17
75–79	0.35	0.37	0.49	0.20
80–84	0.67	0.41	0.50	0.23
85–89	1.34	0.62	0.63	0.21

risk can be computed as a multiple of the risk of an individual with average BMD. Consider, for example, a woman aged 70 years at the threshold of osteoporosis with a *T*-score of –2.5 SD. The gradient of risk for each SD decrease in BMD is 2.78 for hip fracture (*Table 19*), 1.8 for vertebral fracture and 1.6 for a humeral fracture (see *Table 18*). For a 70-year-old woman with an average BMD (*Z*-score = 0 SD), the *T*-score is approximately –1.55 SD, which is 0.95 SD above the threshold for osteoporosis. The risk of hip fracture for a 70-year-old woman with a *T*-score of –2.5 SD compared with a woman of the same age and average BMD is $2.78^{0.95} = 2.64$, the risk ratio for a vertebral fracture is $1.80^{0.95} = 1.75$ and the risk ratio for a humeral fracture is $1.60^{0.95} = 1.56$.

BMD is normally distributed in a population at a given age, whereas there is an exponential relationship between BMD and fracture risk.[3] Hence, individuals with an average BMD have a lower than average risk of fracture.[72] Conversely, the average fracture risk is found in individuals with a lower than average BMD. For this reason, our calculations of fracture risk at any given *T*-score were adjusted accordingly. Fracture risk in men and women with an average BMD is given in *Table 20*.

BMD, gender and fracture risk

Men have higher BMD values than women at most skeletal sites and a lower risk of fractures. The question arises of whether there are differences in fracture risk at a given BMD and whether the gradient of fracture risk differs for each SD decrease in BMD. Many studies have examined fracture risk in men and women, and have variously concluded that the gradient of risk and fracture threshold are the same or differ markedly.[255–259] There are several reasons for this discrepancy. First, the relation between BMD and fracture risk changes with age[3,260] so that age adjustment is required. Second, a difference between sexes in the gradient of risk could be a result of differences in the SD of measurements between men and women.[261] Third, data from referral populations of osteoporotic men and women are likely to be biased. These difficulties are overcome by assessing population-based samples and expressing risk as a function of absolute BMD or standardised *T*-score with age adjustment. The available data indicate that the risk of hip fracture is similar in men and women for any given age and BMD.[3,262,263] The risk of vertebral fractures is also similar when BMD measurements are made at the spine.[257]

In a large meta-analysis of prospective studies using the primary databases, the gradient of fracture risk/SD decrease in BMD was similar in men compared with women for hip fracture, osteoporotic fracture or any fracture[254] (*Table 21*). These considerations suggest that the risk of fracture for any given BMD and age is the same in men as in women and was the assumption used for modelling.

TABLE 21 *Gradient of fracture risk per SD decrease in Z-score of BMD in men and women*[254]

Outcome fracture		RR/SD	95% CI	RR/SD[a]	95% CI
Any	Men	1.47	1.34 to 1.60	1.44	1.32 to 1.58
	Women	1.45	1.39 to 1.51	1.46	1.39 to 1.53
	Combined	1.45	1.39 to 1.51	1.46	1.40 to 1.52
Osteoporotic	Men	1.60	1.43 to 1.79	1.55	1.40 to 1.73
	Women	1.53	1.46 to 1.62	1.56	1.47 to 1.64
	Combined	1.55	1.47 to 1.62	1.56	1.49 to 1.64
Hip	Men	2.42	1.90 to 3.09	2.28	1.81 to 2.87
	Women	2.03	1.87 to 2.21	2.18	1.99 to 2.39
	Combined	2.07	1.91 to 2.24	2.21	2.03 to 2.41

[a] SD used is that of the young female reference range of NHANES III.
Reproduced from Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, *et al*. *J Bone Miner Res* 2005;**20**:1185–94, *Table 2*, p. 1189.

TABLE 22 *Risk of fracture at the sites shown according to the site of a prior fracture*[110]

Site of prior fracture	Site of subsequent fracture									
	Distal forearm		Spine		Proximal humerus[a]		Hip		Pooled	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Forearm	3.0	2.0 to 5.3	1.7	1.4 to 2.1	2.4	1.7 to 3.4	1.9	1.6 to 2.2	2.0	1.7 to 2.4
Spine	1.4	1.2 to 1.7	4.4	3.6 to 5.4	1.8	1.7 to 1.9	2.3	2.0 to 2.8	1.9	1.7 to 2.3
Humerus[a]	1.8	1.3 to 2.4	1.9	1.3 to 2.8	1.9	1.3 to 2.7	2.0	1.7 to 2.3	1.9	1.7 to 2.2
Hip	1.4	–[b]	2.5	1.8 to 3.5	1.9	–[c]	2.3	1.5 to 3.7	2.4	1.9 to 3.2
Pooled	1.9	1.3 to 2.8	2.0	1.6 to 2.4	1.9	1.6 to 2.2	2.0	1.9 to 2.2	2.0	1.8 to 2.1

[a] Assumed to be equivalent to a 'minor fracture' from the meta-analysis.
[b] No studies.
[c] One study.
Adapted from Klotzbeucher CM, Ross PD, Landsman PB, Abbot TA, Berger M. *J Bone Miner Res* 2000;**15**:721–7.

Fracture risk and prior fracture

Risk ratios

The risk of fracture following a fragility fracture has been examined in a large number of studies. Fracture risk is increased over and above that explicable on the basis of age or BMD. The inter-relationship between prior and subsequent fractures has been assessed by meta-analysis using a random effects model to derive summary estimates of RR.[110] The risk estimates derived from peri- or postmenopausal women are shown in *Table 22*, adjusted for age but not BMD. These estimates are comparable to those of a more recent meta-analysis[262] and a large cohort study in the UK.[263] There have been few studies that examine the risk of a forearm fracture following a hip fracture[264] and we used an RR of 1.4 equivalent to the lowest RR between fractures.

The analysis computes (for example) that an individual with a prior spine fracture has a risk of a further spine fracture 4.4 times greater than individuals of the same age and BMD but without fracture. The assumption is an oversimplification, for several reasons. First, the risk estimates are not adjusted for BMD. This overestimates the risk by 10–20%.[112,265]

Second, some downward adjustment of the RR is required since the risks are relative to those without prior fracture rather than relative to the general population. The adjusted RR approximate depends on the prevalence of the outcome (fracture).[266] For example, the RR of hip fracture in the presence of a prior vertebral fracture is given as 4.4. If, at a given age, the prevalence of a prior vertebral fracture is 5%, the RR is 3.76. Where the prevalence is 10% of the population, the RR falls to 3.28.

These overestimates of fracture risk are offset somewhat because the risk of subsequent fracture varies with time after fracture. In the case of vertebral fracture requiring hospitalisation, risks of further osteoporotic fractures are markedly increased immediately after a fracture and tail off to those observed in the meta-analysis after 12–18 months.[264,267] Also, the RR increase varies according to age and is markedly higher in the young than in the elderly.[267] These short-term RRs more than offset the overestimates arising from other simplifications. Hence, the assumptions we used were conservative, particularly in younger individuals.

Fracture risk

The data permit the calculation of fracture risk in established osteoporosis conditional upon the site of prior fracture. For example, the risk of hip fracture in a woman aged 70 years is approximately 0.5%. In women with a *Z*-score of 0, the risk is lower at 0.27%. For a woman with a *T*-score of –2.5 SD this risk would be increased by $2.78^{-0.95} = 2.64$, giving a final risk of 0.71%. In a woman with the same *T*-score but with a prior spine fracture, the risk of hip fracture is increased 2.3-fold (see *Table 22*), giving a hip fracture risk of 1.63%.

Effects of glucocorticoids on fracture risk

The adverse effects of glucocorticoids on bone fragility have been appreciated for many years. A major mechanism relates to the progressive loss of bone that occurs once glucocorticoids are started, but the underlying condition for which they are used may also be a factor. Irrespective of the mechanism, epidemiological data suggest that the risk of hip, forearm and shoulder fractures is increased approximately 2-fold.[10,11,14] The risk for vertebral fracture may be somewhat higher.[14] The largest and most recent study examined fracture risk in the general practice research database of the UK,[14] where approximately 250,000 glucocorticoid users were compared with age- and sex-matched controls. A dose-dependent effect on fracture risk was noted, and at a dose of prednisolone or its equivalent greater than 7.5 mg daily, the RR of vertebral fracture was 5.2, whereas at between 5 and 7.5 mg daily the RR was lower (2.6). The dependence of this risk on BMD is not known, nor is the possible variation of risk with age and sex. The aim of the present study was to examine in an international setting the risk of glucocorticoid use in men and women and to determine its dependence on other risk factors, particularly BMD.

Methods

We studied 42,542 men and women drawn from seven prospective population studies. Details of each of the cohorts are published elsewhere,[23] but are summarised briefly below.

The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK, and surrounding districts between 1993 and 1999. Approximately 35,000 women, identified from GP listings, were contacted by letter and invited to attend for the assessment of skeletal status. A total of 5873 women were willing to attend. Of these, 281 were excluded and the remainder were randomly allocated to treatment with the bisphosphonate clodronate to study its effects on fracture risk. The material for this study comprised 2172 women allocated to treatment with placebo.[268] All women had baseline assessment of BMD undertaken at the femoral neck using the Hologic QDR 4500. Outcomes were assessed by 6-monthly home visits.

The Rotterdam study, begun in 1990, is a prospective cohort study that aimed to examine and follow up all residents aged 55 years and older living in Ommoord, a district of Rotterdam.[269] By 1993, 7983 residents had been included (response rate 78%). BMD was assessed at the femoral neck by DXA using a Lunar DPX-L.[262] Fracture follow-up was achieved through an automated link with GP computer systems and hospital admission data. Fracture data were collected and validated by two independent research physicians. For this analysis, validated fracture follow-up was available for 7774 participants (3065 men) with an average follow-up time of 6 years. Femoral neck BMD was measured in 5778 individuals (2431 men).

The Gothenburg study comprised a randomly drawn population cohort of approximately 10,000 women aged 50–70 years.[270] About 70% of those initially contacted agreed to participate and were followed for 3 years. Assessment included a standardised questionnaire that recorded information on risk factors for osteoporosis. Clinical fractures were identified prospectively through the radiology departments servicing the region. BMD was assessed at baseline at the distal forearm by using an Osteometer DTX-200.

The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple

assessments of skeletal status in men and women aged 60 years or more in Dubbo, Australia.[271] Participation in the study was 56% of the population (2163 individuals). Baseline measurements included BMD at the femoral neck assessed using DXA (GE-Lunar, DPX and Prodigy). Fractures are identified through radiologists' reports from the two centres servicing the region.

The Canadian Multicentre Osteoporosis study (CaMos) is an ongoing prospective age-stratified cohort. The study is documenting the incidence of fractures and risk factors in a random sample of 9424 men and women aged 25 years or more selected by telephone listings. The sampling frame is from nine study centres in seven provinces.[272] Characterisation of individuals was by interview. BMD was measured by DXA at the hip with a Hologic QDR in seven centres and a Lunar DPX Alpha in two centres. Machines were cross-calibrated using the same European Spine Phantom.

The Rochester cohort was recruited from two random population samples stratified by decade of age, one of women who were subsequently followed for up to 20 years[273] and another sample of women and men followed for 8 years.[274] The total sample size was 1001 men and women. BMD of the right femoral neck was measured by dual photon absorptiometry in the first cohort (cross-calibrated to DXA) and by DXA (Hologic QDR 2000) in the second group. Fractures were ascertained by periodic interview combined with review of the inpatient and outpatient medical records of all local care providers.

The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centres in 19 European countries.[275] Equal numbers of men and women were drawn in each centre within six 5-year age bands (50–54 up to 75–79 years). A baseline radiograph for vertebral fracture prevalence was undertaken in 15,570 men and women. BMD was measured in 3461 men and women from 13 centres by DXA at the femoral neck using Pencil Beam machines that were cross-calibrated using the European Spine Phantom. This sample provided the framework for the European Prospective Osteoporosis Study (EPOS) where repeated assessment was undertaken in 29 of the centres.[246,276]

Baseline and outcome variables

Ever use of oral steroids was used to characterise glucocorticoid exposure, since the questionnaires in most cohorts did not distinguish between ever and current use of glucocorticoids. The duration of use was not analysed. For the CaMos study, patients were identified who had ever taken glucocorticoids for more than 1 month and at Rochester for more than 6 months. In three cohorts, documentation of current use was available. In Rotterdam the distinction was made between current use (n = 159) and non-current use (n = 7624). In the DUBBO cohort, the distinction was between never use (n = 2068), past but not current use (n = 25) and current use (n = 58). For Sheffield, the distinction was made between never (n = 1963), ever (n = 137) and current use (n = 64). BMD measurements were available in 83% of these individuals.

BMD was assessed by multiple techniques. For the purposes of this analysis we utilised BMD assessed at the femoral neck by DXA, with the exception of the Gothenburg cohort, where BMD was assessed by DXA at the distal forearm.

Fracture ascertainment was undertaken by self-report (Sheffield, EVOS/EPOS) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam). The EPOS study also included sequential systematic radiography to define incident vertebral deformities, but these were not included in this analysis. Information on all clinical fractures was used for this report. In addition, fractures considered to be due to osteoporosis were analysed, and finally hip fracture alone was considered separately. An osteoporotic fracture was one considered to be due to osteoporosis by the investigator. For the EVOS/EPOS study, osteoporotic fractures comprised hip, forearm, humeral or spine fractures. For the CaMos study they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip. In the other cohorts (Sheffield, Rotterdam, Rochester, Gothenburg, DOES) fractures at sites considered to be characteristic for osteoporosis[233] were extracted.

Statistical methods

The risk of fracture was estimated by Poisson regression applied to each cohort and each sex separately. Covariates included time since start of follow-up, current age, corticosteroids and BMD. We additionally excluded BMD from the model and in further analyses included a history of previous fragility fracture and rheumatoid arthritis. The β coefficients for each sex and each cohort are a linear function of age, $\beta_k + \beta_{k+1}$ age. The estimated value of the β coefficients and their variance were determined for each age from the

TABLE 23 *Details of patients studied and fracture outcomes*[23]

Study	Age		Corticosteroid use (%)	Number of fractures			Prior fractures (%)
	Mean (years)	Range (years)		Hip	Osteoporotic	Any	
Men							
EVOS/EPOS	65	43–95	3.6	16	202	202	40
CaMoS	60	25–97	2.8	9	59	124	50
Rotterdam	68	55–98	2.2	61	146	201	11
Rochester	55	23–90	2.3	0	25	38	18
DOES	70	60–92	6.0	21	90	116	–
Sheffield	–	–	–	–	–	–	–
Gothenburg	–	–	–	–	–	–	–
Women							
EVOS/EPOS	64	41–93	5.9	23	486	486	32
CaMoS	63	25–103	5.3	33	258	461	41
Rotterdam	72	55–106	1.9	223	621	788	16
Rochester	58	21–94	3.5	42	219	251	18
DOES	71	57–96	6.0	64	211	289	–
Sheffield	80	74–96	9.2	62	242	291	51
Gothenburg	59	21–89	3.8	29	308	435	18

Reproduced from Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Melton LJ III, *et al*. *J Bone Miner Res* 2004;**19**:893–9, *Table 2*, p. 896.

age of 50–85 years. The results for each cohort and the two sexes were weighted according to the variance and merged to determine the weighted mean and SD. The risk ratio of those ever treated with glucocorticoids versus those not treated was equal to e^{mean}.

Results

The total sample studied was 42,542 men and women followed for 176,286 person-years. During this time there were 3682 fractures, 2867 fractures thought to be related to osteoporosis including 583 hip fractures. Details by cohort are given in *Table 23*. BMD measurements were available for 72% of individuals.

The exposure to the ever use of glucocorticoids increased almost linearly with age from 3.0% at the age of 30 years, to 3.7% at the age of 50 years and up to 5.2% at the age of 80 years.

The ever use of glucocorticoids was associated with a significantly increased risk of any fracture at all ages compared with those with no history of corticosteroid use (*Table 24*). This increase in risk ratio was not explained by differences in BMD. For example, at the age of 50 years the RR was 1.98 compared with an individual never treated with glucocorticoids but with the same BMD and was 1.99 without BMD in the model. The RR ranged from 1.98 at the age of 50 years to 1.66 at the age of 85 years and the increase in RR was most marked at ages younger than 65 years. There was, however, no statistical difference in RR by age, or between men and women.

For osteoporotic fracture, risk ratios were higher than those for all fractures combined (see *Table 24*). As in the case of all fractures, RR was higher at younger ages, but not significantly so, nor was there a significant difference in relative risk between men and women. There was a small increase in RR by the exclusion of BMD from the model, but the quantitative effect was small, the RR at 50 years being 2.54 and 2.63, respectively.

The highest gradients of risk were observed for hip fracture (see *Table 24*). The risk ratios ranged between 2.13 and 4.42, depending on age. As in the case of osteoporotic fractures, the RR was higher in the younger ages, but not significantly so. Also, there was no significant difference between men and women. When BMD was excluded from the model, the risk ratio was lower up to the age of 75 years.

A summary of the RRs over all ages is also given in *Table 24*. Computed from the entire database, the risk relative to the population was calculated from these RRs and the prevalence of prior exposure to glucocorticoids. Since the exposure to glucocorticoids in the population was low, downward adjustment of the RRs was small.

TABLE 24 *Risk ratio of any fracture and 95% CIs associated with ever use of glucocorticoids according to age and adjusted for BMD*[23]

Age (years)	Any fracture		Osteoporotic fracture		Hip fracture	
	Risk ratio[a]	95% CI	Risk ratio	95% CI	Risk ratio	95% CI
50	1.98	1.35 to 2.92	2.63	1.68 to 4.13	4.42	1.26 to 15.49
55	1.83	1.35 to 2.47	2.32	1.63 to 3.30	4.15	1.50 to 11.49
60	1.67	1.33 to 2.09	2.00	1.52 to 2.62	3.71	1.67 to 8.23
65	1.56	1.29 to 1.88	1.81	1.43 to 2.27	2.98	1.55 to 5.74
70	1.55	1.30 to 1.86	1.76	1.42 to 2.19	2.44	1.37 to 4.36
75	1.64	1.37 to 1.97	1.70	1.36 to 2.11	2.22	1.35 to 3.63
80	1.62	1.31 to 2.00	1.59	1.26 to 2.02	2.13	1.39 to 3.27
85	1.66	1.26 to 2.17	1.71	1.29 to 2.28	2.48	1.58 to 3.89
All ages	1.57	1.37 to 1.80	1.66	1.42 to 1.92	2.25	1.60 to 3.15
All ages[b]	1.53		1.61		2.13	

[a] Ever use versus no use.
[b] Ever use versus population risk.
Reproduced from Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Melton LJ III, *et al*. *J Bone Miner Res* 2004;**19**:893–9, *Table 3*, p. 896.

TABLE 25 *BMD at the femoral neck according to use of corticosteroids*[23]

Study	Parameter	Use of corticosteroids			
		Never	Past	Ever	Current
Rotterdam	Sample size		5665		116
	Age (years)[a]		70.3 ± 9.6		69.7 ± 9.6
	BMD (g/cm^2)		0.84 ± 0.14		0.80 ± 0.12[b]
Sheffield	Sample size	1942		137	64
	Age (years)[a]	80.0 ± 3.9		79.5 ± 3.7	79.6 ± 3.3
	BMD (g/cm^2)	0.65 ± 0.12		0.64 ± 0.13	0.62 ± 0.10[c]
DOES	Sample size	1980		24	56
	Age (years)[a]	70.7 ± 7.2		71.1 ± 7.4	70.0 ± 5.5
	BMD (g/cm^2)	0.83 ± 0.15		0.78 ± 0.13	0.77 ± 0.15[d]

[a] Age in individuals where use is documented.
[b] $p < 0.01$ compared with past use.
[c] $p < 0.05$ compared with never use.
[d] $p < 0.01$ compared with never use.
Reproduced from Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Melton LJ III, *et al*. *J Bone Miner Res* 2004;**19**:893–9, *Table 5*, p. 897.

The exclusion of the Gothenburg cohort in whom BMD was assessed at the forearm made no difference to the overall conclusions (data not shown).

Current use of glucocorticoids was documented in cohorts from Rotterdam, Dubbo and Sheffield. BMD at the femoral neck was lower in current users of glucocorticoids, but the effect was small (*Table 25*).

In a further model, age, glucocorticoid use and prior fracture were examined. Exposure to glucocorticoids was associated with a significantly increased risk of any fracture, an osteoporotic fracture and a hip fracture (*Table 26*). Prior fracture was also associated with an independent risk. There was no significant difference in risk between men and women. Rheumatoid arthritis, documented in three cohorts when current glucocorticoid use was recorded (CaMoS, DOES, Sheffield), was given as a reason for glucocorticoid use in 14%. In a further model there was an independent fracture risk of glucocorticoid use adjusted for rheumatoid arthritis for any fracture (RR 1.68; 95% CI 1.40 to 2.01), for osteoporotic fracture (RR 1.80; 95%

TABLE 26 *Independent risk ratio (with 95% CI) of ever use of corticosteroids and prior fracture according to type of fracture and gender*[23]

Fracture type	Gender	Corticosteroid use	Prior fracture
Any fracture	M	1.67 (1.10 to 2.51)	1.68 (1.39 to 2.02)
	F	1.39 (1.18 to 1.64)	1.71 (1.58 to 1.86)
Osteoporotic fracture	M	2.16 (1.42 to 3.27)	1.68 (1.35 to 2.08)
	F	1.42 (1.18 to 1.70)	1.72 (1.57 to 1.89)
Hip fracture	M	2.62 (0.91 to 7.51)	1.69 (0.98 to 2.94)
	F	2.07 (1.38 to 3.10)	1.66 (1.33 to 2.06)

Reproduced from Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Melton LJ III, *et al*. *J Bone Miner Res* 2004;**19**:893–9, *Table 5*.

CI 1.47 to 2.20) and for hip fracture (RR 2.30; 95% CI 1.50 to 3.55). Conversely, rheumatoid arthritis was associated with a significant risk of any fracture (RR 1.45; 95% CI 1.16 to 1.80), osteoporotic fracture (RR 1.56; 95% CI 1.20 to 2.02) and hip fracture (RR 1.95; 95% CI 1.11 to 3.42). The risk persisted after adjustment for glucocorticoid use in the case of any fracture (RR 1.38; 95% CI 1.11 to 1.72) and osteoporotic fracture (RR 1.46; 95% CI 1.12 to 1.90), but was of borderline significance for hip fracture (RR 1.76; 95% CI 0.97 to 3.19; $p = 0.06$).

Discussion

The principal finding of the present study undertaken in large and internationally drawn population-based cohorts is that prior glucocorticoid use confers a substantial increase in fracture risk, as has been shown in a large UK study based in general practice.[20] The present study additionally demonstrates that this risk is largely independent of BMD or a prior fragility fracture. A strength of the present study is that the estimate of risk is derived from several studies in an international setting from population-based cohorts. The use of primary data from population studies decreases the risk of publication bias. As expected, the risk was higher for osteoporotic fractures than for all fractures, and higher still for hip fracture alone. No significant differences were found in the increase in fracture risk between men and women, nor a significant difference in risk with age, but the estimated dependence of age is substantial (see *Table 24)* as reported for BMD.[277] Much larger samples would be required to verify this.

The mechanism for the BMD-independent increase in risk could not be determined from this study, but could be due, at least in part, to the nature of the underlying diseases for which glucocorticoids were prescribed. In the cohorts in which this could be examined, rheumatoid arthritis was associated with an independent risk of fracture which persisted when adjusted for glucocorticoid use. There was, however, an adverse effect of glucocorticoid treatment even when adjusted for rheumatoid arthritis. Adverse effects of glucocorticoids on muscle strength and metabolism may also have increased the liability of falling and or impaired protective responses to falling, and thereby increased fracture risk. A further possibility is the effects of these agents on skeletal architecture, which appears to differ from the effects of gonadal deficiency at sites of cancellous bone.[47,278] It is also suggested that glucocorticoids affect osteocyte viability[279] and therefore might induce alterations in the material properties of bone.

Irrespective of the mechanism, these data indicate that the risk of all fractures is substantially greater in GIO than in postmenopausal osteoporosis for the same level of BMD. For all osteoporotic fractures, the increase in risk ratio was 1.66, downward adjusted to 1.61 to a population RR, and for hip fracture, the adjusted RR was 2.13, and these were used to compute fracture risk. Similar findings have been described recently for vertebral fracture risk.[280]

In an earlier example, hip fracture risk was estimated at 1.50% in a woman aged 70 years with a *T*-score of –2.5 SD and a prior spine fracture. The same woman exposed to glucocorticoids would have a risk of hip fracture of $1.50 \times 2.13 = 3.45\%$. For a prior spine, forearm or humeral fracture, an RR of 1.61 was used although it should be acknowledged that risk ratios were not obtained for different sites of prior fracture.

The present study has other limitations that should be mentioned. The greatest problem is the construct of the question concerning glucocorticoid

use and the documentation on characterisation of fracture events. These differed substantially between cohorts. The effect of this heterogeneity is likely to weaken rather than strengthen the association that we found. In addition, the majority of cohorts did not document the current use of oral glucocorticoids. Since BMD may recover somewhat when glucocorticoids are stopped, this is likely to explain the modest adjustment of the risks by including BMD in the models. This might substantially underestimate the risk ratio associated with current glucocorticoid use. These limitations indicate the need for further prospective data to characterise more accurately the risk of current use.

It was concluded that every use of glucocorticoids confers a substantial risk for future fractures and that this risk is largely independent of BMD. The consistency of the association in an international setting provides the rationale for the use of this risk factor in case-finding strategies. Moreover, patients identified can be targeted for treatment at lower BMD thresholds than individuals of the same age with osteoporosis due to gonadal deficiency.

For the purposes of modelling, the age-specific data given in *Table 24* were utilised. The risk ratios for osteoporotic fracture were applied to fractures of the forearm and proximal humerus. The risk ratios for hip fracture outcome were applied for hip fracture. In the absence of risk ratios for vertebral fracture, the authors applied those found at the hip since the available data, including data from the UK,[21] indicate that risk ratios for vertebral fractures are higher than for non-vertebral fractures (see *Table 2*, Chapter 1).

Consequences of fracture

There is little information on the consequences of fracture due to treatment with glucocorticoids. For the purposes of this report, the base-case assumption was made that the consequences in terms of death, health stage values and costs are the same as those seen in postmenopausal osteoporosis. Thus, no account is taken of the coexisting morbidity of the underlying disorder for which corticosteroids are given. This deficit cannot be resolved in the absence of adequate prospective studies, so that any basis for making adjustments is lacking.

The consequences of osteoporosis have been extensively reviewed in an earlier Health Technology Assessment (HTA) report[80] and are summarised briefly below, noting where further information is available that gives rise to a change in the assumptions made.

Death due to a hip fracture

Excess mortality is well described after hip fracture. In the first year following hip fracture, mortality risk varies in women from 2.0 to greater than 10 depending on age.[249,281,282] It classically follows a biphasic pattern with a sharp increase in the 6 months to 1 year after the event and thereafter decreases but remains higher than that of the general population.[283] Mortality rates after hip fracture appear to have remained constant over the past 20 years.[281] Since hip fracture patients have high coexisting morbidity, poor prefracture health is likely to contribute to the excess mortality. Case–control studies adjusting for prefracture morbidity indicate that a substantial component can be attributed to co-morbidity.[284,285] Irrespective of the attribution, it is not possible to determine the quantum of excess mortality that would be avoided in the absence of hip fracture. It can be argued that the acute increment in mortality over the first 6 months is reversible by avoiding fracture. During this period, excess mortality risk is estimated at 3.35 (95% CI 1.50 to 7.47) compared with a subsequent risk of 1.30 (95% CI 0.85 to 1.98).[284]

In a large study of 160,000 hip fracture cases in 28.8 million hospital person-years, the risk of death of those with a somewhat earlier hip fracture was compared with the risk of death in individuals of the same age with a later hip fracture. Two individuals of the same age, but with a different time interval between their fractures, had an equal mortality provided that the time interval between the two fractures exceeded 1 year. The difference in mortality of less than 1 year can be ascribed to causally related deaths, that is, the death would have been avoided had the hip fracture not occurred. The analysis suggests that 24% of all deaths might be causally related to the hip fracture itself[286] (*Table 27*) and was used for this analysis.

A review of case-notes by Parker and Anand[283] estimate that 33% of deaths after hip fracture were totally unrelated to the hip fracture, 42% possibly related and 25% directly related. These figures were not, however, stratified by age or sex and causality is based on opinion. Extrapolation of the data to 1 year suggests that 48% of all deaths may be related to the hip fracture event,[80] and this figure was used in sensitivity analysis.

TABLE 27 *Deaths (rate/1000/year) in men and women in the general Swedish population and following hip fracture*[286]

Age (years)	Deaths in men			Deaths in women		
	Population	Associated with hip fracture	Due to hip fracture	Population	Associated with hip fracture	Due to hip fracture
60	7.9	0.1	0.0	4.6	0.1	0.0
65	14.3	0.3	0.1	7.8	0.3	0.1
70	25.9	0.8	0.2	13.4	0.7	0.1
75	42.9	2.0	0.5	24.5	1.8	0.4
80	71.3	4.7	1.1	44.7	3.9	0.8
85	118.5	10.1	2.6	81.6	8.4	2.1
90	196.8	21.0	6.3	149.0	17.0	5.4

Reproduced from Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. *Bone* 2003;**32**:468–73, *Table 3*, p. 471.

In patients discharged to nursing homes, death rates were assumed to be approximately 2-fold higher than those discharged home.[80]

First entry to nursing home following a hip fracture

The proportion of patients who enter nursing homes after hip fracture is age dependent.[287–289] In a small but well-studied group of patients from Sweden, the admission rate to nursing homes in patients admitted to hospital from home was 6.7, 6.5, 10.2 and 14.7% at the ages of 50–59, 60–69, 70–79 and 80–89 years, respectively. These values are consistent with estimates from Scotland,[288] although higher than those given in the East Anglian audit.[289] The latter may be underestimated since patients who initially return to the community, but enter a nursing home thereafter are not counted. The percentage of hip fractures that resulted in a first admission to a nursing home were 4% for those aged 60–79 years, 12% for those aged 80–89 years and 17% for those aged 90 years and over. The latter rates were used as the base case, but examined the effects of using the Swedish rates in a sensitivity analysis.

Death due to vertebral fracture

Several studies have shown an increase in mortality following vertebral fracture.[290,291] In one study, women with one or more vertebral fractures had a 1.23-fold greater age-adjusted mortality rate (95% CI 1.10 to 1.37). Unlike for hip fracture, there was no acute excess documented.[290,291] It is notable that low BMD is also associated with excess mortality,[270,292] but the degree of increased mortality after vertebral fracture is greater than that expected from low BMD.

These studies used morphometric rather than clinical definitions of vertebral fracture. In contrast, other studies that examine mortality after vertebral fracture using clinical criteria have shown more marked increases in mortality.[293–295] In one study in Australia, vertebral fractures in women were associated with an age-standardised risk of 1.92 (95% CI 1.70 to 2.14),[293] and in another study, the risk was more than 8-fold higher.[294] A study on clinical fractures in the UK compared mortality in patients with osteoporosis (and no fracture) with mortality in women with established vertebral osteoporosis.[296] The hazard ratio was 4.4 (95% CI 1.85 to 10.6) and was used for the present model. Although mortality amongst men after vertebral fracture is higher than that amongst women,[295] the risk ratio is similar and the same hazard ratio was used in men as that used for women (*Table 28*).

Unlike for morphometric deformities, the pattern of mortality after clinical vertebral fracture is non-linear, suggesting, as is the case for hip fracture, that a fraction of deaths would not have occurred in the absence of a fracture. Using the patient register for hospital admissions in Sweden, 28% of all deaths associated with vertebral fracture were judged to be causally related[297] (*Table 29*).

Death due other fractures

It was assumed no increase in mortality from forearm fractures, consistent with published surveys.[291,293–295] For humeral fractures, it was conservatively assumed a 2-fold increase in mortality (see *Table 28*) and that 28% of deaths associated with humeral fractures are causally related.

Death due to other causes

Interim life tables were used.[298]

Several studies have shown an increased mortality associated with low BMD of similar magnitude derived from measurements at the radius or

TABLE 28 *Mortality (rate/1000) in the years following fracture in men and women aged 60 years*[295]

Year after fracture	General population	Spine		Hip		Shoulder		Forearm	
		Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
Men									
0	9.2	123	95 to 160	107	82 to 139	43	22 to 86	11	6 to 19
1	10.1	108	85 to 138	103	80 to 131	41	22 to 77	12	7 to 20
2	11.2	95	75 to 121	98	77 to 126	38	20 to 72	13	7 to 22
3	12.3	84	65 to 108	94	73 to 121	36	19 to 69	14	8 to 24
4	13.5	73	55 to 98	90	69 to 119	34	16 to 69	16	9 to 28
5	14.9	64	46 to 90[a]	87	64 to 117	32	14 to 71	17	9 to 33
Women									
0	5.1	66	50 to 86	53	40 to 70	16	8 to 32	9	5 to 16
1	5.6	58	45 to 73	51	40 to 66	15	8 to 29	10	6 to 17
2	6.1	51	40 to 64	49	38 to 63	14	7 to 26	11	7 to 18
3	6.7	44	35 to 57	47	36 to 61	13	7 to 25	12	8 to 20
4	7.3	39	29 to 52	45	34 to 59	12	6 to 25	14	8 to 23
5	8.0	34	25 to 47[a]	43	32 to 58	11	5 to 25	15	8 to 27

[a] Significantly different from time 0.
Reproduced from Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, *et al*. *Osteoporos Int* 2004; **15**:38–42, *Table 3*.

TABLE 29 *Deaths (rate/1000/year) in men and women in the general Swedish population and following hospitalisation for vertebral fracture*[297]

Age (years)	Deaths in men (/1000)			Deaths in women (/1000)		
	Population	Associated with vertebral fracture	Due to vertebral fracture	Population	Associated with vertebral fracture	Due to vertebral fracture
60	7.93	0.01	0.00	4.56	0.01	0.00
65	14.32	0.01	0.00	7.82	0.03	0.00
70	25.86	0.03	0.01	13.42	0.08	0.01
75	42.94	0.07	0.03	24.49	0.23	0.02
80	71.33	0.13	0.06	44.72	0.51	0.04
85	118.48	0.23	0.13	81.63	0.93	0.09
90	196.79	0.34	0.28	149.02	1.60	0.19

Reproduced from Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. *Osteoporos Int* 2004;**15**:108–12, *Table 3*.

heel.[270,292] At the radius, the increase in RR was 1.22 per SD decrease in BMD adjusted for age,[292] and this factor has been used within the model. Where a patient dies from other causes, the costs and quality-adjusted life-years (QALYs) from the previous year are halved for the year in which the patient dies.

It was assumed that interventions that increase the BMD of a patient would not change the risk of death due to a low *T*-score.

In the base case, it was assumed that mortality of patients taking glucocorticoids was the same as that for the general population. Mortality is, however, increased in individuals taking glucocorticoids, most likely related to co-morbidity. The effect of glucocorticoid on the death hazard was examined in the meta-analysis of the effects of glucocorticoids on fracture risk described earlier in this chapter. The death risk was significantly increased in patients taking corticosteroids (RR 1.28; 95% CI 1.03 to 1.59) and was the assumption used in a sensitivity analysis.

Health state utility values

The health states used in the model include healthy individuals, patients on long-term

TABLE 30 *Health state utility values according to site of fracture for women*[243]

Fracture type	Utility in 1st year following fracture	Utility in 2nd year following fracture
Spine (clinical)	0.626	0.909
Hip	0.792	0.813
Forearm	0.977	0.999
Humerus	0.794	0.973
Pelvis	0.794	0.815
Other femoral	0.792	0.813
Tibia	0.794	0.929
Clavicle, scapula and sternum	0.977	0.999
Ribs	0.977	0.999

Reproduced from Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, De Laet C, *et al*. *Osteoporos Int* 2004;**15**:20–6, *Table 1*.

glucocorticoids with or without osteoporosis, and established osteoporosis with hip, vertebral, wrist, or proximal humerus fracture. Previous economic evaluations of the prevention and treatment of osteoporosis have relied on the use of assumptions or judgements obtained from expert panels such as the review undertaken by the National Osteoporosis Foundation (NOF),[89] rather than to use empirical evidence to value these health states. This has been recognised as one of the main weaknesses of work in this area.[299,300] Recently, there have been a number of studies eliciting health state valuations for many of these states using recognised preference-based measures of health-related quality of life [such as the EuroQol-5 instrument (EQ-5D) or Health Utility Index (HUI)-III] or direct preference elicitation techniques such as time trade-off or standard gamble. These have been recently reviewed,[80,301] but are updated by more recent empirical observations.[243]

Normative health state value data by age group for the UK for men and women were taken from Kind and colleagues.[302] These values were obtained from the EQ-5D being administered to over 3000 representative members of the UK general population.

Table 30 gives the health state values following fractures that were used in this report. The multiplier for hip fracture differs from that published previously[80,301] due to the recent availability of empirical data.[243] The multiplier for hip fracture (0.79 in the first year) is marginally higher than that used previously (0.80). As used previously, we assumed a utility of 0.4 for patients admitted to nursing homes.[89]

The revised estimates for vertebral fracture indicate a greater loss of utility than previously assumed by ourselves and the NOF,[80,89,301] but accord with recent empirical estimates[243,303–306] that included patients taking glucocorticoids for rheumatoid arthritis.[305] The most recent empirical estimates in patients studied prospectively give a utility multiplier of 0.626 in the first year and 0.909 in the second year,[243] and were used in this report.

There is a marked difference in the multiplier used for vertebral fracture from that used previously by ourselves (formerly 0.91). The earlier value was based on a study that compared health state values with EQ-5D in cases and in controls, but no account was taken of the time since fracture.[307] In addition, the majority of fractures were likely to be diagnosed by vertebral morphometry rather than present with current clinical symptoms.

On the advice of the clinical collaborators, it had been assumed previously that a fracture of the proximal humerus has the same impact on health status as a wrist fracture. More recent estimates[243] give a multiplier of 0.794 in the first year and 0.973 subsequently.

The multipliers given in *Table 30* were assumed to be the same in men and women, but applied to age- and sex-specific normative health state values.

Costs

The model developed for this report requires cost estimates for the health states associated with established osteoporosis, the treatment costs for the drugs under review and the adverse drug reactions from these treatments. Costing is required for the following health states:

- hip fracture
- confinement to nursing home due to hip fracture
- death due to hip fracture
- vertebral fracture
- wrist fracture
- other fractures
- additional 'healthy' life-years.

The model also requires that costs be disaggregated into year of incidence and subsequent year costs, and that costs be weighted for age. The model potentially requires that costs be estimated for upwards of 120 variables. Ideally, costs would be estimated using prospective resource use data collected alongside an appropriate UK-based randomised trial.

Where appropriate, costing took an NHS and social care perspective. Patient costs and indirect costs on the economy were not considered. In the analyses presented below, costs are quoted using financial year currencies presented in the original sources. For modelling purposes, the derived costs estimates were all inflated to 2004–5 financial year prices using the Health and Community Health Services (HCHS) pay and prices index.[308]

Intervention costs

The estimated annual drug cost for risedronate is £264, as given in the BNF (2006). Monitoring costs included annual costs of two physician visits (£40)[308] and a BMD measurement (£35).[309]

Fracture costs

Dolan and Torgerson[310] presented detailed costings for hip, vertebral, wrist and 'other' fractures. They estimated costs by analysing resource use. Since then, several reports have been published which suggest that these costs have been underestimated.

The cost of hip fractures given by Dolan and Torgerson,[310] was estimated at £4808, based on two studies undertaken more than 10 years ago.[311,312] Later publications demonstrate higher costs. A survey in Nottingham[313] estimated the acute hospital costs of hip fracture at £12,163 (2003 costs) for an average length of stay (LOS) of 23 days. Swedish data show that inpatient care accounts for 64% of the direct costs in the first year,[306] which if applied to the estimate from Nottingham would increase the total direct costs to approximately £19,000.

Recent publications suggest that the costs of vertebral fracture are also underestimated. Dolan and Torgerson[310] estimated an annual cost of £492 (1995–6) per patient for the year of fracture, downward adjusted to £428 when account is taken of the cost of bone active medications. By contrast, Puffer and colleagues[314] estimated the direct costs of a vertebral fracture at £2613 in the UK. In a European-wide study, the acute costs for hospitalised vertebral fracture, estimated on the basis of LOS, represented 63% of the average cost of hip fracture.[315] In another study in Sweden, the direct cost of vertebral fracture was 87% of that of a hip fracture.[306] If such data were applied to the figures from Nottingham, this would imply a cost for a hospitalised vertebral fracture in excess of £10,000.

These various estimates used different methodologies and assumptions. For this reason, costs were recomputed using a more consistent approach. The general approach was based on information on LOS and the proportion of fracture cases admitted to hospital.

The cost of an orthopaedic bed-day in England and Wales is unknown. The cost of a bed-day for elderly patients is given as £159.[308] From Swedish data, the cost of an orthopaedic bed is €700 per day, whereas a geriatric bed costs €374 per day.[306] If the same ratio is applied to the English data, the cost of an orthopaedic bed is estimated at £298 per day. This unit cost was used for all fracture types. Further research is necessary to establish whether this is true of fractures which receive little treatment, such as vertebral fracture.

With regard to LOS, the first step was to use Hospital Episode Statistics (HES) data for 2002–4. In some instances the HES data may be misleading since they cover all ages, rather than more elderly patients. In these circumstances, LOS data from Sweden[316] were used and comment made on the reasons for this in the text. Comparisons of the LOS for hip fracture in the UK and in Sweden (26 and 13 days, respectively) suggest that, where Swedish data are used to estimate length of stay, the costs produced are likely to be conservative.

It was assumed that following a fracture the same outpatient resources will be used regardless of whether a patient was hospitalised or not. These comprise costs for outpatient surgery, physician visits, nurse visits, physiotherapy, X-rays and home help. Using Swedish data,[306] the ratio of the bed-day cost for an average hospitalisation to the outpatient care costs was computed and it was assumed that this ratio was applicable to the UK.

TABLE 31 *Unit costs for fracture*

Age range (years)	Hip fracture (£)	Vertebral fracture (£)	Forearm fracture (£)	Proximal humerus fracture (£)
50–64	9,032	3,666	1,148	2,996
65–74	10,339	3,666	1,148	2,560
75–84	10,919	3,666	1,148	2,446
85+	15,672	3,666	1,148	2,350

These gave an additional 11, 9 and 31% cost for hip, vertebral and forearm fractures, respectively.

The costs for home help following a fracture will be heavily dependent on the health resources within a region and on whether the patient chooses to pay for their own help. Expert opinion [clinicians recommended by members of the Appraisal Committee for the National Institute for Health and Clinical Excellence (NICE) appraisal] has suggested that 2 hours per day for 8 weeks following a hip fracture would be a reasonable estimate. Similar resources are required for vertebral and wrist and proximal humerus fractures, where the dominant arm has been fractured. Assuming costs of £14 per hour for home care,[308] this would imply additional home help costs of £1568 for hip and vertebral fractures and £784 for wrist and proximal humerus fractures. An alternative source for the amount of home help required is from Sweden,[306] which estimates home help costs to be £1143, £1699 and £85 for hip, vertebral and wrist fractures, respectively. The latter estimates were used since they were collected empirically and are more conservative compared with expert opinion.

Where possible, data were used from the UK to estimate the proportion of fractures that require hospitalisation. Where these data were not available, the admission rate was estimated assuming that data from Sweden are applicable for the UK. Admission rates were calculated using data on incidence and Census data for 1996.[233,317] Where hospitalisation rates are known for the UK and Sweden, the Swedish value is typically lower, suggesting that the use of these data as a proxy is likely to be conservative.

Hip fracture

The cost of a 'hip fracture' integrated the cost of hip, pelvic and other femoral fractures.

The average length of stay from HES data for 2002–4 for fracture of the femur is 26.0 days. The mean length of stay for pelvis is not given by HES since it is combined with data for fractures of the lumbar spine (19.2 days), so that the LOS for pelvis fracture cannot be disentangled. Swedish data[317] indicate that the LOS for pelvic and other femoral fractures was 87 and 135% that of a hip fracture, respectively. However the ratio of the incidences of pelvis to other femoral is 25:17, so that the combined LOS is only slightly greater than that for hip fracture alone. Given the possibility of the inclusion of other femoral fractures within the HES data, it was assumed that the mean LOS for all hip, pelvis and other femoral fractures is 26 days.

Hence direct medical inpatient stay costs are estimated at 26 × £298 = £7748. Additional costs due to surgery, radiological tests and laboratory investigations amount to an estimated £1947 per patient,[313] giving a total direct medical cost of £9695 per patient.

Outpatient care for all patients with a hip fracture was computed at £1066 (£9695 × 11%), so that the total inpatient and outpatient cost was £10,761. Costs were weighted for age[306] as shown in *Table 31*.

Admission to a nursing home following a hip fracture

The cost of a nursing home is assumed to be approximately £24,000 per annum, although this varies with age. As previously reviewed, the nursing home admission rate was age dependent.

Vertebral fracture

The average LOS from HES data for 2003–4 for fractures for lumbar spine and pelvis combined is given as19.4 days, and for fractures of ribs, sternum and thoracic spine 11.1 days. The LOS in Sweden for these fractures is pelvis 11.9, spine 9.8 and ribs and sternum 5.9 days.[317] The numbers of fractures were pelvis 3246, spine 4737 and ribs and sternum 1911. Given these relative incidences and LOSs, the mean LOS for all 'vertebral' fractures in the UK was assumed to be 15 days.

On this basis, direct medical inpatient stay costs were 15 × £298 = £4470 per hospitalised vertebral

fracture. Assuming that outpatient care is equal to 9% of direct medical costs,[306] this gives an estimated total cost of vertebral fracture of £402 per patient with a vertebral fracture. Hence a hospitalised fracture is estimated to cost £4872 and a non-hospitalised fracture £402.

A minority of patients with vertebral fractures are hospitalised. An estimate from the Trent region suggested that about 10% of patients with vertebral fractures, as judged by vertebral morphometry, were admitted to hospital.[238] In women from Sweden and in women enrolled into multinational trials, approximately 23% of incident vertebral fractures shown by vertebral morphometry come to clinical attention.[242,243] These data indicate that 35–45% of patients with clinical vertebral fractures are hospitalised. For the purposes of this report, it is assumed that 35% of patients with clinical vertebral fractures are hospitalised, giving a weighted cost per clinical fracture of £1967. An additional ongoing cost of £222 per annum for analgesic drugs was also included.

Admission to a nursing home following a hospitalised vertebral fracture

Data on nursing home admissions following a vertebral fracture are not available from the UK and Swedish estimates were used.[306] This assumed that 0.5% of patients with a clinical vertebral fracture were admitted to a nursing home between the ages of 50 and 59 years. The admission rate varied with age decade (0.4, 1.1 and 3.3% for the age groups 60–69, 70–79 and 80–89 years, respectively). The additional annual costs of a vertebral fracture that would be needed to approximate nursing home costs was estimated £126, £84, £262 and £794, for each decade of age, respectively.

Forearm fracture

This fracture state included forearm, rib, sternal, scapular and clavicular fractures. It was assumed that these bear the same costs as a forearm fracture.

The average LOS from HES data for 2003–4 for fractures of forearm is 3.7 days. However, this includes a large number of children, who are likely to have a shorter LOS. Therefore Swedish data in women aged 50 years or more were used, which was 5.4 days for forearm fracture.[317] Fractures at other sites required a longer hospital stay (rib and sternum = 6.4 days; scapula = 6.3 days and clavicle = 9.7 days). However, an LOS of 5.4 days for all 'wrist' fractures was assumed.

Given these assumptions, the direct medical inpatient stay costs was 5.4 × £298 = £1609 per hospitalised 'wrist' fracture. Outpatient care costs are assumed to be 31% that of inpatient costs (£499). Hence a hospitalised fracture costs £2108 and a non-hospitalised fracture costs £499. From a study in the Trent region,[238] it is expected that 25% of wrist fractures are hospitalised, giving an average inpatient cost of £364 for a wrist fracture.

The 25% admission rate from Kanis and Pitt[238] is broadly similar to that of 22% calculated from Swedish data for hospitalisation following forearm fracture.[233,317] The hospitalisation rates following fracture at the ribs, scapula and sternum are lower at 7% and this cost may be slightly overestimated due to these fracture types being grouped with wrist fractures. However, the conservative assumption regarding the LOS following these fractures redresses this to some degree.

Proximal humerus fractures

This fracture state also includes fractures of the humeral shaft, tibia and fibula.

The average LOS from HES data for 2003–4 for fractures at the shoulder and upper arm is 9.1 days and for fractures of the lower leg 10.2 days. The HES category is not appropriate to use since it incorporates minor fractures, such as scapular and ankle fractures, and also because the LOS is likely to be age related. For this reason, Swedish data were used, which, as noted earlier, are likely to be conservative. This estimated an LOS of 10.6 days for humeral and 13.1 days for tibia and fibula fractures,[317] which are associated with costs of £3159 and £3904, respectively. It was also assumed that the proportion of inpatient costs associated with outpatient care is 10% (the midpoint for hip and vertebral fracture), giving a cost of £316 and £390, respectively.

From Swedish data, it is estimated that 32% of patients with fractures at the proximal humerus and 90% of those with fractures at the tibia and fibula are hospitalised.

The relative incidence of fracture type by age was used to calculate costs at each age group. Due to the relatively higher proportion of tibial and fibular fractures at younger ages, the weighted cost is higher in the 50–59 year age band.

As there were no primary data on the amount of home help required following a 'proximal humerus' fracture, this was assumed to be £784, which was the UK estimate for a proximal humerus fracture.

Chapter 5

Health economics model

Information on the effectiveness of interventions and the risk functions, health states and costs were used to populate a cost–utility health economic model termed the Sheffield Health Economic Model for Osteoporosis (SHEMO). This chapter describes the principles of the model and its inherent assumptions.

Model approach

The approaches used previously were based on cohort analyses using decision analysis and Markov models.[317,318] The present model is an individual patient-based transition-state osteoporosis model created in Excel 2000.[80,319] Patients are modelled as individual cases to determine whether or not an event occurs in the forthcoming year. The full patient history is recorded and factors such as prior fractures and current residential status can be used, therefore, to determine the likelihood of events in successive periods. Following the simulated event, the quality of life of the patient and costs incurred are calculated. Both of these factors take into account any residual costs and quality of life impacts from previous fractures. The model simulates at 1-year intervals until either the patient dies or a user-defined analysis period (e.g. 10 years) has been reached. This process is repeated until all patients have been simulated. A mean estimate is then taken of costs, mortality and QALYs for the cohort. The rationale for using the individual patient approach is that it provides greater accuracy and flexibility than a cohort approach, which is bounded by a limited number of transition states.[319]

An alternative manner in which all data can be taken into consideration is by the use of a decision tree. If a simple model with only four transition states is assumed (no fracture event, hip fracture, vertebral fracture and wrist fracture), the tree would have 4^{10} branches in a 10-year period in order that all conceivable combinations of events are recorded. This totals over 1 million branches at year 10. Clearly, this number would be greatly increased with the addition of extra states (breast cancer, other fracture states) and would need to be duplicated with the tracking of residential status (community or nursing home). To replicate the model using a decision tree format would require over 1 billion branches to maintain the accuracy of the patient-based approach. This is clearly an unmanageable number of branches.

SHEMO differs in a second way from cohort Markov models in that it is stochastic and therefore can incorporate uncertainties underlying key parameters. The obvious example of relevance to systematic reviews of efficacy is the uncertainty in the point estimate. The model works by undertaking the individual level simulations in cohorts and for each cohort the RRs are resampled from the distribution of efficacy using Monte Carlo simulation.

The process of estimation is broken down into two parts. The first phase is concerned with estimating the relationship between the inputs of the model and the outputs in terms of costs and QALYs. To do this, approximately 200 different combinations of the values of the RRs of each clinical condition were selected at each age group. For each combination, at least 8000 patients were simulated to give mean costs and QALY estimates. By undertaking runs that simulate large numbers of patients, it is possible to remove a large proportion of the noise. The relationship between these model inputs and costs and QALYs has been estimated using a non-parametric Gaussian process.[320,321] This effectively produces an equation that allows instant calculation of the expected QALY and costs for any parameter set.

The second phase of the estimation process involves examining the consequences of the uncertainty around the efficacy estimates for each treatment. For each treatment, 1000 values for efficacy of each type of fracture (and CHD and breast cancer for some treatments) are selected by Monte Carlo methods. From the 1000 sample of parameter points, the model formulated in phase one is used to generate 1000 cost and QALY estimates. These form the basis for the estimated mean cost per QALY compared with no treatment and the associated CIs.

The mean cost per QALY is calculated as the mean cost difference divided by the mean QALY

difference for the 1000 points and no treatment. The CIs were calculated by ranking the cost per QALYs from each of the 1000 parameters and ascertaining the 95% CIs. As the results have been generated from an equation which incorporated any random noise from the individual patient model, any differences in the mean cost per QALY and the CIs between treatments are due solely to the RRs around efficacy.

The advantage of the Gaussian process technique is that given the same starting assumptions, the results for a new drug with defined RRs can be instantly calculated.

Overview of model

For the purpose of this report, the transition states between which patients can move were limited to fracture states (hip, wrist, vertebral, proximal humerus and death due to hip fracture) and death from other causes. The probability of a hip fracture causing a patient to reside in a nursing home was estimated, together with the annual costs incurred when this occurs.

The characteristics of the population to be analysed are flexible. The age, *T*-score and prior history of the population are all user defined. For this report, the focus was on those with individuals exposed to glucocorticoids with or without a defined *T*-score for BMD with or without a prior fragility fracture. For the purpose of this report, selected patient groups were chosen for analysis, for example, 60-year-olds having established osteoporosis and a *T*-score of –2.5 SD.

The basic probabilities for moving from transition state to transition state were taken from epidemiological data, where possible from the UK, and transformed where appropriate. The values of these adjustments were in accordance with rates reported in the literature.

Having established the transition probabilities, the model simulates the experiences of the cohort under no treatment. Outputs are the number of life-years gained, the number of QALYs gained, the discounted costs incurred and the number of each transition state events suffered.

As a patient moves into a transition state, there is an initial one-off cost incurred and an ongoing cost incurred that is assumed to last until the end of the simulation. By using such a methodology, states with high ongoing costs can be distinguished from those where the costs incurred are all in the initial year. In circumstances where a patient has already suffered the state before, it has been assumed that only the one-off costs will be incurred, with the ongoing costs from that state remaining constant. For example, if the consequences of a vertebral fracture comprised an initial cost of £2000 and a recurrent cost of £500/year, a further vertebral fracture in the same individual would cost a further £2000, but the recurrent costs would not increase from £500/year. This may underestimate the costs involved but, as mentioned, few data could be found on the additional ongoing costs of second events.

When a patient moves into a transition state, this affects the patient's quality of life. It has been assumed that there will be a QALY multiplier effect within the first year and a QALY ceiling multiplier that will last for the remaining years of the simulation. By using this methodology, states from which the patient will never fully recover can be modelled. It is assumed that when a patient suffers a transition state for a second or more time, only the initial year reduction in quality of life will be taken into consideration. It is noted that in some cases this will underestimate the loss in QALYs, for example second hip or wrist fractures on a different side than the first, or a second vertebral fracture. However, due to lack of data, the approach of assuming no extra residual QALY loss from a second incident was taken.

Having established a baseline 'no treatment' cost for the cohort, the incremental effects from pharmaceutical treatments were calculated.

The duration and the acquisition cost of each treatment are user definable. The efficacy of each treatment is modelled by the use of RRs in entering a transition state. It is expected that a cohort using a treatment with an RR of 0.5 for hip fracture would, in the next period, have half the number of hip fractures as the same cohort receiving no treatment (RR 1), assuming an equal death rate.

The RRs were meta-analysed for treatments from published RCTs with the number of fractures as an end-point. The effectiveness for each treatment has relatively large uncertainties. However, the meta-analyses provided distributions and 95% CIs.

In addition to the treatment RR, the model incorporates offset times, which are defined as the time from when the treatment is stopped to the time when the RR returns to 1 compared with no

treatment. It is assumed that the RR returns to 1 in a linear manner during the offset time.

Each treatment option was also assigned additional costs to drug acquisition, namely GP visits, assumed to be two per annum, and BMD scans, assumed to occur in year 2 and year 5 of treatment. In sensitivity analyses where treatment was given for 10 years, the second BMD scan was assumed to be at year 10. Lack of compliance was modelled assuming that the patient incurs 3 months of drug costs but receives no health benefits. It was assumed that for a year in which death occurred, the QALYs gained are half that for the previous year, that costs are incurred equal to half of the ongoing annual costs and that only half of the drug acquisition cost is paid.

A complex methodology for estimating the cost-effectiveness of each drug was employed, in order that a distinction be made between variations in the results due to the random events (premature death, etc.), and those variations caused by the uncertainties in the true RRs for the efficacy of each drug, as indicated by the 95% CIs.

Population of the model

Population start age

The model has the flexibility to allow the age of the cohort of patients to be set at yearly intervals between 45 and 109 years of age. For the purposes of this report, we chose patients from the ages of 50 to 80 years in 5-year age intervals.

Osteoporotic fracture

The present report considers fractures of the spine, hip and other femoral fractures, proximal humerus, distal forearm, ribs, pelvis, clavicle, scapula, sternum, tibia and fibula. A patient with established osteoporosis is defined as an individual with one or more of these fractures and a *T*-score at the femoral neck below the diagnostic threshold.

Distributions of fractures

The starting distribution between states for established osteoporosis was taken from the incidence of fracture presented in Chapter 4. For each year above the age of 50 years, the expected cumulative number of fractures per site was calculated. These were then proportioned to provide the percentages shown in *Table 32*. In women, for example, 8% of osteoporotic fractures up to the age of 50 years were hip fractures. This figure rose with age and hip fractures accounted for 21% of all osteoporotic fractures at the age of 80 years. Thus in each cohort of 100 individual patients at age 70 years, 11% are assumed to have had hip fractures, 19% vertebral fractures, 56% wrist fractures and 14% proximal humerus fractures.

This approach is likely to cause some bias due to patients with more than one prior osteoporotic fracture. For example, in an extreme case, where all 80-year-olds had one prior hip, vertebral, wrist and proximal humerus fracture, the starting distribution would be set with 25% for each fracture, despite 100% of people having sustained a hip fracture. The alternative strategy would be to compute probabilities of first and subsequent fractures – data that are not available for the UK. As mentioned, such probabilities would need to be adjusted for secular trends in mortality.

Initial BMD score of the population

The initial BMD in terms of a *T*-score can be user defined. Osteoporosis is defined as a *T*-score of –2.5 SD unless indicated otherwise.

TABLE 32 *Estimated starting distributions (%) of established osteoporosis at the ages shown*

Fracture site	Population age (years)			
	50	60	70	80
Men				
Hip	10	14	22	31
Vertebral	27	36	37	37
Wrist	48	33	24	19
Proximal humerus	15	18	18	13
Women				
Hip	8	8	11	21
Vertebral	31	22	19	22
Wrist	50	57	56	43
Proximal humerus	11	13	14	14

Discount rates
The discount rate for costs was set to 6% per annum, in accordance with published guidelines. The default discount rate for QALYs was set to 1.5% per annum.[322]

Default state transition probabilities

For this report, the model uses the following transition states:

1. osteoporotic (never previously been in any other state)
2. sustained a hip fracture
3. hip fracture and confined to nursing home
4. death due to a hip fracture
5. sustained a vertebral fracture
6. death due to vertebral fracture
7. sustained a wrist fracture
8. sustained a proximal humerus fracture
9. death due to other causes.

There is also a 'no event' state, which signifies that the patient did not have an event which would be associated with a change of state.

The model can accommodate 25 different states. Therefore conditions that are suspected, but currently unproven, to have RRs associated with osteoporosis treatments can be entered into a future model were new evidence to be obtained.

The model simulates each patient from entry into the model until death, age 110 years or a maximum period specified by the user. For the purpose of this report, the model used a time frame of 10 years, and 15 years in sensitivity analyses.

Each state is reviewed in Chapter 4 with details of the assumed probabilities of moving into that state. The probability of 'no event' is 1 minus the sum of probabilities for moving to all states. The states are summarised briefly below.

Osteoporotic
This state is reserved purely for those who have not suffered one of the remaining defined states. Hence the probability of moving into this state from any other is zero.

For patients in this state, the probability is equal to that of 'no event', signifying that the patient remains healthy osteoporotic. The focus of this report is on patients with established osteoporosis, so that this state was not populated in the model runs.

Fracture risks
The average population risks were adjusted for an osteoporotic population. The risk of fracture of the general population was adjusted from the known relationship between BMD and fracture risk assuming that BMD was measured at the femoral neck. The gradients of risk/SD decrease in BMD were taken from meta-analyses.[250,254]

The fracture risks were computed for individuals with any given *T*-score using these gradients and the pattern of change of BMD with age as described in Chapter 4. Fracture risks were further adjusted to accommodate the BMD-independent risk of the use of corticosteroids.

Death due to hip fracture
It is assumed that 24% of all deaths in the first year associated with hip fracture are causally related to the fracture, and would be avoided, therefore, by preventing hip fracture. The attributable fraction was changed in a sensitivity analysis for the reasons described in Chapter 4.

First entry to nursing home after hip fracture
Probabilities taken from the second Anglian audit of hip fracture were used as detailed in Chapter 4.[289]

Death due to vertebral fracture
It is assumed that 28% of all deaths in the first year associated with a clinical vertebral fracture are causally related to the fracture, and would be avoided by preventing vertebral fractures.

Death due to other fractures
A doubling of the mortality rate following a proximal humerus or tibial fracture was assumed. For other fractures, no excess mortality was assumed other than that accounted for by low BMD. Note that it is assumed that interventions which increase the BMD of a patient will not change the *T*-score (BMD) adjusted risk of death due to other causes.

Death due to other causes
These were computed from interim life tables and adjusted for deaths due to fracture. Note that excess mortality is assumed for low BMD.

Adjustments to the default transition probabilities

The model has the facility to allow prior patient states to influence the transition matrix. This is

needed since the risk of a second fracture is higher than the risk of an initial fracture.

Each state is summarised below, together with the transition probabilities that can be altered.

Osteoporotic
This state does not impact upon any transition probabilities.

All fracture states
A prior fracture substantially increases the risk of subsequent fractures. The meta-analysis of Klotzbeucher and colleagues[110] was used with some additional assumptions. It was assumed that future fractures at the proximal humerus are equivalent to future fractures that were in the non-spinal category. It was also assumed that proximal humerus had the predictive power equal to that of the 'other' category. All populations were assumed to be peri/postmenopausal. There have been no prior studies on the future effect that hip fractures have upon wrist fractures. As a conservative estimate, this risk was set at 1.4, equivalent to the lowest RR of all other fracture sites.

It is assumed that for individuals who have suffered fractures in two different sites only the greatest risk adjustment will be applied. For example, were a patient to have both a prior hip and wrist fracture; the RR adjustment for a vertebral fracture would be 2.5 (from the hip fracture) and that for a second wrist fracture would be 3.3 (from the wrist fracture).

Compliance
It is assumed, in consultation with clinicians that the patient, if non-compliant, will incur 3 months' drug intervention costs, but accrue no health benefit.

Treatment

For each therapeutic intervention, the efficacy was assumed to equal the estimate of the entire frequency distribution of relative risk derived by meta-analysis, as described in Chapter 3. The effect of treatment on fracture probability was instantaneous and persisted unchanged throughout the treatment period. It was assumed, therefore, that the effectiveness did not change with time. There is increasing evidence that anti-fracture efficacy is greater in the first year of treatment than thereafter and therefore the assumption of consistent risk reduction becomes unsafe the longer is the duration of treatment. This is one of the reasons for selecting a 5-year treatment which corresponds to the duration of exposure in RCTs, particularly those undertaken in the past 10 years.

The treatment effect is not bounded by the 95% CI, but the entire distribution of effect was included in the analysis. In other words, efficacy was assumed to vary in different cohorts according to the probability density. For some outcomes the 95% CI for efficacy exceeded one, for example the RR of non-vertebral fracture with risedronate. Since osteoporosis is a systemic disease and the risk of any fragility fracture at the spine, wrist, forearm or shoulder is increased in the presence of a prior fracture at any of these sites, the notion that hip fracture rates may be increased where RCT evidence suggests that other fragility fractures are significantly decreased is counter-intuitive. For the reasons discussed earlier, a major reason for the paucity of robust information on non-vertebral fracture risk relates to the regulatory framework, which does not encourage such studies for registration. For this reason, we set the RR at an absolute value of 1.0.

TABLE 33 *Efficacy of agents on fracture risk at the sites shown for the base case (A) and sensitivity analyses (B)*

		Spine fracture		Hip fracture		Forearm		Humerus	
Agent		**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Risedronate	A	0.33	0.14 to 0.80	1.0		1.0		1.0	
	B[a]	0.61	0.50 to 0.75	0.66	0.49 to 0.90	0.66	0.50 to 0.87	0.66	0.50 to 0.87
Bisphosphonates[b]	A	0.57	0.50 to 0.66	0.61	0.47 to 0.81	0.81	0.73 to 0.90	0.81	0.73 to 0.90

[a] Efficacy in postmenopausal osteoporosis.
[b] Aggregate of bisphosphonate data in postmenopausal osteoporosis.

When treatment was stopped, the effect of treatment was assumed to wane in a linear manner over time. The persistence of some therapeutic effect is well documented with some interventions (see Chapter 3). Offset time was assumed to be 5 years for all interventions. In other words, the fracture risk increased progressively after stopping treatment and at the end of the offset period was the same as that predicted in untreated individuals. Offset time was changed in sensitivity analyses.

Base-case assumptions and sensitivity analyses for efficacy are shown in *Table 33*.

The bisphosphonates have been shown to have side-effects. In most instances, the prevalence is not well documented and the consequences on quality of life expressed in utilities are not known (Chapter 3). Also, the impact of side-effects on compliance is conjectural. Adverse effects were not included in the analysis, although it should be recognised that even small gains or decrements in quality of life due to side-effects could have a marked impact on cost-effectiveness.

All analyses are based on a 10-year time frame unless stated otherwise, rather than over a lifetime. In the context of treatments that are currently developed for 3–5 years, 10-year intervals were considered to be more appropriate. They take account of the intervention period and also the offset time of therapeutic effect once treatment is stopped.[214] In addition, the predictive value of risk factors such as low BMD becomes less over intervals greater than 10 years.[323] A time frame of 15 years was used in sensitivity analysis to model a change in the assumption concerning offset time.

Chapter 6
Results

Analytical approach

The results for each modelling scenario are presented in terms of a central estimate of cost per QALY gained and a cumulative frequency distribution represented in the tables by CIs. Note that the CI is not the CI of the central estimate of cost-effectiveness, but the range of costs per QALY gained that is incurred in a given percentage of runs sampled over the range of efficacy for the intervention. An example is provided in *Figure 7*, which shows the cost-effectiveness ratio of a hypothetical agent in women aged 60 years. The mid-point estimate of cost-effectiveness was £22,557. Cost-effectiveness ratio varied from £13,562 to £546,604. In 90% of the estimates, the cost-effectiveness ratio lay between £17,362 and £40,779.[80]

In cases where the cost-effectiveness curve intersects the *y*-axis, the intercept denotes the proportion of estimates where treatment is dominant (i.e. cost savings with health benefits compared with no treatment). Where the curve does not reach 100%, the value on the *y*-axis denotes the proportion of estimates that are dominated (i.e. increasing costs and detrimental to health).

The treatment considered is confined to risedronate, since this was the sole agent identified with efficacy on fractures that is available for use in the UK. The data derived from the meta-analysis in glucocorticoid-induced osteoporosis were utilised as a test example of the direct empirical database. For the purposes of exploring case-finding strategies, the pooled bisphosphonate data were used as described in Chapter 3.

The cost for risedronate is £264 per annum and the same cost was assumed for other bisphosphonates.

For the base-case assumptions, costs were discounted at 6% and QALYs at 1.5% for each treatment. The total costs and QALYs are given for 100 patients and can be compared with those for untreated patients given in *Table 34* to derive the marginal costs and QALYs. Each treatment is

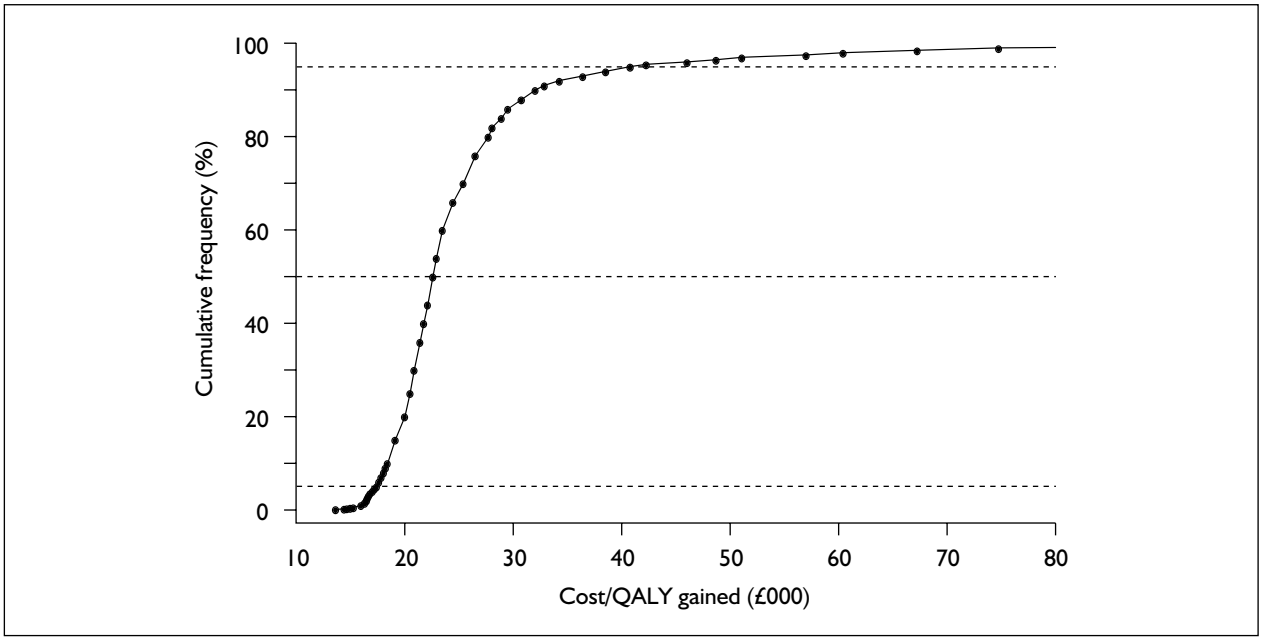

FIGURE 7 *Distribution of cost-effectiveness of a hypothetical agent in women aged 60 years with established osteoporosis. Horizontal lines denote the cost-effectiveness ratio of 5, 50 and 95% of the cohort (£17,362, £22,557 and £40,779, respectively). Reproduced from Kanis JA, Brazier JE, Stevenson, M, Calvert NW, Lloyd Jones M. Treatment of established osteoporosis: a systematic review and cost–utility analysis.* Health Technol Assess *2002;***6***:(29),* Figure 19, *p. 87.*

TABLE 34 *Costs and QALYs for no intervention for a cohort of 100 patients over 10 years*

Age (years)	Total cost (£000)[a]	Total QALYs (000)[b]
50	228.8	689.3
55	266.3	687.5
60	272.6	657.8
65	310.7	655.4
70	405.6	525.3
75	539.9	520.4
80	964.6	360.8

[a] Discounted at 6%.
[b] Discounted at 1.5%.

given to a population of individuals with a defined *T*-score for BMD. Patients with prior fracture have a predetermined ratio of prior fractures of different types. Results of cohorts with specific fracture types are shown subsequently in sensitivity analysis.

For the purposes of this report, a threshold of £30,000 per QALY gained for cost-effectiveness was utilised; that is treatments that have on average a cost–utility ratio of £30,000 or less are considered to be cost-effective.[324] Since the methodology gives 'confidence intervals' or, more accurately, 'credibility intervals', for cost-effectiveness, this permits several categories to be derived, based on the 95% CIs as shown in *Table 35*. Note that the 95% CI describes the cost-effectiveness ratio computed in 95% of the samples and not the confidence estimate of the mid-point estimate. A grade of A or B is considered to be cost-effective for the purpose of this report.

Treatment scenarios

Risedronate in GIO

Risedronate significantly reduced the risk of vertebral fracture (RR = 0.33), but had no significant effect on appendicular fractures, for which the RR was set at 1.0.

Cost-effectiveness was determined in men and women with and without a prior fracture according to age (*Table 36*). In these scenarios, the *T*-score for BMD was set at the average value for age. The cost-effectiveness ratio in general fell with age. Although cost-effectiveness ratios decreased with age, none of the treatment scenarios showed a cost-effectiveness ratio that was below the threshold of £30,000 per QALY gained.

The effects of risedronate in men and women without a prior fracture according to *T*-score and age are summarised in *Table 37*. As expected, the cost-effectiveness ratio decreased progressively

TABLE 35 *Classification of cost-effectiveness*

		Cost-effectiveness (£/QALY gained): 95% CI		
Grade	Description	Mid-point	Lower	Upper
A	Always cost-effective	<30,000	<30,000	<30,000
B	Probably cost-effective	<30,000	<30,000	>30,000
C	Possibly cost-effective	>30,000	<30,000	>30,000
D	Never cost-effective	>30,000	>30,000	>30,000

TABLE 36 *Cost-effectiveness of risedronate (£000/QALY gained) in patients with or without a prior fracture by age*

Age (years)	No prior fracture		Prior fracture	
	Mean	95% CI	Mean	95% CI
50	351	258 to 1023	175	128 to 511
55	178	131 to 520	88	65 to 259
60	200	147 to 587	101	74 to 298
65	119	88 to 351	65	47 to 193
70	78	57 to 233	38	27 to 115
75	72	53 to 215	35	25 to 106
80	107	77 to 328	49	34 to 159

TABLE 37 *Cost-effectiveness of risedronate (£000/QALY gained) in men and women without a prior fracture according to age and T-score*

Age (years)	*T*-score (SD units)							
	–1.0	–1.5	–2.0	–2.5	–3.0	–3.5	–4.0	–4.5
50	287	214	159	118	88	65	48	35
55	170	126	94	70	52	38	28	21
60	222	165	123	91	68	50	37	27
65	154	115	85	63	47	34	25	18
70	119	88	65	48	36	26	19	14
75	127	95	70	52	39	28	21	15
80	226	167	124	91	66	47	33	23

TABLE 38 *Cost-effectiveness ratios (£000/QALY gained) and 95% CIs for risedronate in patients without a prior fracture where cost-effectiveness lay close to or below the threshold for cost-effectiveness*

Age (years)	*T*-score (SD units)	Mean	95% CI	Grade
50	–4.5	35.4	25.7 to 105.9	C
55	–3.5	38.1	27.7 to 113.6	C
	–4.0	28.0	20.3 to 84.4	B
	–4.5	20.5	14.7 to 62.5	B
60	–4.0	36.8	26.6 to 110.4	C
	–4.5	26.9	19.3 to 81.7	B
65	–3.5	34.4	24.9 to 103.4	C
	–4.0	25.2	18.1 to 76.6	B
	–4.5	18.4	13.1 to 56.6	B
70	–3.0	35.6	25.6 to 108.1	C
	–3.5	26.0	18.6 to 80.3	B
	–4.0	18.9	13.3 to 59.5	B
	–4.5	13.5	9.4 to 43.9	B
75	–3.0	38.5	27.7 to 116.7	C
	–3.5	28.3	20.2 to 86.9	B
	–4.0	20.6	14.6 to 64.6	B
	–4.5	14.9	10.3 to 47.8	B
80	–4.0	33.4	22.4 to 112.8	C
	–4.5	22.8	14.6 to 82.1	B

with declining *T*-score. Cost-effectiveness ratios decreased with age up to the age of 70 years and thereafter rose slightly, since the incidence of vertebral fracture was highest at this age. In the absence of a prior fracture, cost-effective scenarios were not found with a *T*-score of greater than –3.0 SD. With a *T*-score of –4.5 SD, it was cost-effective to treat at the age of 55 years or older.

The 95% CIs and grades of cost-effectiveness are summarised in *Table 38* for men and women with low *T*-scores and without a prior fracture where cost-effectiveness lay close to or below the threshold for cost-effectiveness.

In the presence of a prior fracture, cost-effectiveness was improved compared with patients without a prior fracture, and several cost-effective scenarios were found at high ages and low *T*-scores. Although cost-effective scenarios were found at all ages, they depended critically on the *T*-score (*Table 39*). At the age of 50 years it was cost-effective to treat with a *T*-score of –4.0 SD, whereas between the ages of 55 and 65 years it was cost-effective to intervene at a *T*-score of –3.0 SD. At the ages of 70 and 75 years it was cost-effective to intervene with a *T*-score of –2.5 SD or less.

Mid-point estimates, 95% CIs and grades of cost-effectiveness are summarised in *Table 40*. It should be noted that cost-effectiveness did not decrease smoothly with decreasing age. For example, with a *T*-score of –2.5 SD (see *Table 39*), cost-effectiveness decreased from the age of 60 years until the age of 70 years, and thereafter rose. The fluctuations relate to variations in the estimated incidence of vertebral fracture. These effects become less marked when other fracture types are taken into

TABLE 39 *Cost-effectiveness of risedronate (£000/QALY gained) in men and women with a previous fracture according to age and T-score*

Age (years)	*T*-score (SD units)							
	–1.0	–1.5	–2.0	–2.5	–3.0	–3.5	–4.0	–4.5
50	143	106	79	58	43	32	23	17
55	84	62	46	34	25	18	13	9
60	112	83	62	46	33	24	18	13
65	84	62	46	34	25	18	13	9
70	58	43	32	23	17	12	8	6
75	62	46	34	25	18	13	9	6
80	109	80	58	41	29	19	12	7

TABLE 40 *Cost-effectiveness ratios (£000/QALY gained) and 95% CIs for risedronate in patients with a previous fracture where cost-effectiveness lay near or below the threshold for cost-effectiveness*

Age (years)	*T*-score (SD units)	Mean	95% CI	Grade
50	–3.5	31.7	23.0 to 95.2	C
	–4.0	23.2	16.7 to 70.5	B
	–4.5	16.9	12.0 to 51.9	B
55	–2.5	34.0	24.7 to 101.9	C
	–3.0	25.0	18.0 to 75.6	B
	–3.5	18.3	13.1 to 56.0	B
	–4.0	13.2	9.4 to 41.3	B
	–4.5	9.5	6.6 to 30.4	B
60	–3.0	33.5	24.2 to 100.9	C
	–3.5	24.5	17.5 to 74.6	B
	–4.0	17.7	12.6 to 55.0	B
	–4.5	12.6	8.8 to 40.2	B
65	–2.5	33.9	24.5 to 102.2	C
	–3.0	24.8	17.8 to 75.7	B
	–3.5	18.0	12.8 to 55.9	B
	–4.0	12.9	9.0 to 41.1	B
	–4.5	9.1	6.2 to 29.9	A
70	–2.0	31.5	22.6 to 96.3	C
	–2.5	23.0	16.3 to 71.5	B
	–3.0	25,7	11.6 to 52.9	B
	–3.5	18.5	8.1 to 38.9	B
	–4.0	12.9	5.4 to 28.5	A
	–4.5	8.8	3.5 to 20.7	A
75	–2.0	34.0	24.4 to 103.6	C
	–2.5	24.9	17.7 to 77.1	B
	–3.0	18.1	12.7 to 57.2	B
	–3.5	12.9	8.9 to 44.2	B
	–4.0	9.1	6.1 to 31.0	B
	–4.5	6.2	3.9 to 22.6	A
80	–2.5	41.0	28.1 to 135.2	C
	–3.0	28.6	18.9 to 99.1	B
	–3.5	19.3	12.0 to 71.8	B
	–4.0	12.2	6.8 to 51.2	B
	–4.5	6.8	2.9 to 35.6	B

consideration (see below), since variations at different ages with multiple outcomes tend to smooth the effects.

From the preceding analysis, it is evident that rather few cost-effective scenarios are found for risedronate and these were confined to individuals with very low *T*-scores for BMD. The proportion of the population in whom cost-effective treatment could be applied is small. The distribution of the population by age and *T*-score is shown in *Table 41*. Patients without a prior fracture comprise 87% of

TABLE 41 *The proportion of the population (%) with or without a previous fracture that fell into the respective categories for age and T-score*

Age range (years)	*T*-score (SD units)				
	>–3.0	–3.0 to –3.5	–3.5 to –4.0	–4.0 to –4.5	<–4.5
No previous fracture					
50–54	14.7	0.1	0		
55–59	14.4	0.1	0		
60–64	14.9	0.2	0.1		
65–69	15.3	0.2	0.1		
70–74	12.9	0.2	0.1		
75–79	11.0	0.3	0.1		
80+	14.0	0.7	0.3	0.1	0.1
Previous fracture					
50–54	0.4	0.1	0	0	0
55–59	1.7	0.6	0.2	0	0
60–64	3.7	1.5	0.5	0.1	0
65–69	6.7	3.1	1.1	0.3	0.1
70–74	9.2	4.8	2.0	0.6	0.2
75–79	11.3	6.7	3.1	1.1	0.4
80+	18.0	12.2	6.4	2.7	1.1

TABLE 42 *Cost-effectiveness of bisphosphonate (£000/QALY gained) in patients with or without a prior fracture by age*

Age (years)	No prior fracture			Prior fracture		
	Mean	95% CI	Grade	Mean	95% CI	Grade
50	235	198 to 298	D	115	96 to 147	D
55	135	113 to 170	D	65	53 to 83	D
60	98	78 to 138	D	46	35 to 66	D
65	56	44 to 82	D	27	19 to 41	B
70	46	35 to 67	D	17	11 to 29	A
75	23	14 to 42	B	3	–2 to 14	A
80	5	–2 to 20	A	–9	–13 to 0	A

all individuals aged 50 years or more on long-term glucocorticoid treatment. The proportion of this population in whom cost-effective treatment can be given amounts to 0.3% (calculated from the distribution of the population represented in *Table 37*). In the 13% of the total population with a prior fracture, cost-effective intervention can be given to 68% (calculated from the distribution of the population represented in *Table 39*). Hence cost-effective treatment is confined to less than 10% of the total population.

Bisphosphonates

For the purposes of developing strategies for case finding, the information on anti-fracture efficacy with bisphosphonates in postmenopausal osteoporosis was combined. This approach rests on the assumption that responses to intervention do not differ between the bisphosphonates and that the risk reduction is similar in patients taking glucocorticoids, as seen in women with postmenopausal osteoporosis. The evidence for this is discussed in Chapter 3. The intervention cost used for bisphosphonates was priced at that of risedronate, but the term 'bisphosphonate' is used to denote that the assumptions detailed above apply. Efficacy on hip fractures is assumed to be an RR of 0.61 (95% CI 0.47 to 0.81). For non-vertebral fractures (forearm and humeral fractures), the RR was set at 0.81 (95% CI 0.73 to 0.90). For vertebral fracture the RR was set at 0.57 (95% CI 0.50 to 0.66).

The cost-effectiveness of bisphosphonate in men and in women, with or without a prior fracture, is given in *Table 42* for individuals without a BMD measurement. For this purpose, the average BMD at each specific age was modelled. Cost-effectiveness ratios were lower, as expected, than in the case of risedronate. The effect was more

TABLE 43 *Cost-effectiveness of bisphosphonate (£000/QALY gained) in men and women according to* T*-score and age*

Age (years)	*T*-score (SD units)							
	–1.0	–1.5	–2.0	–2.5	–3.0	–3.5	–4.0	–4.5
No prior fracture								
50	175	109	63	33	13	4	–3	–7
55	126	81	49	27	13	4	–2	–6
60	115	71	41	22	10	2	–3	–6
65	85	53	31	16	6	0	–4	–7
70	89	56	33	17	5	–3	–8	–12
75	67	40	21	8	–1	–8	–12	–15
80	44	24	10	0	–8	–13	–17	–20
Prior fracture								
50	84	51	27	12	2	–3	–7	–9
55	60	37	21	10	2	–3	–6	–8
60	54	32	16	6	0	–4	–7	–8
65	43	25	12	4	–2	–5	–8	–10
70	39	22	10	1	–5	–9	–12	–14
75	27	12	2	–5	–9	–13	–16	–17
80	12	1	–6	–12	–16	–19	–21	–23

marked at higher ages. For example, in patients with a prior fracture at the age of 50 years the cost-effectiveness of risedronate was £175,000 per QALY gained (see *Table 36*). For bisphosphonate, the estimate was £115,000 per QALY gained. At the age of 75 years, the cost-effectiveness ratios were £35,000 and £3,000, respectively, a decrement of 91%. The reason for the greater effect with advancing age is that the assumptions concerning bisphosphonate include an effect on hip fracture, which increases in importance with age. An effect on vertebral fracture is assumed for both risedronate and bisphosphonate, and these fractures also occur in younger individuals. As expected, the 95% CIs were tighter when modelling the effects of bisphosphonate than for risedronate, and fluctuations with age were less evident than for risedronate.

Cost-effective scenarios were only found at the age of 75 years or more without a previous fracture, and at the age of 65 years or more in individuals with a prior fragility fracture.

The mid-point estimates for bisphosphonates according to age and *T*-score are shown in *Table 43*. Cost-effectiveness was improved compared with the empirical data for risedronate alone in glucocorticoid-treated patients (compare *Tables 37* and *39* with *Table 43*). Cost-effectiveness improved with decreasing BMD and increasing age. In patients without a prior fracture, the cost-effectiveness ratio lay below the threshold of £30,000 per QALY gained in all patients at the threshold of osteoporosis aged 55 years and above. Treatment was always cost-effective with a *T*-score of –3.0 SD or less. In patients with a prior fragility fracture, cost effective scenarios were found at the threshold of osteoporosis, irrespective of age. Indeed, more moderate reductions in *T*-score were cost-effective at higher ages. For example, at the age of 80 years, cost-effectiveness was found irrespective of BMD.

The grade of cost-effectiveness which takes into account the 95% CI is shown in *Table 44*. In both patients with and without a prior fracture, it was cost-effective to intervene with a *T*-score of –3.0 SD or less. Cost-effective scenarios were found with less stringent *T*-scores at higher ages. At the extremes of *T*-score and age, cost savings were found even at the upper 95% CI (grade A*).

Sensitivity analysis

The computations given in this chapter included sensitivity analysis for variations in effectiveness where appropriate. For the purposes of this section, we focus further analyses on bisphosphonate treatment in patients with a *T*-score of –2.5 SD. The reason for this preference is that a range of cost-effectiveness is shown, from cost-ineffective to cost-saving (*Table 45*).

Cost-effectiveness acceptability curves (CEACs) are shown for the base case in *Figure 8*. Cost-effectiveness improved with age and the presence of a prior fracture. At the ages of 50 and 60 years, cost-effectiveness was found in 30 and 85% of

TABLE 44 *Grade of cost-effectiveness for men and women treated with bisphosphonate according to age and* T*-score*

Age (years)	No fracture *T*-score (SD units)							
	–1.0	–1.5	–2.0	–2.5	–3.0	–3.5	–4.0	–4.5
No prior fracture								
50	D	D	D	C	A	A	A	A*
55	D	D	D	B	A	A	A	A*
60	D	D	D	B	A	A	A	A*
65	D	D	C	A	A	A	A	A*
70	D	D	C	B	A	A	A*	A*
75	D	C	B	A	A	A	A*	A*
80	D	B	A	A	A	A*	A*	A*
Prior fracture								
50	D	D	B	A	A	A	A*	A*
55	D	C	B	A	A	A	A*	A*
60	D	C	A	A	A	A	A*	A*
65	D	B	A	A	A	A*	A*	A*
70	D	B	A	A	A	A*	A*	A*
75	B	A	A	A	A*	A*	A*	A*
80	A	A	A	A*	A*	A*	A*	A*

TABLE 45 *Cost-effectiveness of bisphosphonate (£000/QALY gained) and 95% CIs in patients with a* T*-score of –2.5 SD according to age*

Age (years)	No prior fracture				Prior fracture			
	Mean	95% CI	Grade[a]	Grade[b]	Mean	95% CI	Grade[a]	Grade[b]
50	33	24 to 53	C	D	12	7 to 23	A	B
55	27	20 to 43	B	D	10	6 to 18	A	A
60	22	15 to 39	B	C	6	3 to 15	A	A
65	16	10 to 29	A	B	4	0 to 12	A	A
70	17	10 to 30	B	B	1	–3 to 10	A	A
75	8	1 to 22	A	B	–5	–8 to 4	A	A
80	0	–7 to 13	A	A	–12	–15 to –4	A*	A*

[a] Grading of cost-effectiveness is given using a threshold of £30,000/QALY gained.
[b] Grading of cost-effectiveness is given using a threshold of £20,000/QALY gained.

simulations in the absence of a prior fracture. In the presence of a prior fracture, cost-effectiveness was found in 95% and 100% of simulations, respectively. At higher ages cost-effectiveness improved. At the age of 80 years, cost-effectiveness below the £30,000 threshold was found in 99% of simulations, irrespective of fracture status. Cost savings were found in 55% of simulations in the absence of fracture and in 95% of simulations in the presence of a prior fracture history.

Age

Age was clearly an important determinant of cost-effectiveness, since the risk of fractures increases with age. It is clearly illustrated in all scenarios (see *Table 43*). For example, in individuals with a *T*-score of –2.0 SD without a prior fracture, the range of cost-effectiveness varied from £63,000 at the age of 50 years to £10,000 per QALY gained at the age of 80 years. Note that improving cost-effectiveness with age was not invariant, in part because of fluctuations in vertebral fracture risk with age.

Effect of changing *T*-score

Treating individuals with a *T*-score lower than –2.5 SD had a very marked effect on cost-effectiveness (see *Table 43*). For bisphosphonate treatment in individuals without a prior fracture, intervention was at the threshold of cost-effectiveness at the age of 55 years. Increasing the stringency of the cut-off value for *T*-score from –2.5 to –3.0 SD made treatment cost-effective at the age of 50 years and cost savings were found with a *T*-score of –4.0 SD.

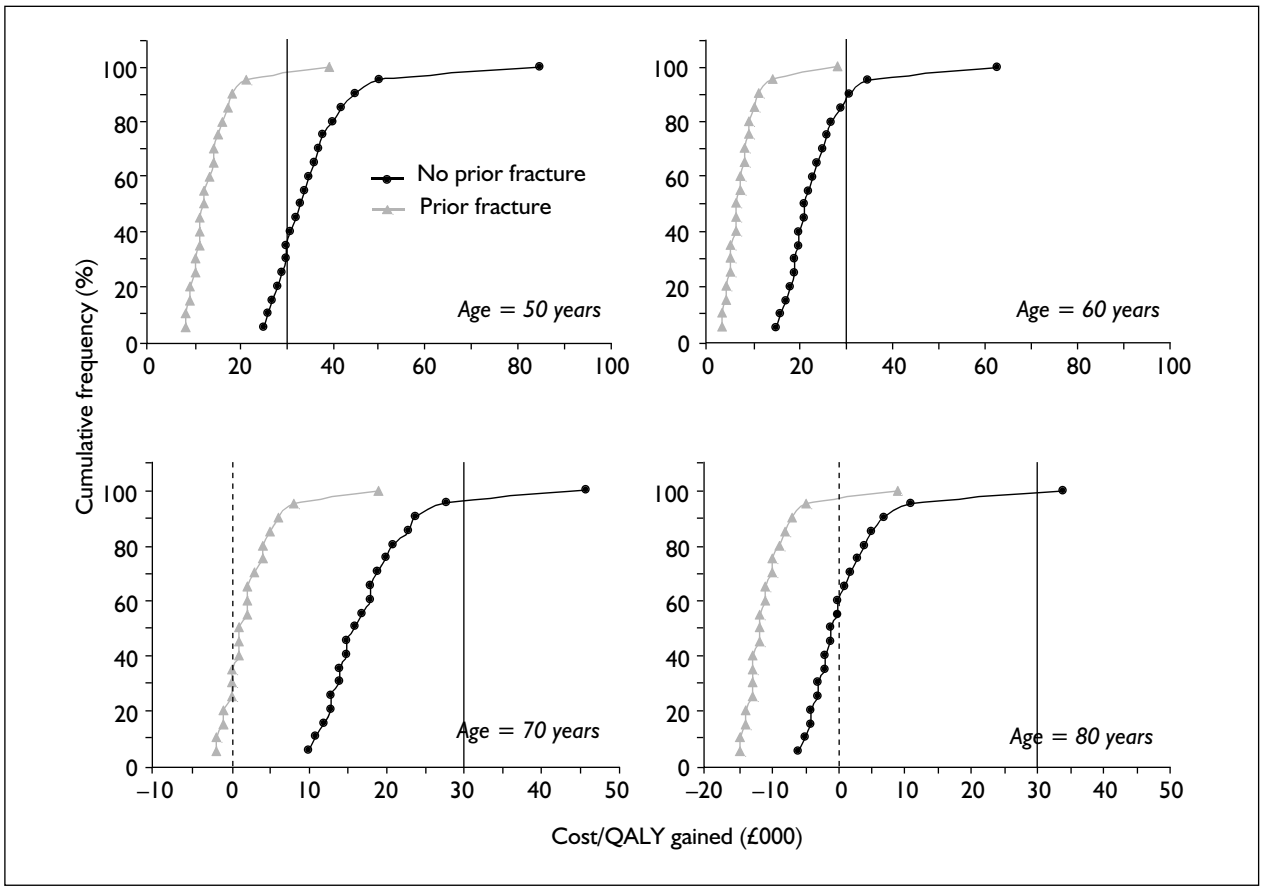

FIGURE 8 *Distribution of cost-effectiveness of treatment with bisphosphonate in patients at the ages shown with a* T*-score of –2.5 SD with and without a prior fragility fracture*

Cost of intervention

Lower costs of intervention would be associated with better cost-effectiveness. For several treatment scenarios, it might be argued that intervention is worthwhile without recourse to BMD tests. Moreover, it might be further argued that without a BMD test, patients would not require additional GP visits since medical supervision would already be received for the underlying disease. The impact of excluding these costs is shown in *Table 46*. Cost-effectiveness ratios decreased. The decrement associated with the avoidance of BMD was modest (approximately £1000 per QALY gained). When both BMD and extra physician visits were avoided, cost-effectiveness ratios decreased by £5,000–10,000 per QALY gained in patients without a prior fracture, depending on age, and by £2000–5000 per QALY gained in patients with a prior fracture.

Criteria for cost-effectiveness

For the purposes of this report, we used criteria for cost-effectiveness based on cost-effectiveness being shown in 95% of cohorts. For example, grade A was allocated to a treatment scenario where, in 95% of the model runs, cost-effectiveness was less than £30,000 per QALY gained (see *Table 35*). Decreasing the range to 80% of runs had a modest effect on the range of cost-effectiveness, particularly on the lower estimate (*Table 47*).

Altering the threshold value for cost-effectiveness from £30,000 to £20,000 also had a modest effect on the grading of cost-effectiveness (see *Table 45*). A decrement in grading was observed such that it was no longer cost-effective to treat individuals without a prior fracture at the age of 60 years or less.

Discounting

The base case used a discount rate of 6% for costs and 1.5% for QALYs gained. When costs and benefits were both discounted at 3.5%, there were modest effects only on cost-effectiveness (*Table 48*). The change in discount rate for costs from 6 to 3.5% gives early costs (GP visits and bone density scans) more weight, but is more than offset by the savings afforded by fracture reduction. The increase in the discount rate for benefits has an

TABLE 46 *Cost-effectiveness of bisphosphonate (£000/QALY gained) and 95% CIs in patients with a* T-score *of –2.5 SD according to age*[a]

Age (years)	Base case			Without BMD			Without physician		
	Mean	95% CI	Grade	Mean	95% CI	Grade	Mean	95% CI	Grade
No prior fracture									
50	33	24 to 53	C	32	23 to 51	C	23	16 to 39	B
55	27	20 to 43	B	26	19 to 41	B	19	13 to 31	B
60	22	15 to 39	B	21	14 to 37	B	15	9 to 28	A
65	16	10 to 29	A	15	9 to 27	A	10	5 to 20	A
70	17	10 to 30	B	15	9 to 29	A	10	4 to 21	A
75	8	1 to 22	A	7	1 to 21	A	2	–3 to 14	A
80	0	–7 to 13	A	–1	–7 to 12	A	–5	–10 to 6	A
Prior fracture									
50	12	7 to 23	A	11	7 to 22	A	7	3 to 16	A
55	10	6 to 18	A	9	5 to 17	A	5	2 to 12	A
60	6	3 to 15	A	6	2 to 14	A	3	0 to 10	A
65	4	0 to 12	A	3	0 to 11	A	1	–2 to 7	A
70	1	–3 to 10	A	1	–3 to 9	A	–2	–5 to 5	A
75	–5	–8 to 4	A	–5	–9 to 3	A	–7	–11 to 0	A
80	–12	–15 to –4	A*	–12	–16 to –4	A*	–14	–17 to –7	A*

[a] The base-case scenario is shown in the left-hand panels. The centre panels show the effect of not measuring BMD and the right-hand panels of additionally not having extra medical supervision.

TABLE 47 *Cost-effectiveness of bisphosphonate (£000/QALY gained) with 95% and 80% CIs in patients with a* T-score *of –2.5 SD according to age and prior fracture status*

Age (years)	Base case		
	Mean	95% CI	80% CI
No prior fracture			
50	33	24 to 53	26 to 45
55	27	20 to 43	22 to 36
60	22	15 to 39	16 to 31
65	16	10 to 29	11 to 23
70	17	10 to 30	11 to 24
75	8	1 to 22	3 to 15
80	0	–7 to 13	–5 to 7
Prior fracture			
50	12	7 to 23	8 to 18
55	10	6 to 18	7 to 14
60	6	3 to 15	3 to 11
65	4	0 to 12	1 to 8
70	1	–3 to 10	–2 to 6
75	–5	–8 to 4	–8 to 0
80	–12	–15 to –4	–15 to –7

adverse effect of cost-effectiveness due to the decrease in QALYs gained.

Compliance

Patients who were deemed to be non-compliant were assumed to have received 3 months of drug and accrued no health benefit. With this definition, variations in compliance had a modest effect on cost-effectiveness since both costs and effectiveness change in the same direction. The effect of assuming 80% compliance was quantitatively much less than that of the variation in discount. Cost-effectiveness ratios rose by less than £250 and did not alter overall conclusions concerning cost-effectiveness. Base-case examples in patients with a prior fracture are shown in *Table 49*.

TABLE 48 *Cost-effectiveness of bisphosphonates in patients with a* T-score *of –2.5 SD and a prior fracture*[a]

Age (years)	Base case		Sensitivity analysis	
	Mean	95% CI	Mean	95% CI
50	12	7 to 23	13	8 to 27
55	10	6 to 18	11	6 to 21
60	6	3 to 15	7	3 to 18
65	4	0 to 12	4	0 to 13
70	1	–3 to 10	1	–4 to 11
75	–5	–8 to 4	–6	–11 to 4
80	–12	–15 to –4	–15	–20 to –6

[a] For the base case, costs were discounted at 6% and benefits at 1.5%. For the sensitivity analysis, costs and benefits were discounted at 3.5%.

Offset time

The base case assumed that the effects of treatment wear off in a linear fashion over 5 years. Hence a 5-year treatment incurs some benefit when

TABLE 49 *Effect of compliance on cost-effectiveness (£000/QALY gained) of bisphosphonate in patients with a T-score of –2.5 SD and a prior fracture*

Age (years)	Base case	Compliance (%)			
		80	60	40	20
50	12.2	12.4	12.8	13.5	15.8
55	9.7	9.9	10.2	10.9	12.8
60	6.5	6.6	6.9	7.5	9.2
65	3.8	4.0	4.2	4.7	6.2
70	1.5	1.6	1.9	2.5	4.3
75	–4.5	–4.4	–4.2	–3.7	–2.2
80	–11.8	–11.6	–11.4	–10.9	–9.4

TABLE 50 *Effects of offset time on cost-effectiveness of bisphosphonate treatment in patients with a T-score of –2.5 SD and a prior fragility fracture*

Age (years)	Offset time (years)	Cost/QALY gained (£000)	
		Mean	95% CI
50	0	21	14 to 37
	3	15	9 to 28
	5	12	7 to 23
	10	10	6 to 20
55	0	17	11 to 28
	3	12	7 to 21
	5	10	6 to 18
	10	8	4 to 15
60	0	12	7 to 25
	3	8	4 to 18
	5	6	3 to 15
	10	5	2 to 13
65	0	9	4 to 19
	3	5	1 to 14
	5	4	0 to 12
	10	3	0 to 10
70	0	6	1 to 17
	3	3	–2 to 12
	5	1	–3 to 10
	10	1	–3 to 9
75	0	–1	–6 to 9
	3	–4	–8 to 5
	5	–5	–8 to 4
	10	–5	–8 to 3
80	0	–9	–14 to 1
	3	–11	–15 to –3
	5	–12	–15 to –4
	10	–12	–15 to –4

TABLE 51 *Additional direct costs (£) in patients with a T-score of –2.5 SD and a prior fragility fracture that survive as a result of treatment with bisphosphonate (per 100 women treated)*

Age (years)	Additional cost (£)
50	89
55	181
60	390
65	1,534
70	2,722
75	8,004
80	16,068

treatment is stopped. A reduction in offset time to zero had a marked effect on cost-effectiveness. *Table 50* shows scenarios for offset time following bisphosphonate treatment in patients with a *T*-score of –2.5 SD and a prior fragility fracture.

At age 50 years, the cost effectiveness ranged from £10,000 per QALY when assuming a 10-year offset time to £21,000 per QALY when assuming zero offset time. However, changing the offset time did not alter the overall conclusions concerning cost-effectiveness. It should be noted that the analytic time frame was for 10 years. Thus, benefit due to a 10-year offset time would only be partially accounted for.

Cost of added years of life

The inclusion of future years of direct medical costs had effects on cost-effectiveness ratios over the analytic time frame (10–15 years), but the effect at all ages was small since indirect costs are excluded. In patients who survived as a result of treatment, additional costs varied from £89 to £16,000 (*Table 51*), but the overall effect of treatment on deaths averted is small.

Duration of intervention

Cost-effectiveness improved when the duration of treatment was decreased from 5 to 3 or 1 years (*Table 52*). For bisphosphonate, at the age of 50 years in an individual with a prior fracture and a *T*-score of –2.5 SD, the cost per QALY gained decreased from £12,000 to £9000 with a decrease in treatment time from 5 to 3 years. At older ages, the effect was smaller due to the higher mortality. Decreasing the duration of treatment still further

TABLE 52 *Cost-effectiveness of bisphosphonate (£000/QALY gained) and 95% CIs in patients with a prior fracture and a T-score of –2.5 SD according to age and duration of treatment*

Age (years)	Duration of treatment (years)					
	5		3		1	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
50	12	7 to 23	9	4 to 18	0	–2 to 6
55	10	6 to 18	6	3 to 13	0	–2 to 4
60	6	3 to 15	4	0 to 11	–2	–4 to 2
65	4	0 to 12	1	–2 to 8	–4	–6 to 0
70	1	–3 to 10	–1	–5 to 6	–7	–9 to -2
75	–5	–8 to 4	–7	–10 to 1	–11	–14 to –6
80	–12	–15 to –4	–14	–17 to –6	–17	–20 to –12

TABLE 53 *Effects of changing mortality assumptions on cost-effectiveness*[a]

Age (years)	Mortality 24%		Mortality 48%		Mortality (RR = 1.28)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
50	12	7 to 23	12	7 to 23	12	7 to 23
55	10	6 to 18	10	6 to 18	10	6 to 18
60	6	3 to 15	6	3 to 15	7	3 to 16
65	4	0 to 12	4	0 to 11	4	1 to 12
70	1	–3 to 10	1	–3 to 10	2	–2 to 11
75	–5	–8 to 4	–4	–8 to 4	–4	–8 to 4
80	–12	–15 to –4	–11	–15 to –3	–10	–15 to 2

[a] The two left-hand panels show the cost-effectiveness of bisphosphonate (£000/QALY gained) and 95% CIs in patients with a *T*-score of –2.5 SD and a prior fracture according to age and the proportion of hip fracture deaths ascribed to the hip fracture event. The right-hand panel shows the effect of increasing the mortality risk amongst patients taking glucocorticoids (RR = 1.28).

to 1 year had a very marked beneficial effect on cost-effectiveness.

Although these data indicate a very important effect of the duration of treatment, they should be interpreted with caution since the offset time was set at 5 years for each scenario. Decreasing offset time in proportion to the duration of treatment would not show marked improvements. Indeed, shorter treatments are likely to show marginally poorer cost-effectiveness since the initial assessments costs are invariant. There is, however, no information available to determine the effects of duration of treatment on offset times.

Mortality attributed to hip fracture

In the base case, we assumed that 24% of all deaths following hip fracture were causally related to the hip fracture (see Chapter 4). Reviews of case records in the UK suggested that up to 48% of all deaths may be related to the fracture event. When this latter assumption was included in the model, the cost-effectiveness ratio decreased, although the effect was very small and the overall conclusions (i.e. grade of cost-effectiveness) did not change markedly (*Table 53*). For example, treatment of a patient with a prior fracture with bisphosphonate at the age of 60 years and at the threshold of osteoporosis gave a cost-effectiveness ratio of £6500. When 48% of deaths were assumed to be causally related, the cost-effectiveness improved to £6200. The relatively modest effect is due to the relatively few numbers of hip fractures averted.

Mortality in patients taking glucocorticoids

In the base case, we assumed that the mortality of the population taking glucocorticoids but without fracture was the same as that in the general population. Our meta-analysis indicated that the mortality risk was 1.28 times higher than that of the general population. When this increased mortality risk was included, there was a very small adverse effect on cost-effectiveness (see *Table 53*).

TABLE 54 *Cost-effectiveness of bisphosphonate (£000/QALY gained) in patients with a* T*-score of –2.5 SD according to the type of previous fracture*

Age (years)	Mean	95% CI
Base case		
50	12	7 to 23
55	10	6 to 18
60	6	3 to 15
65	4	0 to 12
70	1	–3 to 10
75	–5	–8 to 4
80	–12	–15 to –4
Prior hip fracture		
50	11	5 to 23
55	8	4 to 18
60	4	0 to 13
65	1	–2 to 9
70	–2	–6 to 7
75	–9	–13 to 0
80	–16	–20 to –7
Prior vertebral fracture		
50	8	4 to 17
55	6	3 to 12
60	3	0 to 9
65	0	–2 to 6
70	–2	–5 to 4
75	–7	–10 to –1
80	–14	–17 to –7
Prior forearm fracture		
50	12	7 to 23
55	10	6 to 19
60	6	2 to 14
65	3	0 to 11
70	1	–3 to 9
75	–5	–9 to 3
80	–11	–14 to –3
Prior proximal humeral fracture		
50	12	7 to 24
55	10	5 to 19
60	5	2 to 14
65	3	–1 to 11
70	0	–4 to 9
75	–6	–10 to 2
80	–12	–16 to –4

Prior fracture

The cohort modelled with a prior fracture at any age is a population within which there is a mixed pattern of prior fragility fractures. The distribution of fracture types is age dependent. Since different prior fractures have different consequences for further fracture, it is appropriate to examine the effect of the type of prior fracture on treatment outcomes.

- prior forearm fracture
- prior shoulder fracture
- prior vertebral fracture
- prior hip fracture.

Table 54 shows the effect of bisphosphonate treatment in patients with a *T*-score for BMD of –2.5 SD in the presence of specific prior fractures, compared with the base-case scenario (a population with a given distribution of prior fractures).

Compared with the base case, there were moderate differences in cost-effectiveness when compared with patients with a prior forearm or humeral fracture. For patients with a prior vertebral fracture, cost-effectiveness was markedly improved due to the high risks of further vertebral fractures in untreated patients. For patients with a prior hip fracture, cost-effectiveness was markedly improved at higher ages but only moderately improved at younger ages due to the increasing importance of hip fracture risk with age.

Criteria for vertebral fracture

Our estimates (Chapter 4) suggest that vertebral fractures that come to clinical attention comprise approximately 22% of all vertebral fractures in women. Clinically covert fractures diagnosed by vertebral morphometry are associated with significant morbidity,[325] and their exclusion will underestimate cost-effectiveness. For the purposes of this sensitivity analysis, we assumed that the utility loss is one-third of that of a clinically overt fracture, based on estimates of hospital stay and changes in activities of daily living.[243] If for every 100 fractures on X-ray 20 will be clinically overt, then the overall incidence of vertebral fractures is five times greater than our estimate of clinical vertebral fractures. If the utility loss of clinically covert fractures is one-third of that of clinically overt fractures, then the mean utility loss for all fractures would be 48% of that for clinically overt fractures alone.

Increasing the apparent incidence of vertebral fracture by a factor of five and using the lower utility decrement associated with all vertebral fractures improved cost-effectiveness (*Table 55*). Grades of cost-effectiveness improved, particularly in patients without a prior fracture. For example, at the age of 65 years, treatment with bisphosphonate decreased the cost-effectiveness ratio from £49,000 to £8000. At the age of 70 years, the ratio fell from £17,000 to £7000.

In men, a greater proportion of vertebral fractures are clinically apparent than in women (42 versus 22%).[243] Hence the proportion of covert fractures

TABLE 55 *Cost-effectiveness of bisphosphonate (£000/QALY gained) and 95% CIs in patients with a* T-score *of –2.5 SD according to age, prior fracture and the criteria used to define a vertebral fracture*

Age (years)	Clinical vertebral fracture			Morphometric vertebral fracture		
	Mean	95% CI	Grade	Mean	95% CI	Grade
No prior fracture						
50	33	24 to 53	C	21	16 to 30	B
55	27	20 to 43	B	15	11 to 21	A
60	22	15 to 39	B	13	9 to 19	A
65	16	10 to 29	A	8	6 to 13	A
70	17	10 to 30	B	7	4 to 13	A
75	8	1 to 22	A	3	0 to 10	A
80	0	–7 to 13	A	–3	–7 to 4	A
Prior fracture						
50	12	7 to 23	A	7	4 to 12	A
55	10	6 to 18	A	5	3 to 8	A
60	6	3 to 15	A	3	1 to 7	A
65	4	0 to 12	A	1	–1 to 5	A
70	1	–3 to 10	A	–1	–3 to 2	A
75	–5	–8 to 4	A	–4	–7 to 0	A
80	–12	–15 to –4	A*	–11	–14 to –6	A*

TABLE 56 *Cost-effectiveness of bisphosphonate (£000/QALY gained) and 95% CIs in men with a* T-score *of –2.5 SD according to age, prior fracture and the criteria used to define a vertebral fracture*

Age (years)	Clinical vertebral fracture			Morphometric vertebral fracture		
	Mean	95% CI	Grade	Mean	95% CI	Grade
No prior fracture						
50	33	24 to 53	C	27	20 to 42	B
55	27	20 to 43	B	21	15 to 31	B
60	22	15 to 39	B	17	12 to 28	A
65	16	10 to 29	A	12	8 to 20	A
70	17	10 to 30	B	12	7 to 20	A
75	8	1 to 22	A	6	1 to 15	A
80	0	–7 to 13	A	–2	–7 to 9	A
Prior fracture						
50	12	7 to 23	A	10	6 to 18	A
55	10	6 to 18	A	7	4 to 12	A
60	6	3 to 15	A	5	2 to 11	A
65	4	0 to 12	A	2	0 to 8	A
70	1	–3 to 10	A	0	–3 to 6	A
75	–5	–8 to 4	A	–4	–8 to 2	A
80	–12	–15 to –4	A*	–12	–15 to –5	A*

is less. When this was accounted for (*Table 56*), cost-effectiveness improved, but the incremental effect was more modest compared with women (compare *Tables 55* and *56*).

First admission to nursing home

For the base case, we assumed that the proportion of patients entering a nursing home for the first time after a hip fracture was similar to that described in the East Anglian audit.[289] These rates were lower than those described for Sweden or Scotland.[287,288] For example, between the ages of 50 and 69 years, approximately 6.6% of Swedish women were admitted to nursing homes following hip fracture, whereas in the East Anglian audit the figure was 0% for women aged 50–59 years and 4% in women aged 60–69 years. The effect of using admission rates for Sweden, given in *Table 57*, gave very modest improvements in cost-effectiveness.

TABLE 57 *Cost-effectiveness of bisphosphonate (£000/QALY gained) and 95% CIs in patients with a T-score of –2.5 SD according to age, prior fracture and nursing home entry rate following hip fracture*

Age (years)	Base case (English data)			Swedish data		
	Mean	95% CI	Grade	Mean	95% CI	Grade
No prior fracture						
50	33	24 to 53	C	32	23 to 53	C
55	27	20 to 43	B	27	20 to 42	B
60	22	15 to 39	B	21	14 to 38	B
65	16	10 to 29	A	15	10 to 28	A
70	17	10 to 30	B	16	9 to 30	A
75	8	1 to 22	A	7	1 to 21	A
80	0	–7 to 13	A	–2	–7 to 12	A
Prior fracture						
50	12	7 to 23	A	11	6 to 22	A
55	10	6 to 18	A	9	5 to 17	A
60	6	3 to 15	A	6	2 to 14	A
65	4	0 to 12	A	3	0 to 11	A
70	1	–3 to 10	A	1	–3 to 9	A
75	–5	–8 to 4	A	–5	–9 to 3	A
80	–12	–15 to –4	A*	–13	–16 to –5	A*

Intervention strategies

Glucocorticoid use has been recognised as a significant risk factor in current clinical guidelines for the assessment of osteoporosis.[5,25,65,67,69,70,224] Under most of these guidelines, patients taking glucocorticoids should be considered for treatment where BMD is found to be below a given threshold, such as the threshold for osteoporosis. If, as has been shown in the present report, the risk of fracture with the use of corticosteroids is not wholly dependent on BMD, then fracture risk assessment should take into account the independent risk associated with glucocorticoids and a history of prior fracture. Moreover, since the risk of fracture at any BMD is age dependent, age becomes another important variable to consider. These factors, age, BMD, prior fracture and the independent effects of glucocorticoids, have been accommodated in the most recent guidelines available for the UK.[5,224]

As mentioned in Chapter 3, the starting point in the assessment algorithm for the UK is the eligibility for case finding which comprises a patient either committed to long-term glucocorticoids or who has been exposed to long-term treatment for more than 3 months. No distinction is made between men and women, but the first dichotomy is at the age of 65 years. At or above this age, the risk of fractures is considered to be sufficiently high that treatment with skeletally active agents is considered to be appropriate. Below the age of 65 years treatment is appropriate with a history of a prior fragility fracture. In the absence of a prior fracture, a BMD test is recommended and active intervention recommended where the *T*-score is –1.5 SD or lower. Since the approach has been widely endorsed and is readily applied to a clinical context, we based our first approach on this management strategy within a health economic perspective.

Current guidelines

The first branch point is age, and current guidance gives 65 years as a threshold age. When populations are examined irrespective of the presence or absence of a prior fracture, the average cost per QALY was £34,965 at the age of 50 years and above, and decreased progressively with age so that cost-effectiveness was found at the age of 55 years and above (*Table 58*). Cost-effectiveness in this age group is, however, dominated by the good cost-effectiveness of individuals without a prior fracture aged 75 years or more (see *Table 42*), who comprise a substantial minority of patients aged 65 years or more (39%, see *Table 41*).

A subsequent branch point in the current guidance for individuals aged less than 65 years is the presence or absence of a prior fragility fracture. Individuals with a prior fracture are considered eligible for treatment. Whereas, over all ages, that is, aged 50 years or more, treatment of individuals with prior fracture is cost-effective (see *Table 58*), it is evident that intervention in

TABLE 58 *Cost-effectiveness of bisphosphonate treatment in men and women according to age and the presence or absence of a prior fragility fracture*

Age (years)	Cost/QALY gained £(000)		
	No prior fracture	Prior fracture	Irrespective of fracture status
≥50	49.7	1.6	35.0
≥55	41.7	1.5	29.0
≥60	34.4	1.0	23.4
≥65	26.7	–0.1	17.4
≥70	19.2	–2.2	11.0
≥75	11.5	–5.1	4.7
≥80	4.8	–8.9	–1.2

TABLE 59 *T-score below which intervention with bisphosphonate becomes cost-effective as judged by a threshold value of £30,000/QALY gained*

Age (years)	*T*-score at which intervention is cost-effective		
	Prior fracture	No prior fracture	Irrespective of fracture status
≥50	–1.0	–2.0	–2.0
≥55	–1.0	–2.0	–2.0
≥60	–1.0	–2.0	–1.5
≥65	–1.0	–2.0	–1.5
≥70	–1.0	–2.0	–1.5
≥75	–1.0	–2.0	–1.5
≥80	–1.0	–1.5	–1.0

individuals is cost-ineffective up to the age of 65 years (see *Table 42*). Treatment of patients without prior fracture is even less cost-effective (see *Table 42*). It should be noted that the analyses in *Table 42* have costs of GP visits and BMD included, but overall conclusions would not change markedly with the exclusion of these costs. Hence a prior fracture alone in patients under the age of 65 years does not confer a risk high enough for the delivery of cost-effective interventions.

The implication of these considerations is that additional risk factors should be used to identify those in whom treatment can be justified from a health economic perspective. The additional risk factor is obviously BMD assessment. The *T*-score below which intervention becomes cost-effective for populations of patients is given in *Table 59*. In populations of individuals aged ≥60 years, for example, cost-effectiveness lies below £30,000 per QALY with a *T*-score of –1.5 SD irrespective of fracture status. In patients without prior fracture, however, a *T*-score of –1.5 SD does not provide a cost-effective intervention threshold except in individuals aged 80 years or more. A further problem with this analysis is that any threshold is still influenced by individuals over the age of 65 years where treatment is more cost-effective. Thus, intervention thresholds for the population up to the age of 65 years should be modelled in this population.

Intervention thresholds on this basis are shown in *Table 60*, and show that a *T*-score of –1.5 SD

TABLE 60 *T-score for BMD below which intervention with bisphosphonate becomes cost-effective as judged by cost/QALY gained of £30,000*

Age (years)	*T*-score at which intervention is cost-effective		
	Prior fracture	No prior fracture	Irrespective of fracture status
50–65	–1.5	–2.5	–2.0
55–65	–1.5	–2.5	–2.0
60–65	–1.5	–2.5	–2.0

provides a cost-effective threshold for BMD in populations under the age of 65 years with a prior fracture and a *T*-score of –2.5 SD for individuals without a prior fracture.

These considerations suggest that from a health economic perspective the current guidance is appropriate in several respects, but fails in others:

1. A threshold age of 65 years does not provide an adequate cut-off in that treatment at the age of 65 years is not cost-effective (£56,000 per QALY gained; *Table 42*), although treatment of all patients above the age of 65 years is cost-effective (£17,400 per QALY gained; *Table 58*).
2. In patients under the age of 65 years with a prior fracture, no cost-effective scenarios are found (see *Table 42*).
3. In patients under the age of 65 years without a prior fracture, a *T*-score threshold for BMD of –1.5 SD does not provide a cost-effective treatment. Rather, a *T*-score of –2.0 SD would be appropriate.

Individual patient scenarios

From an individual patient perspective, BMD appears to provide a more discriminatory threshold than does age (see *Table 44*). Thus, treatment is always cost-effective below a *T*-score of –2.5 SD, whereas age alone does not provide an effective threshold, except in patients aged 75–80 years and above (see *Table 42*).

The implication is that if cost-effective scenarios are to be judged on an individual patient basis, then BMD should be incorporated as the first step in patient assessment. From *Tables 43* and *44*, it can be inferred that all individuals with a *T*-score of less than –2.5 SD can be treated cost-effectively. Thereafter, cost-effective treatment can be offered depending upon age, *T*-score (at –2.5 SD or above) and prior fracture status, as shown in *Table 61*.

There are several problems with this approach. The first is that BMD tests are required in all patients who are committed to long-term treatment with glucocorticoids. This incurs the costs of BMD assessment and additional physician visits. Although these costs are already within our estimates, their exclusion would deliver greater cost-effectiveness, as shown in the sensitivity analysis. It could be argued, for example, that patients with a prior fracture aged 75 years can be treated very cost-effectively irrespective of BMD (cost per QALY = £3000; see *Table 42*). If the costs of BMD and physician visits are excluded, treatment would become even more cost-effective. Notwithstanding, some patients (e.g. with a *T*-score of –1.0 SD or higher) would be treated cost-ineffectively (see *Table 61*). However, the mean *T*-score of women at the age of 75 years is –1.94 SD and the number of women with a *T*-score of ≥–1SD is very small (<1%). This raises the second consideration, namely whether it is imperative to ensure that cost-effectiveness is delivered to all individuals, or whether it is sufficient to justify intervention on the basis of cost-effectiveness in sub-populations. A further problem is that it is counter-intuitive to clinical practice because some individuals with complications of the disease (a previous fragility fracture) would remain untreated, even if they had more than one fracture, whereas some individuals without a fracture would be offered treatment. For these reasons, a 'population based' approach is considered.

Population scenarios

The approach used was to determine the cost-effectiveness in populations of patients. The age distribution of the population was taken from the England and Wales Census data.[326] The proportion of patients at each age with a prior

TABLE 61 *Cost-effective treatment scenarios (given as a + sign) according to age, T-score and prior fracture*

Age (years)	*T*-score									
	No prior fracture					Prior fracture				
	–1	–1.5	–2.0	–2.5	–3.0	–1	–1.5	–2.0	–2.5	–3.0
50					+			+	+	+
55				+	+			+	+	+
60				+	+			+	+	+
65				+	+		+	+	+	+
70				+	+		+	+	+	+
75			+	+	+	+	+	+	+	+
80		+	+	+	+	+	+	+	+	+

fracture was adjusted for the prevalence of glucocorticoid use as described in Chapter 1.

The approach used was to ask the following questions:

1. At what age does age alone confer a sufficient risk that treatment becomes cost-effective?
2. In individuals who have a prior fragility fracture, at what age does treatment become cost-effective?
3. In individuals below a watershed age, at what *T*-score for BMD (measured at the hip) does intervention become cost-effective in the presence or absence of a prior fragility fracture?

Age threshold

Treatment of all individuals (aged 50 years or more) in the absence of a prior fracture would be effected with a cost per QALY of £35,000, which is above the cost-effectiveness threshold (see *Table 58*). As mentioned, treatment of all individuals at the age of 60 years or more would fall below an intervention threshold at a cost per QALY gained of £23,400 (see *Table 58*). It might be argued, therefore, that a threshold age of 60 years might be used, rather than the age of 65 years as provided by the current guidance. If such a policy were adopted, however, the range of cost-effectiveness in individuals would vary from £150,000 at age 60 years to £4000 at the age of 80 years in patients without a prior fracture (see *Table 42*). Indeed, at most ages from 60 years on treatment is cost-ineffective, and is confined to individuals aged 80 years or more. Of all patients aged 60 years or more, 25% are aged 80 years or more (see *Table 41*). Hence the majority of patients are given a cost-ineffective treatment using a threshold age of 60 years. If a threshold age of 75 years is used, 38% of the population receive treatment that is not cost-effective. The only viable age threshold is, therefore, at the age of 80 years, but would comprise a small proportion of all patients (18%). These considerations suggest that age may be an inappropriate criterion for the primary dichotomy.

Prior fracture

A somewhat different situation pertains to individuals with a prior fracture, since treatment is more cost-effective at any given age. A policy to treat all such patients would have a very favourable cost-effectiveness ratio of £1600 per QALY gained (*Table 58*). At specific ages, treatments would be cost-effective from about the age of 65 years. Since the incidence of fracture and therefore the prevalence of prior fracture increase with age, 91% of patients with prior fracture would lie above this age and receive cost-effective intervention. Conversely, cost-ineffective interventions are confined to a minority (9%). It seems reasonable, therefore, to consider treatment in all individuals with a prior fracture. The size of the population in whom cost-ineffective treatment would be given is small, BMD is avoided and would improve cost-effectiveness still further, and the decision rule is intuitive to patients and physicians.

No prior fracture

In patients without a prior fracture, it is evident that cost-effective scenarios are found for all individuals with a *T*-score of –3.0 SD or less (see *Table 61*). The question arises of whether less stringent criteria than that shown in *Table 61* might be used based on cost-effectiveness when populations above specific ages or below specific *T*-scores for BMD are modelled.

The relationship of cost-effectiveness with age range and *T*-score range is shown in *Table 62*. Also shown is the proportion of patients without prior fracture in each category. At the age of 50 years and above, for example, it is cost-effective to treat

TABLE 62 *Cost-effectiveness (£000/QALY gained: left-hand columns) and proportion of population without prior fracture (right-hand columns) according to* T*-score and age*

Age (years)	*T*-score				*T*-score			
	<–1	<–1.5	<–2.0	<–2.5	<–1	<–1.5	<–2.0	<–2.5
>50	83	49	26	11	61	42	22	6
>55	78	46	24	10	56	39	21	6
>60	73	43	23	8	49	35	19	5
>65	67	40	21	7	41	30	17	5
>70	62	36	18	5	31	23	14	4
>75	53	30	14	2	22	17	10	3
>80	44	24	10	0	13	10	6	2

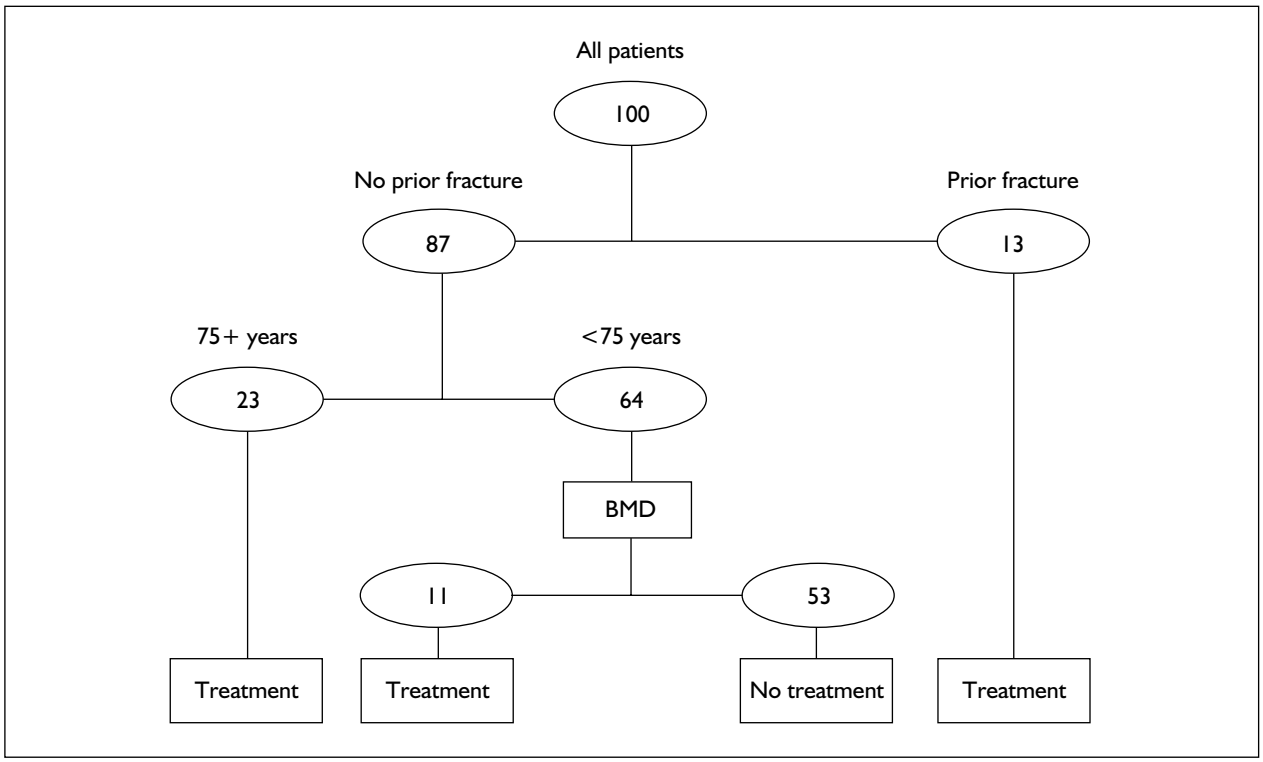

FIGURE 9 *Proportion of all patients (%) according to prior fracture status, age and BMD*

individuals with a *T*-score of <–2.0 SD (cost per QALY gained = £26,000), and this population comprises approximately 22% of patients without a prior fracture. A *T*-score of –2.0 SD is also appropriate as an intervention threshold for individuals aged 55 years.

At the age of 75 years and above or 80 years and above, a threshold *T*-score of –1.5 SD is cost-effective. However, very few individuals at age 80 years or more have a BMD that is ≥1.5 SD. Indeed, it is cost-effective to treat all individuals at the age of 75 years or more irrespective of BMD (see *Table 42*).

Assessment algorithm

The analysis above suggests that the following algorithm would be feasible:

1. The starting point is the determination of prior fracture status. Patients with a prior fracture would be considered for intervention irrespective of age or BMD.
2. In patients without a prior fracture, individuals at the age of 75 years or more would be considered for intervention without the requirement for a BMD test.
3. In patients aged less than 75 years and with no prior fracture, a BMD test would be considered and intervention considered where the BMD *T*-score was lower than a *T*-score threshold of –2.0 SD.

Impact of algorithm

The requirements for BMD testing are confined to patients without a fragility fracture. Of these, 26.6% would not require a BMD test by virtue of age. Thus, BMD tests would be required in 73.4%. Some 83.4% of individuals scanned would not fulfil the criteria for intervention, so that 12.2% of patients without a fracture (16.6% of patients scanned) would be eligible for treatment. Including patients aged 75 years or more, 38.8% of patients without a prior fracture would be eligible for treatment with bisphosphonate.

The overall impact of the assessment algorithm is summarised in *Figure 9*. BMD tests would be required in 64.1% of the glucocorticoid-treated population. Patients eligible for treatment include those with a prior fracture (13%), those without a prior fracture and aged 75 years or more (23%) and those fulfilling the criteria based on BMD testing (11%). Hence the algorithm would permit intervention in 47% of the entire population.

Chapter 7

Discussion and conclusions

This report has focused on a cost-effectiveness analysis of intervention with bone-specific agents in glucocorticoid-induced osteoporosis. The approach used was to review systematically the evidence for efficacy from RCTs. Systematic reviews from a previous HTA report were used to determine costs and health state utility values and updated with more recent information. An additional meta-analysis of primary data from population-based cohorts determined the fracture risk associated with long-term use of glucocorticoids and its dependence on BMD. An individual patient-based model was used and populated with hazard functions, drawn whenever possible from the UK. A particular feature of the model was that ranges of cost-effectiveness could be determined that took into account the uncertainties surrounding the effectiveness of intervention.

The principal finding of the systematic review on intervention was that evidence of anti-fracture efficacy was confined to a minority of agents used in the management of GIO. Only risedronate and calcidiol were shown to have significant effects on vertebral fracture risk, but neither had significant effects on non-vertebral fracture risk. In further meta-analyses, the effects of risedronate in GIO were compared with effects combining all available data for bisphosphonates in GIO and in postmenopausal osteoporosis. Since calcidiol is not licensed for use in the UK, cost-effectiveness analysis was confined to risedronate and to a pooled bisphosphonate effect.

Analysis of cost-effectiveness of risedronate using the empirical data in GIO showed better cost-effectiveness with increasing age, but at no age did cost-effectiveness ratios fall below the threshold value of £30,000 per QALY gained. When account was taken of BMD, cost-effectiveness was confined to less than 10% of patients with very low *T*-scores for BMD.

Further analysis was directed to 'bisphosphonate' assuming that its efficacy on fracture risk was comparable to that observed with bisphosphonates in postmenopausal osteoporosis. Cost-effectiveness was shown in patients with a prior fracture. In patients with no prior fracture, cost-effectiveness was observed in individuals aged 75 years or more. In younger patients without a prior fracture, cost-effective scenarios were found contingent upon a *T*-score for BMD that was ≤2.0 SD. The proposed assessment algorithm derived from these analyses is shown in *Figure 10*.

The observation that intervention is not cost-effective at all ages and at all probable *T*-scores indicates that conclusions are very sensitive to the assumptions used to populate the model and the modelling technique. Many of these assumptions and simplifications have been reviewed in previous chapters, and only those of particular importance to the conclusions or recommendations are detailed below. However, most of the assumptions used are conservative. This in turn should modulate the interpretation of the health economics analyses, in the sense that scenarios that demonstrate cost-effectiveness are likely to be robust, but that scenarios, without or with borderline cost-effectiveness may well be cost-effective but are surrounded by uncertainty. Moreover, lack of cost-effectiveness is not the sole arbiter of clinical utility. Assumptions that give rise to uncertainties of major importance include:

- the time frame of analysis
- treatment effects
- health state values in CIO
- the hazard functions.

Time frame of analysis

The time frame that we used is over a 10-year period. Modelling over a restrictive period rather than for a lifetime will affect apparent cost-effectiveness, particularly in younger individuals. In men and women at the age of 80 years, the remaining lifetime probability of fracture and their costs and consequences will be similar to those of a remaining lifetime at that age. By contrast, the same does not pertain to those at much younger ages. The impact of the use of different time horizons is shown in *Table 63*. A 10-year time horizon markedly decreases cost-effectiveness compared with a lifetime horizon . For example, women at the threshold of osteoporosis (*T*-score = –2.5) can be treated cost-effectively

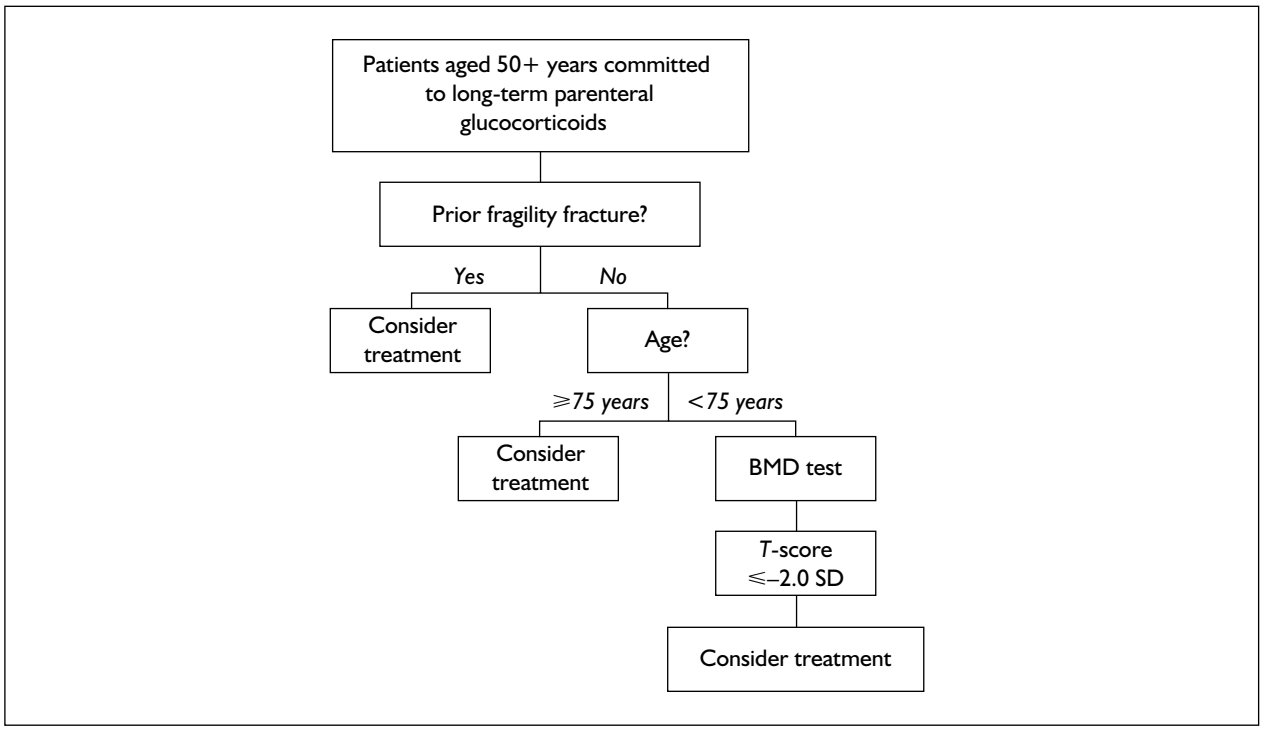

FIGURE 10 *Assessment algorithm for patients committed to long-term treatment with oral glucocorticoids*

TABLE 63 *Cost-effectiveness [cost (£000)/QALY gained] of intervention with risedronate in different clinical scenarios in women according to age*[a]

Age (years)	Osteoporosis (*T*-score = –2.5)		Prior fracture (no BMD test)[b]		Prior fracture and osteoporosis	
	10 years	Lifetime	10 years	Lifetime	10 years	Lifetime
50	119.0	35.0	150.9	49.1	34.2	11.6
55	91.7	29.4	110.6	39.0	25.1	9.2
60	70.6	24.8	81.3	30.6	18.3	7.4
65	43.7	17.8	42.5	18.0	9.8	4.7
70	26.3	13.0	21.2	10.9	3.8	2.5
75	18.8	11.8	12.2	8.0	0.4	1.0
80	12.7	10.2	4.8	4.3	Cost saving	Cost saving

[a] The time horizon is set at 10 years or for the remaining lifetime. Costs and benefits discounted at 3.5%. For all other assumptions used, see Kanis and colleagues.[94]
[b] Mean population BMD assumed.

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 is seen from the age of 70 years.[94]

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 our osteoporosis models was assumed to be 5 years. 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[219,223] for some of the bisphosphonates. Hence the constraints of a 10-year time horizon misrepresent the cost-effectiveness of interventions.

Treatment effects

There are sparse data concerning the efficacy of agents to reduce fractures in GIO and the data are more robust concerning the effects of interventions on BMD.[5] It was preferred, however, to focus on fracture outcomes rather than BMD for the several reasons discussed previously. The most important reason is that, although BMD is a predictor of fracture, there is an uncertain and ill-defined relationship between treatment-induced changes in BMD and changes in fracture outcome.[97,102] Within this framework, the analysis indicates an effect only of risedronate and calcidiol on vertebral fracture risk. No significant effect on non-vertebral fractures was demonstrated.

The few data available on anti-fracture effects may at first sight seem surprising in a disorder that is the most important secondary cause of osteoporosis and fracture. The major reason for this is that registrations in Europe and the USA for the use of agents in GIO are not dependent on the finding of fracture reduction. Rather, they depend on the demonstration of fracture efficacy (usually only for vertebral fracture) in postmenopausal osteoporosis and the subsequent demonstration that treatment-induced changes in BMD are comparable in postmenopausal osteoporosis and GIO. Hence fracture outcomes are not classical primary end-points in Phase 3 studies of GIO. This has led to the somewhat unsatisfactory position that the empirical data on fracture outcomes are limited for vertebral fracture and even more limited for non-vertebral fracture. This in turn has restricted the health economic analyses that are possible on specific agents using empirical data in GIO. Instead, we had to use the same argument as that used by registration authorities, that anti-fracture efficacy in postmenopausal osteoporosis is an adequate surrogate for anti-fracture efficacy in GIO. In addition, we pooled data available in GIO from all bisphosphonates for the comparison. This further assumes, as has been assumed by NICE and by ourselves in a previous review,[80] that anti-fracture efficacy between bisphosphonates is comparable. Insofar as is possible, our meta-analyses suggest that these assumptions are reasonable, but they nevertheless remain assumptions and an important limitation. The limitation is perhaps more relevant for hip fracture and other non-vertebral fracture than for vertebral fracture, since the empirical data in GIO for these outcomes are even fewer than for vertebral fracture.

The logic of including non-vertebral fractures in the analyses is that osteoporosis including GIO is a systemic disease affecting all regions of the skeleton. It may, therefore, be counter-intuitive, where agents acting systematically have demonstrated efficacy on vertebral fracture, to assume no effect on hip fracture risk, particularly where this is supported by RCT data in postmenopausal osteoporosis.

A further problem relating to bisphosphonates is that the responses to intervention in terms of vertebral fracture outcome may be non-linear. With risedronate, for example, the greatest risk reduction appears to occur in the early years of intervention. If true, this suggests that the longer the duration of treatment, the lower the RRR. Until these uncertainties are resolved, analyses of treatments for more than 5 years become progressively more speculative and this is the principal reason why the treatment time frame was restricted to 5 years. Conversely, however, shorter interventions might usefully be modelled when more information becomes available on offset times. Where offset time is fixed (e.g. 5 years), shorter durations of treatment have a very marked effect on improving cost-effectiveness.

There is good evidence that the offset of effect of intervention is not instantaneous. Offset times have not been systematically studied, although they form a recommendation by the WHO in drug development,[97] a view that we endorse because of its importance in the assessment of cost-effectiveness. A review of the available evidence suggests that the chosen offset time of 5 years might be conservative. The offset time has been shown to be a critical component of apparent cost-effectiveness,[214] although the effect is underestimated in the sensitivity analyses.

Also, most studies have compared the test agent plus calcium and/or vitamin D with a placebo with calcium and/or vitamin D. In effect, they are trials of superiority. On the assumption that calcium with or without vitamin D has intrinsic therapeutic effects, then the efficacy of the bisphosphonates may be underestimated. Such an assumption would only be valid if it could be shown that the effect observed with combination treatment was greater that the effect of the bisphosphonate alone. Such data are not available. Moreover, the effects of calcium and/or vitamin D appear to be greater in individuals with poorer nutritional status, so that any effect of calcium and vitamin D alone in RCTs of new agents is uncertain. For these reasons, the observed effects of bisphosphonates were not adjusted to take account of potential effects of calcium and vitamin D,

although it is acknowledged that this may be a conservative position.

We have not explicitly modelled the effect of possible side-effects of bisphosphonate in this report for several reasons. First, no excess side-effects have been shown for the bisphosphonates (alendronate and risedronate) when comparing placebo and test wings of large Phase 3 RCTs. Post-marketing surveillance does suggest that gastrointestinal upset occurs in a minority of patients, but the consequences on health state values are not known. In any event, patients with side-effects are likely to stop treatment with loss of both treatment effects and costs, so that cost-effectiveness is little affected, in much the same way as in non-compliant patients (see *Table 49*). It is possible, however, that side-effects would require an additional GP consultation. It is relevant that omitting a GP consultation had a very modest effect on cost-effectiveness, so that adding a GP consultation for a small minority of patients would have negligible effects.

Health state utility values in GIO

A previous systematic review highlighted the paucity of data available on health state utility values in established osteoporosis.[80,301] Since then, substantially more data have been generated for postmenopausal osteoporosis, but few data are available for GIO. The health state values for each fracture are based on those observed for postmenopausal osteoporosis, and clearly further work needs to be done in this area, using standardised methodology over the different health states.

There is also an information gap in established osteoporosis. Such individuals have already sustained a fragility fracture. The relevant question is the impact of a second fracture on existing health states and there is no literature available whatsoever. This posed problems in modelling. It was assumed that a second fracture at a different site will incur disutility attributable to both fractures using a multiplier. For example, an individual with a Colles' fracture who sustained a hip fracture would be assigned a utility equivalent to that of a hip fracture times the remaining disutility of the Colles' fracture. It was also assumed that an individual with a prior hip fracture would incur no further morbidity if a second fracture was sustained other than in the first year of the second fracture. Similarly, a patient with a vertebral fracture would sustain no further disutility from a second vertebral fracture other than that in the first year. This may well be a conservative scenario and again underestimate the utility losses in GIO.

Hazard functions in GIO

Due to the lack of available information for the UK, certain assumptions had to be made concerning the risks of death and fracture in GIO. With regard to mortality, it was assumed that the death hazard is similar in GIO to that observed in postmenopausal osteoporosis. This may be an underestimate because of the coexisting morbidity due to the underlying disorder for which glucocorticoids are given. Sensitivity analysis suggests, however, that any effect is modest. Also, for hip fracture, it was assumed that 24% of excess deaths were causally related to the hip fracture event, and this too may be underestimated by a small amount.

A further possible limitation of the analysis concerns the risk of vertebral fractures, which was confined to clinical vertebral fractures rather than morphometric vertebral fractures. The distinction is important since the available evidence indicates that vertebral fractures are rarely diagnosed by physicians in the UK, but nevertheless have attendant morbidity. When these were modelled in the sensitivity analysis (see *Table 55*), their inclusion had a marked effect on lowering the cost-effectiveness ratio and improving the grade of cost-effectiveness. For example, in patients aged 50 years with a *T*-score of –2.5 SD and without a prior fracture, treatment with bisphosphonates was cost-ineffective (grade C), but became cost-effective (grade B) when all vertebral fractures were included.

In this analysis, no account was taken of the likely relationship of dose and duration of use of glucocorticoids on fracture risk. For this reason, cost-effectiveness is likely to be improved in patients taking higher than average doses of glucocorticoids (and vice versa). Fracture risks are particularly high after solid organ transplantation. Account needs to be taken of this limitation of the analysis in the management of such patients, where for example less stringent *T*-score deficits for BMD might be used as intervention thresholds.

A further problem is that the risk of fracture appears to be particularly high immediately after an osteoporotic fracture. After about 12 months, the risk decreases to values derived in meta-analysis. Hence the risk is underestimated immediately after a fracture. The problem arises in part by the constraints of the model that do not

account for multiple fractures within each 1-year modelling interval.

This has little significance for the overall cost-effectiveness analysis, but has significance for the management of those patients who have very recently sustained a fragility fracture. Early, rather than later, intervention, would be more worthwhile.

A final limitation with regard to hazard functions is that it was assumed that patients with prior fractures have a basket of prior fractures determined by their frequency in the general population. This may be an oversimplification in GIO since vertebral fractures may occur earlier than non-vertebral fractures in the natural history of GIO compared with postmenopausal osteoporosis. This is of potential importance because cost-effectiveness is markedly better in patients with a prior vertebral fracture than in patients with prior fracture at another site (see *Table 54*).

All these considerations reinforce the view that the approach used is conservative.

Implications for practice

The results presented in Chapter 6 permitted a framework for assessment of patients with GIO, summarised in *Figure 10*. They provide important information for policy makers on the cost-effective management of GIO. The principal finding is that, within the assumptions previously discussed, there are cost-effective scenarios for a very substantial minority of patients committed to long-term treatment with glucocorticoids.

It should be noted that there are resource implications with regard to the assessment of BMD. The assessment algorithm suggests that 64% of all patients would require a BMD test (see *Figure 9*), which is greater than that suggested by current guidance.

The provision of DXA in the UK is probably suboptimal to service the requirements for osteoporosis,[327] and the likelihood of receiving treatment for GIO is much increased by access to densitometry.[12]

Recommendations for further research

There are several acknowledged deficiencies in this study that form the basis of these recommendations.

1. Intervention thresholds: the accepted operational definition of osteoporosis rests on the measurement of BMD at the hip. Osteoporosis is defined as a *T*-score of –2.5 SD or less. The widespread acceptance of this criterion has meant that *T*-score thresholds have been used for drug development, and also for practice guidelines.[25,69,88] It is notable, however, that the same *T*-score has a different significance at different ages and in different clinical contexts. As shown in this report, the presence of a prior fracture increases fracture risk over and above that accounted for by BMD and the risk of fracture in the absence of a prior fracture depends critically upon age. It is evident, therefore, that diagnostic thresholds should differ from intervention thresholds, even without consideration of health economics. Indeed, it is the view of the International Osteoporosis Foundation that in the future intervention thresholds should be based on absolute fracture probabilities such as 10-year risk.[251,328] As assessment guidelines develop, it will be important to change the analytic framework of health economic assessment to accommodate these concepts.
2. Monitoring of treatment: there is no consensus as to how to monitor treatment of osteoporosis with BMD, or indeed whether the monitoring of treatment is required. Since this has important consequences for resource utilisation, it is recommended that this be an important area of further research.
3. The cohorts of patients modelled had a range of osteoporotic fractures. However, different prior fractures have different future consequences, as shown in our sensitivity analysis. For example, treatment of women with a prior vertebral fracture is more worthwhile than treatment of women with a prior forearm fracture. The analysis of this context is not exhaustive and is amenable to further research.
4. There is a dearth of empirical data available on health state utility values in GIO using standardised methodology. This will require the administration of standardised preference-based generic measurements of health status to a large prospective population cohort with long-term follow up.
5. There is increasing evidence that some vertebral fractures that do not come to medical attention are associated with significant morbidity. Failure to account for these will affect conclusions concerning cost-effectiveness. More precise information on the incidence of vertebral deformities and their associated

impact on quality of life is required in the UK and is an important area of further research.
6. The epidemiology of fractures in GIO is incomplete. In particular, the pattern of fracture incidence at different sites needs to be compared with the pattern in postmenopausal osteoporosis.
7. The evidence base on the costs and effectiveness of interventions is changing rapidly. New agents are undergoing clinical development. Examples include parathyroid hormone, strontium and several new SERMs. In addition, new formulations are likely to become available in the UK with lower intervention costs than those used here. As further information becomes available, it will be important to update the present analysis.

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Contribution of authors

Matt Stevenson (Senior Operational Researcher) and Sarah Davis (Operational Researcher) were responsible for the population of the economic model and data analysis. Eugene McCloskey (Senior Lecturer in Bone Metabolism) carried out the meta-analysis of the effects of glucocorticoids and Myfanwy Lloyd-Jones (Senior Research Fellow) carried out the meta-analysis of the effects of interventions. John Kanis (Professor of Human Metabolism, now Emeritus Professor) was responsible for the supervision of the project and was lead writer.

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Appendix 1

Review of clinical effectiveness

Methods for reviewing effectiveness

Search strategy

Because of the range of interventions and comparators under review, the literature search was aimed to identify all literature relating to the prevention and treatment of corticosteroid-induced osteoporosis. The main searches were conducted in May and July 2002 and updated in September and October 2002.

Sources searched

Fourteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature. A list of the databases searched is provided in Appendix 2.

In addition, the reference lists of relevant articles were handsearched, and various health services research-related resources were consulted via the Internet. These resources included health economics and HTA organisations, guideline-producing agencies, registers of generic research and trials and specialist sites. These additional sources are listed in Appendix 3.

Search terms

A combination of free-text and thesaurus terms was used. General 'population' search terms (e.g. osteoporosis, bone, density, diseases, fracture) were used in order to identify all potentially relevant studies. 'Intervention' terms were not used in the main searches since it was felt that these might restrict the results and cause possibly relevant articles to be missed. The MEDLINE search strategy is included in Appendix 4. Search strategies for the other databases are available on request.

Search restrictions

No language, date or study-type restrictions were applied to the searches. However, in order to keep the number of hits to a sensible level, some more specific 'population' terms (e.g. steroid, glucocorticoid, corticosteroid, prednisolone) were used in the initial BIOSIS and Citation Indexes searches. Also, the updated BIOSIS search was performed as title only, and the updated Citation Indexes searches were limited with brief clinical trials, systematic reviews, guidelines and economics filters, and to title only.

An economics and quality of life evaluations filter and a systematic reviews filter were used in the main searches performed in MEDLINE and EMBASE to assist the identification of articles of these types (see Appendix 5). After the searches were completed, because of the large number of references retrieved, only the articles identified using these specific filters, the articles from the databases that were not searched with filters (such as BIOSIS), and the papers found through handsearching, etc., were reviewed.

Inclusion and exclusion criteria

Inclusion criteria

Participants

- any participants receiving oral corticosteroids for any reason, irrespective of BMD at study outset.

Interventions

- bisphosphonates
- SERMs
- parathyroid hormone
- vitamin D
- 1α-hydroxylated derivatives of vitamin D (referred to as vitamin D derivatives)
- calcitonin
- pharmacological doses of calcium
- oestrogens (opposed and unopposed)
- oestrogen-like molecules
- anabolic steroids
- fluoride salts
- thiazide diuretics
- testosterone.

Comparators

- any of the above interventions
- placebo
- no treatment.

Outcome measures

- vertebral fracture
- non-vertebral fracture
- associated effects
- continuance
- compliance.

Study design

- RCTs; trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind.

Discussion of outcome measures

Vertebral fractures may be symptomatic or asymptomatic. Symptomatic, or clinical, vertebral fractures are those which cause sufficient discomfort to be brought to the attention of a health professional. Their presence can be confirmed by X-ray. However, X-rays may also identify vertebral fractures which do not cause sufficient discomfort to be reported by the patient. Many studies report all vertebral fractures which are identified by X-ray: these are termed radiographic or morphometric, and will include both symptomatic and asymptomatic fractures. For the most part, therefore, the vertebral fracture data used in this report relate to radiographically identified fractures. However, data from one large study which reported both clinical and radiographic fractures suggests that, at least in postmenopausal osteoporosis, although the incidence of radiographic fracture is higher, the RR of suffering either type of fracture is very similar.[1] (Note: all references cited in the Appendices are given as a separate list in Appendix 10.)

Various definitions of radiographic fractures have been developed. Definitions which require a 20% reduction in vertebral height are generally recognised as producing fewer false negatives and false positives than those which only require a 15% reduction. In this report, therefore, data based on a 20% fracture definition were preferred, as the reduction in specificity associated with the use of a 15% definition would reduce the perceived efficacy of the intervention being studied. The use of a semiquantitative method also results in greater specificity than the use of a 15% definition alone.

RCTs generally cannot provide definitive information about drug toxicity. They may underestimate the incidence of drug-related adverse events, both because their populations may not be wholly typical of the target population (as they tend to exclude older participants and those with co-morbidities), and because they are not powered to identify rare, although potentially serious, adverse events; moreover, they do not always measure all potential side-effects.[2] For this reason, in addition to data drawn from the studies under review, relevant evidence from other sources has been used in discussing the various incidental effects, whether adverse or beneficial, associated with the various treatments for corticosteroid-induced osteoporosis.

Continuance and compliance are particularly important in relation to preventive therapies: both may be poor as, because of the lack of immediate benefit, there is no obvious stimulus to take the medication, and adverse effects may consequently increase in significance. Continuance is here understood to mean continuing in principle to take the relevant medication, while compliance relates to taking it consistently and in accordance with the dosage regimen. The risk of non-continuance or non-compliance with prescribed medication is particularly high in patients with asymptomatic chronic diseases or risk factors which require long-term preventive medication.[3] Continuance and compliance depend on a number of properties of the medication in question, including tolerability, convenience of administration, the patient's perception of its safety and quality of life while on treatment.[3] Adherence to and compliance with medication are clearly important in relation to the actual, rather than theoretical, efficacy of the interventions under study and therefore, as with adverse effects, data drawn from the studies under review will be supplemented with data from other sources when relevant.

However, continuance is particularly complex in relation to the studies reviewed in this report. In many studies, patients whose daily corticosteroid dose fell below a prespecified level (generally 7.5 mg of prednisone or equivalent) were withdrawn from the study per protocol. In addition, because of the often serious health problems suffered by the study participants, a relatively high proportion either died during the course of the study or were withdrawn because of exacerbation of their underlying condition. Hence, although only a low proportion of patients may complete the study protocol, this is not necessarily a reflection of the acceptability of the study medication.

Exclusion criteria

Only published studies were included, including those available only as abstracts. As unpublished studies are more likely than published studies to demonstrate small or absent treatment effects, it is recognised that this approach is likely to overestimate the true effects of treatment. However, it was not possible in the time available to seek out unpublished studies.

Sifting

In principle, the references identified by the literature searches were sifted in two stages, being screened for relevance first by title and then by abstract. However, as it was not possible to identify all relevant studies with fracture outcomes from titles alone, the title sifting stage was used essentially to reject studies which were clearly irrelevant. Following this, the abstracts of all studies which used the relevant interventions in the relevant populations were screened (for studies which did not provide abstracts, the full studies were screened). Seventeen studies which had been identified by the literature searches were not identified as relevant at the abstract[4–19] (or, in one case,[20] title) sifting stage; they were identified from other reviews as reporting fracture outcomes. The failure of the sifting process to identify so many studies was because fracture was only a secondary outcome measure in many studies, and therefore was not always mentioned in the abstract.

Data extraction strategy

Data were extracted by one reviewer, using customised data extraction forms.

Where available, data relating to the following were extracted:

- incident vertebral fractures
- incident non-vertebral fractures
- incident hip fractures
- incident wrist fractures
- associated effects (both adverse and beneficial)
- continuance and compliance.

Quality assessment strategy

The methodological quality of all trials which met the inclusion criteria was assessed using the tool developed by Gillespie and colleagues.[21] This tool was selected because it was intended specifically for the assessment of randomised or quasi-randomised trials of interventions designed to prevent fractures associated with osteoporosis.

The quality assessment tool included the following items:

- adequacy of randomisation and of masking of randomisation
- blinding of outcome assessors to subjects' treatment allocation
- withdrawals – whether the outcomes of people who withdrew were described and included in the analysis
- comparability of groups at baseline
- confirmation of diagnosis of hip or other appendicular skeleton fracture
- method of diagnosis of vertebral fracture.

Definitions of the various levels of randomisation and concealment of randomisation derived from Prendiville and colleagues[22] were incorporated in the tool (see Appendix 6).

It is recognised that the quality assessment tool assesses reporting quality, and not necessarily the true methodological quality of each study. However, where trials were reported in more than one publication, the quality score was calculated on the basis of the combined data from all relevant publications.

The quality assessment of studies included in the review of clinical effectiveness was carried out by one researcher. Blinding of the quality assessor to author, institution or journal was not considered necessary.[23,24]

Meta-analysis strategy

Studies which met the review's entry criteria were eligible for inclusion in the meta-analyses provided that they reported fracture incidence in terms of the number of subjects suffering fractures: this allowed the calculation of the RR of subjects in the intervention group developing a new fracture or fractures, compared with subjects in the control group. Studies which reported only numbers of fractures, or fracture rates (i.e. numbers of fractures per hundred or thousand patient years), could not be included in the meta-analyses unless it was possible to obtain from the authors unpublished information on the number of subjects who suffered fractures. The meta-analysis of data relating to numbers of fractures or fracture rates would have violated the basic statistical assumption that the occurrence of one event does not increase the likelihood of a subsequent event[25] since, once a subject has suffered an osteoporotic fracture, the risk of a subsequent fracture increases.[26,27]

Ideally, only those studies which had fracture as a primary end-point would have been included in the meta-analyses. However, pragmatically this was not possible as only one study[28,29] met this criterion. Meta-analysis was carried out using Review Manager.[30] A fixed-effects model was used.

Since the end-point of interest was fracture, it seemed appropriate (*pace* Meunier[31]) to include open-label studies. Especially in relation to the identification of radiographic vertebral fractures,

the most commonly used fracture end-point, it is more important that the outcome assessor be blinded to treatment allocation than that the patient or healthcare provider be so blinded.

To ensure comparability, when possible the meta-analyses of vertebral fractures only pool data from studies which use the same definition of vertebral fracture – ideally, a definition which required a 20% or greater reduction in anterior, middle or posterior vertebral height because, as noted above, such a definition was felt to identify fractures more reliably than one which required only a 15% or greater reduction.

In general, anti-osteoporotic therapies are termed preventive if given to patients with normal or unidentified BMD, or as treatment if they are given to patients with low BMD or pre-existing osteoporotic fracture. However, in the context of corticosteroid-induced osteoporosis, it has been suggested that the distinction should be drawn on the basis not of BMD but of duration of corticosteroid therapy, as bone loss is greatest in the earlier stages of corticosteroid therapy and slower thereafter.[32] So, Homik and colleagues[33] define as primary prevention the therapy of patients initiating corticosteroid treatment, and as secondary prevention the therapy of patients currently being treated with corticosteroids; they suggest that primary prevention trials are unlikely to show any difference in fracture efficacy unless they are of long duration. Adachi and colleagues[34] define as prevention studies those in which patients commence corticosteroid therapy at a mean daily dose ≥7.5 mg/day no more than 100 days before study entry, and as treatment studies those in which patients had received a mean daily dose between 5 and 20 mg/day for at least 3 months before study entry. In this review, therefore, where possible the results from studies recruiting patients who commenced corticosteroid therapy no more than 100 days before study entry will be analysed separately from those in which patients received treatment for at least 3 months before study entry.

Meta-analysis results are reported as RRs, using a fixed-effects model.

Results: general

Quantity and quality of research available

Number of studies of clinical efficacy identified

The electronic literature searches identified 12,375 potentially relevant articles. Of these, 48 articles related to 44 trials which compared an intervention of interest with a relevant comparator; an additional trial was identified from a citation only.

The standard sifting process yielded 31 papers which related to 28 relevant studies of clinical effectiveness (*Figure 11*).

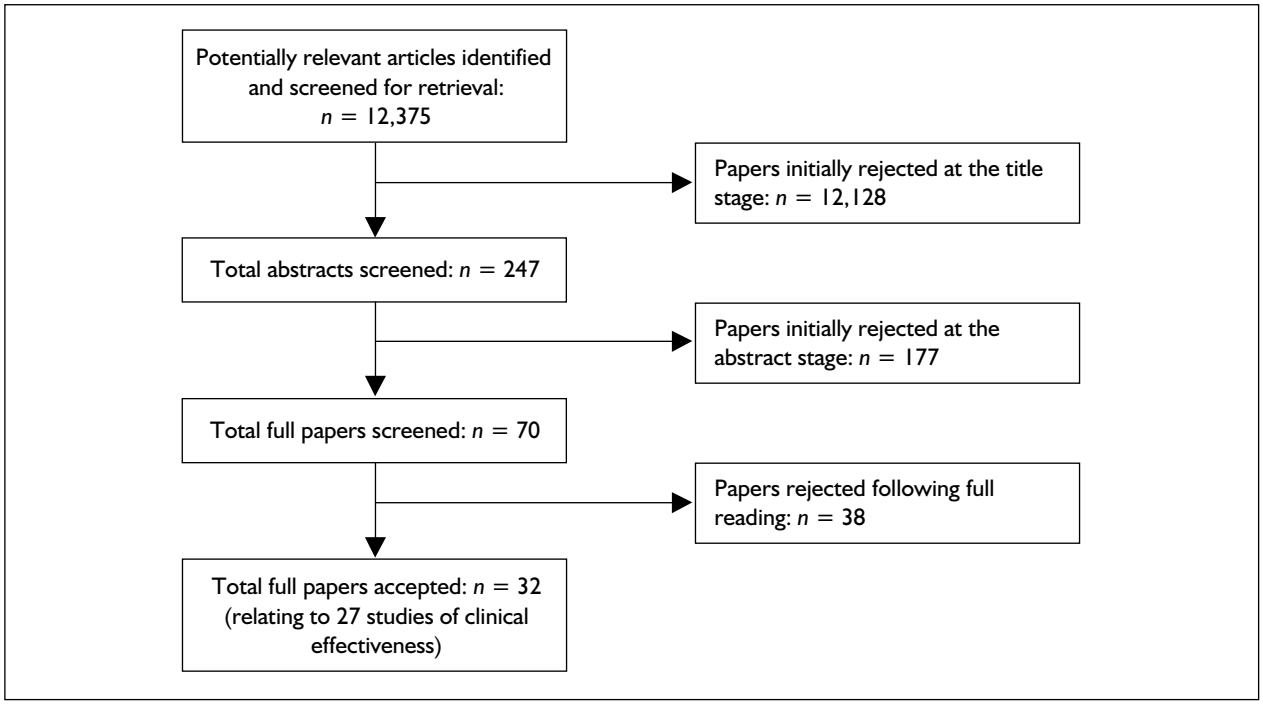

FIGURE 11 *Summary of study selection and exclusion: electronic literature searches*

However, as noted earlier, papers identified by the electronic literature searches relating to 17 relevant studies were initially rejected as irrelevant at either the title or the abstract stage; it was only realised that they contained relevant data as a result of references in other sources. In addition, a further relevant study[35] was identified only from a citation.

Number and type of studies included

A total of 45 individual RCTs met the review inclusion criteria; these are listed in Appendix 7. Given the volume of the evidence, it was not felt necessary to include other study designs.

Number and type of studies excluded, with reasons

As can be seen from the section 'Number of studies of clinical efficacy identified' (p. 94), over 12,000 studies which did not meet the inclusion criteria were excluded as part of the sifting process. Details are therefore given only of those studies which were excluded at the full paper stage, and even then only if the reason for exclusion was not immediately apparent from the full text. Such studies, and the reasons for their exclusion, are listed in Appendix 8.

Reporting of results of included studies

This report reviews evidence relating to a large number of interventions. The nature of the evidence relating to each intervention is discussed in turn below, and their effectiveness is assessed. In each case, studies which compare two or more active interventions are discussed before those which compare an active intervention with placebo or no treatment.

Studies in which both the intervention and control groups receive either calcium and/or vitamin D or HRT in comparable doses are treated as comparisons with placebo/no treatment.

As noted in the section 'Inclusion criteria' (p. 91), where appropriate, evidence from other studies will be used to supplement data from the studies under review in relation to the non-skeletal beneficial and adverse effects of the interventions, and in relation to continuance and compliance with treatment.

Results: alendronate

Alendronate: quantity and quality of research available

Only two relevant publications were identified. These reported the pooled results of a US and a multinational RCT of near-identical design which compared various doses of oral alendronate with placebo. All subjects, including those in the placebo group, received 800–1000 mg/day calcium and 250–500 IU/day vitamin D (for details, see Appendix 9, *Table 102*).

The original 48-week study, reported by Saag and colleagues[36] enrolled men and women aged 17–83 years who were expected to require therapy for at least 1 year with at least 7.5 mg of prednisone or its equivalent for rheumatological, pulmonary, dermatological, gastrointestinal or other diseases. Patients from the USA were randomised to receive either 5 or 10 mg/day alendronate or placebo; those from other countries were randomised to 2.5, 5 or 10 mg/day alendronate or placebo. In all, 477 patients were randomly allocated to receive either 5 or 10 mg/day alendronate or a matching placebo; 83 patients were randomly allocated to 2.5 mg/day alendronate[36] (clarification from Daifotis A: personal communication, 2003). Randomisation was stratified by duration of previous glucocorticoid therapy at baseline. Some 34% of postmenopausal women in the study were taking HRT; they continued taking the same dose throughout the study. Although low BMD was not an inclusion criterion, 32% of subjects had a *T*-score below –2 at baseline[36] (for details, see Appendix 9, *Table 103*).

A total of 389 patients were eligible to enter the subsequent 12-month extension study, reported by Adachi and colleagues,[37] by virtue of completing the original study and still receiving at least 7.5 mg/day oral prednisone or equivalent. However, 97 of these eligible patients were at sites which ceased to participate in the study, either because of the investigator's concerns about continuing patients on masked treatment for a further year or because of low patient enrolment. Seventy-five of the remaining 292 patients (26%) refused to participate and a further nine were switched to 10 mg open-label alendronate The remaining patients continued to receive the medication to which they had been randomised at the beginning of year 1, with the exception of those originally assigned to 2.5 mg alendronate, who were blindedly switched to 10 mg. Of the 208 patients who continued in the trial, 166 (80%) completed the second year.[37]

The treatment groups appeared comparable in relation to potential prognostic factors (for details, see Appendix 9, *Table 104*).

As published, this study did not provide evidence of appropriately masked randomisation (for details, see Appendix 9, *Table 105*). However, vertebral fracture outcomes were evaluated at a central facility by assessors who were blinded to treatment group.

Alendronate: assessment of effectiveness

Fracture data relating to those patients who had received 2.5 mg/day alendronate were not reported and only pooled data were presented from the 5- and 10-mg groups.

Vertebral fracture

As can be seen from *Table 64*, the original 48-week study failed to achieve statistical significance even when a *post hoc* analysis was undertaken using a visual semiquantitative assessment. Marginal significance ($p = 0.05$) was achieved with the semiquantitative method using data relating only to the postmenopausal women in the study,[36] but such an analysis is inappropriate since randomisation was not stratified by gender and menopausal status.

Although the extension study produced a statistically significant overall result which favoured alendronate (*Table 64*), this cannot be accepted uncritically. Because only 208 of the original 560 subjects (37%) took part in the extension study, the original randomisation was weakened, not least since patients who had suffered incident vertebral fractures during the original 48-week period were disproportionately under-represented in the extension study. Although the analysis at 2 years was said to be by intention-to-treat, overall 2-year data were only presented in relation to those patients who completed the 2-year study (45% of the pooled alendronate group and 37% of the placebo group), and not in relation to all those who were enrolled in the original 48-week study. The results may therefore be overly favourable to alendronate, and full confidence can only be placed in the 48-week data.

Non-vertebral fracture

Alendronate was not shown to have a statistically significant effect on non-vertebral fracture (*Table 65*). Again, full confidence can only be placed in the 48-week data.

Alendronate: side-effects

Bisphosphonates have been associated with adverse upper gastrointestinal (GI) events. In the above study, no significant differences were reported between treatment groups, at either 48 weeks or 2 years, in the incidence of adverse events that were considered serious or that led to withdrawal from the study. At 48 weeks, the most

TABLE 64 *Alendronate: vertebral fracture data*

Study	Alendronate dose	Fracture definition	Number in each group suffering vertebral fracture
Saag, 1998;[36] Adachi, 2001[37]	5 or 10 mg/day	A decrease of ≥20% and ≥4 mm between baseline and follow-up in anterior, middle or posterior vertebral-body height	Year 1 (all subjects): Alendronate: 6/266 Placebo: 5/134 RR 0.60; 95% CI 0.19 to 1.94
			Year 1 (patients entering 2nd year of study only): Alendronate: 1/143 Placebo: 1/59 RR 0.41; 95% CI 0.03 to 6.49
			Year 2: Alendronate: 0/143 Placebo: 3/59 RR 0.06; 95% CI 0.00 to 1.13
			Overall at 24 months: Alendronate: 1/143 Placebo: 4/59 RR 0.10; 95% CI 0.01 to 0.90 (not true intention-to-treat analysis)
		An increase in at least 1 grade using a visual semiquantitative assessment[38] (used in year 1 only)	Year 1 (all subjects): Alendronate: 8/268 Placebo: 8/134 RR 0.50; 95% CI 0.19 to 1.30

TABLE 65 *Alendronate: non-vertebral fracture data*

Study	Alendronate dose	Number in each group suffering non-vertebral fracture
Saag, 1998;[36] Adachi, 2001[37]	5 or 10 mg/day	At 48 weeks: the incidence of non-vertebral fracture was said to be identical at 4.4% in both the placebo and the combined alendronate groups (exact numbers not given); the most common fracture sites were the ribs and forearm At 2 years: Alendronate: 8/147 Placebo: 6/61 RR 0.55; 95% CI 0.20 to 1.53

common adverse events were musculoskeletal pain, upper respiratory infection, headache and urinary tract infection. Upper GI adverse events (mainly abdominal pain) were significantly more common in the 10-mg group than in the other two groups, but seldom resulted in study discontinuation. At 2 years, no meaningful differences were identified between study groups in terms of either adverse events leading to withdrawal or upper GI adverse events (for details, see Appendix 9, *Table 106*); however, the possibility cannot be excluded that the subjects most susceptible to adverse events had refused to participate in the extension study.

Postmarketing studies have found that around one-third of alendronate users report GI adverse events.[39] Some develop chemical oesophagitis, including severe ulcerations, which mostly resolves when alendronate is stopped.[40] Most patients who suffer oesophageal complications do so soon after the start of alendronate administration; in many instances, these complications seem to be associated with failure to take the drug with adequate quantities of water, or to remain upright afterwards, or both.[40]

A UK questionnaire survey found that, in 1523 patients who had been prescribed alendronate, dyspepsia, nausea/vomiting and abdominal pain were the most frequently reported adverse events, and also the most common reasons for discontinuation of therapy; 1.3% of all patients in this survey experienced possible oesophageal reactions to alendronate.[41] However, a US retrospective cohort study found no statistically significant difference between 6432 patients dispensed 10 mg/day alendronate and an age- and sex-matched unexposed group in terms of the incidence of hospitalisations for gastric or duodenal perforations, ulcers and bleeding after adjustment for age, sex, chronic disease score, recent exposure to prescription non-steroidal anti-inflammatory drugs (NSAIDs) or oral corticosteroids and number of hospitalisations in the year preceding alendronate prescription (or the referent date for the non-exposed group) (RR alendronate versus controls 1.8, 95% CI 0.8 to 3.9).[42]

Alendronate has no documented extra-skeletal benefits.

Alendronate: continuance and compliance

In the study reviewed above, between 84 and 87% of patients in each treatment group completed the original 48-week study (see Appendix 9, *Table 105*). However, as noted above, 75 (26%) of the 289 patients who were eligible for inclusion in the extension study by virtue of completing the 48-week study and remaining on corticosteroid therapy, and who were neither on sites which ceased to participate in the study nor switched to open-label alendronate for clinical reasons, refused to continue in the trial. Thus, although 80% (166/208) of the patients who entered the extension trial completed 2 years of treatment, it should be noted that they formed only 57% of those who might have participated.

A US survey of continuance in 813 women treated with alendronate found that 28.7% stated that they had discontinued treatment, whereas prescription refill records suggested that 30.2% had actually discontinued. GI problems were most commonly given as the reason for discontinuation, being cited by 51.9% of women who had stopped taking the drug.[43]

Clodronate

Clodronate: quantity and quality of research available

Only one relevant RCT was identified.[9] This studied patients who had received renal allografts

more than 6 months previously and who had a *T*-score of –1.5 or below; 44 of the 46 patients (96%) received corticosteroids for immunosuppression. Four patients had one or more vertebral fractures at baseline.

The study compared 800 mg/day oral clodronate with 200 IU/day intranasal calcitonin, taken as a divided dose, and with no treatment. Both clodronate and calcitonin were taken cyclically, with 14 days of treatment followed by 75 treatment-free days. All subjects, including untreated controls, received 500 mg/day calcium gluconate. Supplementary vitamin D was not given. One postmenopausal woman in the clodronate group had received HRT for several years; this was continued through the study period (for details, see Appendix 9, *Table 107*).

As reported, the quality of this study is not ideal. It appears to have been open-label, although this is never stated. Patients were allocated to treatment using sealed envelopes, a method which is not tamper-proof, and the outcome assessors were not said to have been blinded to study allocation. Although the groups were comparable in most respects at baseline, the distribution of postmenopausal women was uneven ($p = 0.043$); it was not stated to which treatment groups the patients with prevalent fractures at baseline were allocated (see Appendix 9, *Tables 108–110*).

Clodronate: assessment of effectiveness

Vertebral fracture

No incident vertebral fractures were reported in any group.

Non-vertebral fracture

There was no statistically significant difference between treatment groups in terms of non-vertebral fracture (*Table 66*). One patient in the calcitonin group fractured an upper arm bone and one in the untreated group a lower arm bone.

Clodronate: side-effects

As noted above, bisphosphonates have been associated with adverse upper GI events. However, clodronate is much less gastrotoxic than the aminobisphosphonates (alendronate, ibandronate, pamidronate and risedronate).[44] In the study reviewed above, upper GI adverse events (diarrhoea and abdominal discomfort) occurred in two patients in the clodronate group; one patient in the untreated group suffered vomiting. These adverse effects were mild or moderate in severity and did not cause withdrawal from the study.

Clodronate has no documented extra-skeletal benefits.

Clodronate: continuance and compliance

In the study reviewed in this section, all patients completed the protocol with the exception of one patient in the untreated control group who died of coronary heart disease. Compliance was not reported.

Etidronate

Etidronate: quantity and quality of research available

Twelve RCTs were identified which compared etidronate with another intervention or with placebo or no treatment, and which reported fracture outcomes.[8,10,11,16,17,19,45–50] Three of these compared etidronate with active treatments (calcidiol, calcitonin, calcitriol and alfacalcidol);[10,47,49] the remainder compared etidronate with placebo[8,11,16,17,45,46] or no treatment.[19,48,50] For details of treatment regimens, see Appendix 9, *Table 112*.

Three studies were undertaken in transplant patients,[10,47,49] two in patients with inflammatory rheumatic diseases,[11,46] one in patients with diffuse connective tissue disease,[48] one in asthma patients[50] and the remainder in patients who were receiving corticosteroids for a variety of diagnoses. One study was carried out specifically in postmenopausal women.[8]

Only one study[48] was carried out in patients specifically selected as having osteoporosis (as defined by the Japanese Society for Bone and

TABLE 66 *Clodronate: non-vertebral fracture*

Study	Comparator	Number of subjects suffering fracture		RR of fracture (95% CI): clodronate vs comparator
		Clodronate	Comparator	
Grotz, 1998[9]	Intranasal calcitonin	0/15	1/16	0.35 (0.02 to 8.08)
	No treatment	0/15	1/15	0.33 (0.01 to 7.58)

TABLE 67 *Etidronate: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): etidronate vs comparator
			Etidronate	Comparator	
Garcia-Delgado, 1997[47]	Calcidiol	Vertebral	3/14	0/13	6.53 (0.37 to 115.49)
	Calcitonin	Vertebral	3/14	4/13	0.70 (0.19 to 2.54)
Henderson, 2001[10]	Calcitriol	Symptomatic vertebral	3/20	0/21	7.33 (0.40 to 133.57)
		Non-vertebral	0/20	2/21	0.21 (0.01 to 4.11)
Van Cleemput, 1996[49]	Alfacalcidol	Symptomatic vertebral	3/19	0/22	8.05 (0.44 to 146.59)
		Radiographic vertebral (20% definition)	Year 1: 4/19	Year 1: 1/22	4.63 (0.57 to 37.96)
			Year 2: 4/19	Year 2: 1/22	4.63 (0.57 to 37.96)
			Overall: 5/19	Overall: 2/22 (it is just possible that both fractures in this group occurred in 1 patient)	2.89 (0.63 to 13.24)

Mineral Research's 1996 criteria for primary osteoporosis[51]); 28% of patients in this study had vertebral fractures at baseline. In another study,[19] most subjects had already suffered at least one vertebral fracture, although low BMD was not an entry criterion. However, in one study,[16] normal BMD was a requirement of study entry. For further details, see Appendix 9, *Table 113*.

The studies varied in their entry requirements in relation to corticosteroid therapy. Those studies which were carried out in transplant patients[10,47,49] did not stipulate a minimum corticosteroid dose. The other studies stipulated starting doses ranging from a minimum of 5 mg/day prednisolone equivalent (for further details, see Appendix 9, *Table 113*). In one study,[19] all patients whose prednisolone dose fell below 5 mg/day were withdrawn per protocol.

In the majority of studies, all subjects received the same calcium regimen, in most cases without supplementary vitamin D. However, in one study,[48] neither arm received supplementary calcium although both received vitamin D_3. In another study,[50] both groups received supplementary calcium but only the etidronate group received vitamin D, whereas in the comparison with calcitriol[10] only the etidronate arm received supplementary calcium. For further details, see Appendix 9, *Tables 112–114*.

As reported, the quality of the above studies was variable: only one[8] provided evidence of adequately masked randomisation and only three[16,19,45] stated that the fracture outcome assessors were blinded to study allocation (see Appendix 9, *Table 115*). In one study, 'randomisation' was undertaken by alternate allocation.[49]

Etidronate: assessment of effectiveness

Comparisons with active treatment

All of the comparisons with active treatment were carried out in transplant patients. In the van Cleemput study,[49] the alfacalcidol group, having a higher mean age and a slightly higher steroid dose, appeared to be at higher risk of fracture than the etidronate group (see Appendix 9, *Table 113*). None of the studies was large enough to demonstrate a statistically significant result in relation to fracture outcomes (*Table 67*).

Comparisons with placebo or no treatment

Vertebral fracture

Ten studies provided some information relating to the incidence of vertebral fracture. These used a variety of fracture definitions. All but one[16] (the only study in which normal BMD was an entry criterion) yielded point estimates which favoured etidronate, but again none was large enough to produce a statistically significant result (*Table 68*).

Ideally, data from studies with different fracture definitions would not be pooled. However, as noted in the section 'Inclusion criteria' (p. 91), data relating to clinical fractures seem comparable, at least in postmenopausal osteoporosis, to data relating to radiographic

TABLE 68 *Etidronate: vertebral fracture data*

Study	Etidronate dose (mg/day)	Fracture definition	Number in each group suffering vertebral fracture
Adachi, 1997[45]	400	Any increase in the vertebral deformity score (where grade 0 = normal, grade 1 = a 20–25% reduction in anterior, middle or posterior vertebral height relative to adjacent vertebrae, grade 2 = a 26–40% reduction and grade 3 = a greater than 40% reduction)	Etidronate group: 5/57 Placebo group: 10/65 RR 0.57 (95% CI 0.21 to 1.57)
Cortet, 1999[46]	400	Symptomatic	Etidronate group: 1/44 Placebo group: 1/39 RR 0.89 (95% CI 0.06 to 13.70)
Geusens, 1998[8]	400	Symptomatic	Etidronate group: 0/18 Placebo group: 1/19 RR 0.35 (95% CI 0.02 to 8.09)
Jenkins, 1999[11]	400	Symptomatic	Etidronate group: 0/6 Placebo group: 1/7 RR 0.38 (95% CI 0.02 to 7.93)
Jinnouchi, 2000[48]	200	Not clear	Etidronate group: 1/16 Control group: 1/9 RR 0.56 (95% CI 0.04 to 7.95)
Pitt, 1998[16]	400	Semiquantitative (method of Genant *et al*.[52])	Etidronate group: 2/26 Placebo group: 1/23 RR 1.77 (95% CI 0.17 to 18.26)
Roux, 1998[17]	400	Symptomatic (Roux C, personal communication)	Etidronate group: 2/59 Placebo group: 3/58 RR 0.66 (95% CI 0.11 to 3.78)
Skingle, 1997[19]	400	Method of Eastell *et al*.[53]	Gives numbers of fractures in each year, and numbers of patients suffering fractures in 2nd year. However, the denominator is not clear, and it is not clear how many patients suffered new fractures in the full 2-year period
Worth, 1994[50]	7.5 mg/kg/day	15%	Etidronate group: 0/14 Control group: 4/19 RR 0.15 (95% CI 0.01 to 2.55)

fractures measured using a 20% fracture definition.[1] It therefore does not seem wholly inappropriate to pool data from those studies which started treatment with etidronate within 100 days of commencement of treatment with high-dose corticosteroids (i.e. prevention studies), even though three of these reported only symptomatic fractures. This meta-analysis yielded an RR of vertebral fracture of 0.59 (95% CI 0.27 to 1.32) in patients receiving etidronate compared with those receiving placebo (*Figure 12*).

Those studies in which patients had received corticosteroids for at least 3 months[8,48,50] used a wider range of fracture definitions (*Table 68*). If the data from these studies are pooled, the RR of vertebral fracture in patients receiving etidronate is 0.48 (95% CI = 0.14 to 1.64) compared with those receiving placebo or no treatment (*Figure 12*). However, it is questionable whether such pooling is appropriate, and indeed the central estimate yielded by the study of Pitt and colleagues in which normal BMD was an inclusion criterion[16] appears to be anomalous. Removal of this study yields an RR for treatment studies of 0.27 (95% CI 0.05 to 1.40).

As can be seen, the treatment effect demonstrated by this pooling of data is similar in both prevention and treatment, but does not achieve statistical significance in either case. Even when the data from both prevention and treatment studies are pooled, the results fail to achieve significance (RR 0.55; 95% CI 0.28 to 1.08).

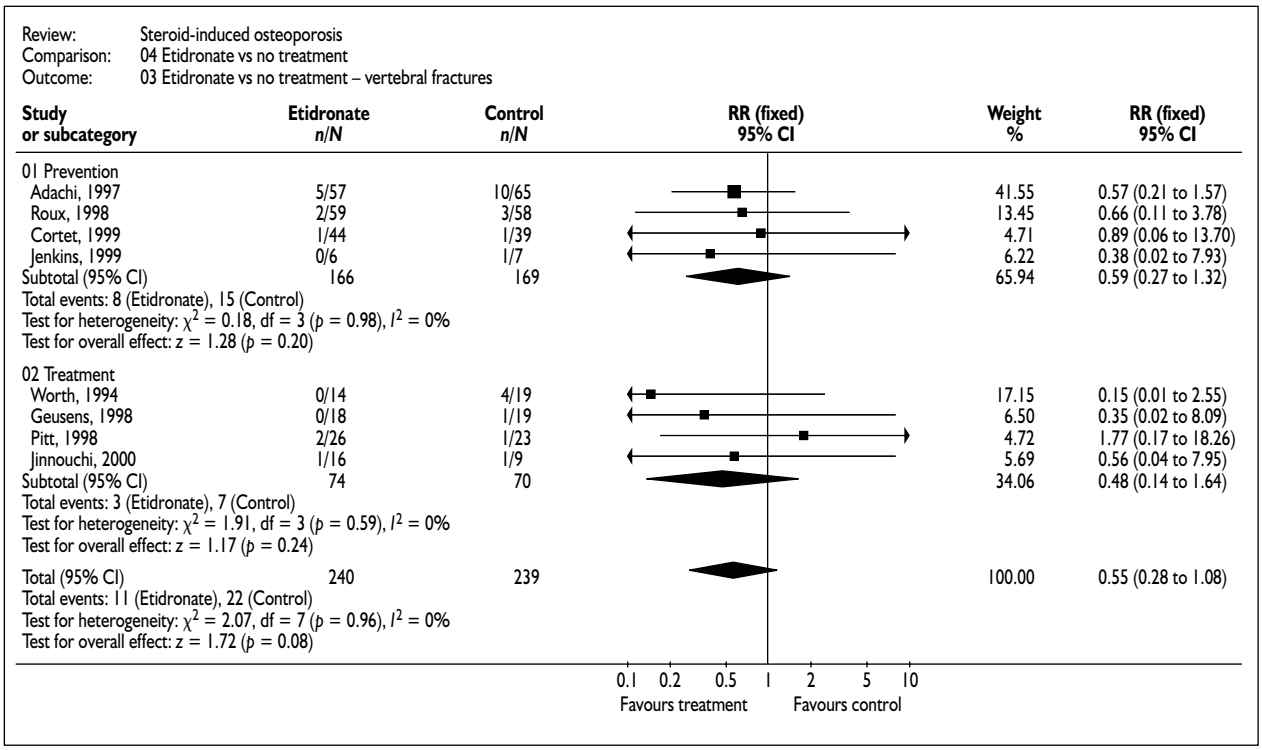

FIGURE 12 *Etidronate: vertebral fracture*

One study[45] stratified randomisation by sex and menopausal status, and presented the results in that format (*Table 69*). Although the point estimate of RR was lowest in postmenopausal women, the group at highest risk of fracture, the study was not large enough to achieve statistical significance even in this group.

Non-vertebral fracture

Two studies presented data relating specifically to the number of patients suffering non-vertebral fractures (*Table 70*). A third study[46] stated the number of patients in each group who suffered clinical fractures of any type; in the absence of information on how many fracture occurred, it is not clear how many patients suffered non-vertebral fractures since the one vertebral fracture in each group might have occurred in a patient with or without a non-vertebral fracture.

None of the studies were large enough to demonstrate a significant result in relation to non-vertebral fracture and pooling of the data from the two studies which provided separate data on non-vertebral fracture did not achieve significance (RR 0.38; 95% CI 0.10 to 1.38; *Figure 13*).

Etidronate: side-effects

Like alendronate, etidronate has been associated with upper GI adverse events. Although some of the RCTs included in this review reported such adverse events, in most cases there was no significant difference between treatment groups in this respect (see Appendix 9, *Table 116*). In only one study[50] were any withdrawals attributed to upper GI adverse events; three of the 20 patients in the etidronate group withdrew for this reason.

TABLE 69 *Etidronate: vertebral fracture data by sex and menopausal status*

Subgroup	Number of subjects suffering fracture		RR of fracture (95% CI)
	Etidronate	Placebo	
Postmenopausal women	1/31	7/32	0.15 (0.02 to 1.13)
Premenopausal women	0/7	0/8	Not estimable
Men	4/19	3/25	1.75 (0.44 to 6.92)

TABLE 70 *Etidronate: non-vertebral fracture data*

Study	Etidronate dose (mg/day)	Number in each group suffering non-vertebral fracture
Cortet, 1999[46]	400	All fractures (including vertebral fractures): Etidronate group: 2/44 Placebo group: 4/39 RR 0.44 (95% CI 0.09 to 2.29)
Geusens, 1998[8]	400	Etidronate group: 1/18 Placebo group: 4/19 RR 0.26 (95% CI 0.03 to 2.14)
Roux, 1998[17]	400	Etidronate group: 2/59 Placebo group: 4/58 (Roux C, personal communication) RR 0.49 (95% CI 0.09 to 2.58)

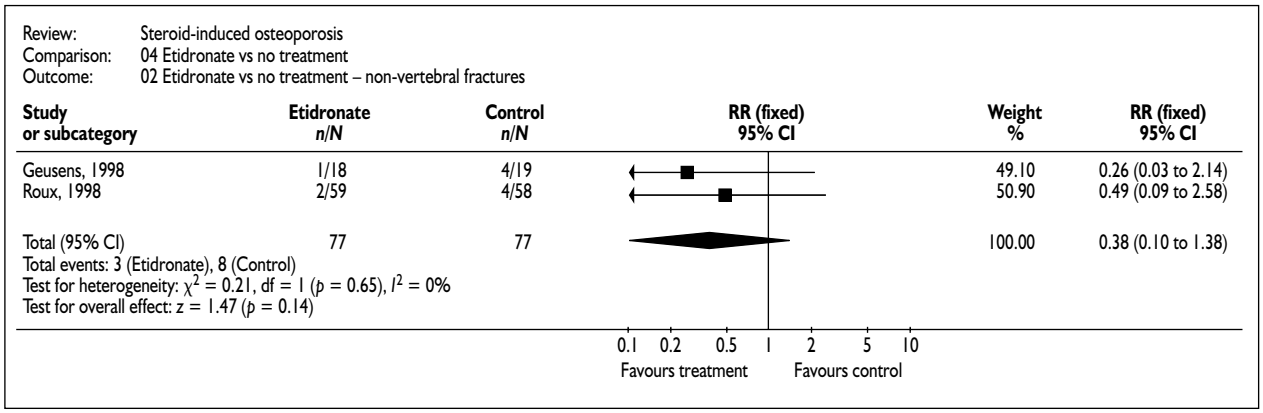

FIGURE 13 *Etidronate: non-vertebral fracture*

Like alendronate, etidronate has no documented extra-skeletal benefits.

Etidronate: continuance and compliance

In the studies reviewed in this section, the percentage of subjects receiving etidronate who completed the protocol ranged from 70 to 100% (see Appendix 9, *Table 115*). In only one case[50] was the proportion of patients who completed the study substantially lower in the etidronate group than in the control group; this is not necessarily significant given the small numbers involved. One study[19] had a very low overall completion rate (38%), largely due to the study policy of withdrawing all patients whose prednisolone dose fell below 5 mg/day.

Only one study[10] commented specifically on compliance, as monitored by tablet count at 3 and 6 months: this was said to be excellent, and similar in both groups. Three other studies noted only the number of patients excluded for poor compliance: these included 3/20 patients from the treatment group in one study,[50] 2/19 from the placebo group in another[8] and 3/35 overall in a third.[19]

Ibandronate

Ibandronate: quantity and quality of research available

Only one relevant RCT was identified;[54] this compared bolus injections of ibandronate with no treatment in male and female renal allograft recipients aged 20–60 years. Although patients were not selected for low BMD, three of the 40 patients (8%) in the ibandronate group and four of the 40 (10%) in the control group had vertebral fractures at baseline.

All patients received counselling designed to achieve a dietary intake of at least 1000 mg/day calcium. Patients with an intolerance to dairy products were supplemented with 500 mg/day calcium. In addition, those with initial vitamin D deficiency (below 15 ng/ml) were supplemented with a single dose of 10,000 U cholecalciferol. One postmenopausal

TABLE 71 *Ibandronate: vertebral fracture data*

Study	Ibandronate dose	Fracture definition	Number in each group suffering vertebral fracture
Grotz, 2001[54]	3-monthly bolus injections	20%	Ibandronate: 1/36 Control: 1/36 RR 1.00 (95% CI 0.07 to 15.38)

TABLE 72 *Ibandronate: non-vertebral fracture data*

Study	Ibandronate dose	Number in each group suffering non-vertebral fracture
Grotz, 2001[54]	3-monthly bolus injections	Ibandronate: 1/36 Control: 1/36 RR 1.00 (95% CI 0.07 to 15.38)

woman in each group was taking HRT at study entry; they continued this therapy during the study (see Appendix 9, *Tables 117–119* for details).

This appears to have been an open-label study. It is not clear from the published study whether allocation to treatment groups was appropriately masked, but fracture outcome assessors were blinded to treatment allocation (see Appendix 9, *Table 120*).

Ibandronate: assessment of effectiveness

Vertebral fractures

There was no difference between study groups in terms of the numbers of patients suffering vertebral fractures (*Table 71*).

Non-vertebral fractures

There was no difference between study groups in terms of the numbers of patients suffering non-vertebral fractures (*Table 72*).

Ibandronate: side-effects

In the study reviewed in this section, three patients in the ibandronate group reported side-effects (bone pain, flatulence) in temporal relation to ibandronate administration. However, there were no withdrawals because of side-effects. No side-effects were reported in the control group (see Appendix 9, *Table 121*).

Like alendronate, ibandronate has no documented extra-skeletal benefits.

Ibandronate: continuance and compliance

About 90% of subjects in each arm of the study completed the study protocol. No information was provided regarding compliance.

Pamidronate

Pamidronate: quantity and quality of research available

Four relevant RCTs were identified.[5,6,55,56] One[5] compared pamidronate with calcitriol plus intranasal calcitonin in patients who had undergone cardiac transplantation. Another[56] studied the effect of a pretransplant infusion of pamidronate on patients undergoing liver transplant. A third[55] compared 3-monthly intravenous infusions of pamidronate with no treatment in adults with cystic fibrosis who had received lung transplants 1–12 months previously. The fourth study[6] compared an initial intravenous infusion of pamidronate, with or without subsequent 3-monthly infusions, with no treatment in in- or outpatients aged over 18 years requiring first-time glucocorticoid therapy for a variety of diagnoses who were expected to require a dose of at least 10 mg/day prednisolone for at least 3 months.

None of the studies selected subjects for low BMD. One[6] was specifically a prevention study carried out in patients who required first-time long-term glucocorticoid therapy. Another[5] recruited patients very shortly after transplant and presumably, therefore, shortly after commencement of corticosteroid therapy. In a third,[56] although patients received pamidronate prior to transplant, some already had vertebral fractures at baseline. In the fourth study,[55] at study entry the mean time since transplant was 4 months; 68% of subjects were osteoporotic by the WHO definition, and they were evenly distributed between treatment groups. In the study which compared pamidronate with calcitriol,[5] the mean baseline T-score was substantially lower in the calcitriol group (see Appendix 9, *Table 124*).

TABLE 73 *Pamidronate: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): pamidronate vs comparator
			Pamidronate	Comparator	
Bianda, 2000[5]	Calcitriol plus calcitonin	Clinical vertebral	0/14	1/12	0.29 (95% CI 0.01 to 6.50)
		Non-vertebral	0/14	0/12	Not estimable

TABLE 74 *Pamidronate: vertebral fracture data*

Study	Pamidronate dose	Fracture definition	Number in each group suffering vertebral fracture
Aris, 2000[55]	30 mg i.v. every 3 months	'Determined by measuring anterior and posterior vertebral body height and expressing the difference divided by the posterior height as a percentage'	Pamidronate: 3/16 Control: 1/18 RR 3.38 (95% CI 0.39 to 29.28)
Boutsen, 2001[6]	90 mg i.v., with or without subsequent infusions of 30 mg every 3 months	Method of Minne *et al*.[57]	Pamidronate single infusion: 0/9 Pamidronate 3-monthly: 0/9 Control: 0/9 RR: not estimable
Ninkovic, 2002[56]	Single infusion of 60 mg	A reduction of >20% in anterior, middle or posterior vertebral height	Pamidronate: 3/34 Control: 1/41 RR 3.62 (95% CI 0.39 to 33.21)

In three studies, all subjects received supplementary calcium at a daily dose of either 800[6] or 1000 mg.[5,55] In one study,[55] all subjects also received 800 IU of ergocalciferol (vitamin D_2) daily (see Appendix 9, *Tables 122–124* for details).

All four studies appeared to be open-label. None provided evidence of appropriately concealed randomisation. Indeed, in one study,[5] 'randomisation' was by alternate allocation, whereas in another,[6] the method of allocation used would make fully blinded randomisation impossible. In this study, allocation to treatment took into account the starting dose of steroid (daily prednisolone dosage 10–20, 20–40 or >40 mg), sex, and pre- or postmenopausal status, with or without HRT, as follows: a patient with a combination of these four parameters not found in a patient already allocated to treatment was randomly allocated to treatment. A patient with a combination already present in one other patient was randomly allocated to one of the other two groups. If the combination was already present in two subjects, the new patient was allocated to the third group. Thirty patients were matched and allocated in this way; an additional two were assigned to the 3-monthly pamidronate group.

Only one study[56] stated that the fracture assessors were blinded to treatment allocation (see Appendix 9, *Table 125*).

Pamidronate: assessment of effectiveness

Comparison with active interventions

The study which compared pamidronate with calcitriol plus intranasal calcitonin did not yield a statistically significant result in relation to either vertebral or non-vertebral fractures (*Table 73*).

Vertebral fracture

All three studies which compared pamidronate with no treatment reported on the incidence of vertebral fracture; none yielded a statistically significant result (*Table 74*). The results have not been pooled because of the differences in patient groups and treatment regimens.

Non-vertebral fracture

All three studies reported on the incidence of vertebral fracture but none yielded a statistically significant result (*Table 75*). Again, the results have not been pooled because of the differences in patient groups and treatment regimes.

TABLE 75 *Pamidronate: non-vertebral fracture data*

Study	Pamidronate dose	Number in each group suffering non-vertebral fracture
Aris, 2000[55]	30 mg i.v. every 3 months	Pamidronate: 3/16 Control: 6/18 RR 0.56 (95% CI 0.17 to 1.89)
Boutsen, 2001[6]	90 mg i.v., with or without subsequent infusions of 30 mg every 3 months	Pamidronate single infusion: 0/9 Pamidronate 3-monthly: 0/9 Control: 0/9 RR: not estimable
Ninkovic, 2002[56]	Single infusion of 60 mg	Pamidronate: 1/37 Control: 1/43 RR 1.16 (95% CI 0.08 to 17.94)

Pamidronate: side-effects

The main side-effects associated with intravenous pamidronate are injection-site reaction and flu-like syndrome. The latter occurs in one-quarter to one-third of patients and is most marked at the first infusion, waning progressively thereafter.[44]

A recent analysis of reports submitted to the WHO, the FDA and the USA National Registry of Drug-Induced Ocular Side Effects found that pamidronate administration is also associated with a number of ocular side-effects. The most common of these is non-specific conjunctivitis, which appears in the first 48 hours after intravenous injection and is usually mild, resolving within a few days without treatment; it is generally progressively less severe or absent after several exposures to pamidronate. Uveitis is the most commonly reported ocular side-effect with serious clinical implications: this necessitates discontinuation of medication in some patients, a few of whom require hospitalisation and have residual vision-threatening sequelae.[58]

In the studies reviewed above, the only reported adverse events were three episodes of mild hypervitaminosis D in subjects receiving supplementary ergocalciferol; all resolved spontaneously.[55] Information was not provided as to the treatment groups in which these occurred (see Appendix 9, *Table 126*).

Pamidronate: continuance and compliance

In the studies reviewed in this section, a substantial majority of subjects receiving pamidronate completed the study protocol (see Appendix 9, *Table 125*). Only one study[55] specifically assessed compliance with medications, using patient interview; however, it did not report those findings.

Risedronate

Risedronate: quantity and quality of research available

Three RCTs[7,59,60] were identified which compared risedronate with placebo and which reported fracture outcomes.

One study was carried out in postmenopausal women with rheumatoid arthritis.[7] The other studies were undertaken in men and women who required corticosteroid therapy for a range of diseases. One study[59] was undertaken in patients who had initiated corticosteroid therapy in the previous 3 months and another[60] in patients who had been receiving therapy for at least 6 months. In the third study,[7] the median duration of corticosteroid therapy in each group exceeded 13 years (see Appendix 9, *Tables 127* and *128*).

In none of the studies were subjects selected for low BMD. However, a proportion of patients in all of the studies had at least one vertebral fracture at study entry (see Appendix 9, *Table 129*).

All three studies had two active treatment arms. In two studies,[59,60] one arm received a daily dose of 2.5 mg of risedronate and the other a dose of 5 mg. The third study[7] compared a continuous daily dose of 2.5 mg with a dose of 15 mg taken daily for 2 weeks, followed by placebo for 10 weeks. In one study,[59] the 2.5-mg risedronate group was discontinued when evidence became available to suggest that a 5-mg dose was more effective, but the blind was maintained for the other two groups. However, as fewer than one-third of patients in the 2.5-mg group were discontinued for this reason (mostly after 6 months), data for that group were reported.

TABLE 76 *Risedronate: vertebral fracture data*

Study	Risedronate dose (mg/day)	Fracture definition	Number in each group suffering vertebral fracture
Cohen, 1999[59]	2.5 or 5	A decrease of ≥15% for vertebrae intact at baseline, or of ≥4 mm in vertebrae fractured at baseline, in anterior, middle or posterior height	Risedronate 2.5 mg: 3/27 Risedronate 5 mg: 3/53 Placebo: 9/52 RR 2.5 mg vs placebo 0.64 (95% CI 0.19 to 2.18) RR 5 mg vs placebo 0.33 (95% CI 0.09 to 1.14)
Eastell, 2000[7]	2.5 or 15 for 2 weeks followed by placebo daily for 10 weeks	A decrease of ≥15% for vertebrae intact at baseline, or of ≥4 mm in vertebrae fractured at baseline, in anterior, middle or posterior height	At 2 years: Daily risedronate: 7/31 Cyclical risedronate: 2/30 Placebo: 3/33 RR daily risedronate vs placebo 2.48 (95% CI 0.70 to 8.76) RR cyclical risedronate vs placebo 0.73 (95% CI 0.13 to 4.09)
Reid, 1988[60]	2.5 or 5	Reduction of ≥15% in vertebral height in a previously intact vertebra or of ≥4 mm in a previously fractured vertebra	Risedronate 2.5 mg: 3/60 Risedronate 5 mg: 3/60 Placebo: 9/60 RR 2.5 mg vs placebo 0.33 (95% CI 0.09 to 1.17) RR 5 mg vs placebo 0.33 (95% CI 0.09 to 1.17)

In two studies, all subjects received supplementary calcium, at a dose of 500[59] or 1000 mg/day.[60] In the latter study, all patients also received 400 IU/day vitamin D (see Appendix 9, *Table 127*), whereas in the former vitamin D supplementation (up to 500 IU/day) was recommended for patients whose baseline serum levels of 25-hydroxyvitamin D_3 were below the lower limit of the normal range.

None of the studies provided evidence of appropriately concealed randomisation and only one[59] stated that the fracture assessor was blinded to treatment allocation (see Appendix 9, *Table 130*).

Risedronate: assessment of effectiveness

Vertebral fracture

All three studies reported vertebral fracture data, using the same fracture definition; none was large enough to yield a statistically significant result (*Table 76*).

The two studies which used a 2.5-mg dose in patients who had received corticosteroids for on average more than 4 years yielded divergent point estimates, although their CIs overlapped; their pooled results therefore did not achieve statistical significance (*Figure 14*). When the data from all trials were pooled, regardless of whether they used risedronate for prevention or treatment, the 2.5-mg dose was not demonstrated to have a statistically significant effect on vertebral fracture; moreover, pooling of the results of the two studies with consistent point estimates still failed to achieve statistical significance (RR 0.46; 95% CI 0.19 to 1.09).

Again, individually, neither study which used a 5-mg dose was large enough to achieve statistical significance alone in terms of vertebral fracture. However, if the data are pooled, regardless of the fact that one study is of prevention and the other of treatment, a statistically significant reduction in fracture risk is demonstrated (RR 0.33; 95% CI 0.14 to 0.80) (*Figure 15*).

One of the studies which stratified randomisation by sex and menopausal status also presented the results in that format[59] (*Tables 77* and *78*). However, the study was not large enough for the results to achieve statistical significance. Pooling of the results obtained by Cohen and colleagues[59] in postmenopausal women receiving 2.5 mg/day with those for that dose from the study of Eastell and colleagues,[7] which only recruited postmenopausal women, again failed to achieve significance (RR of fracture 1.60, 95% CI 0.66 to 3.92).

The two studies[59,60] which stratified randomisation by sex published separately their pooled results relating to vertebral fracture in men.[61] Risedronate at both 2.5 and 5.0 mg/day was associated with a reduction in the risk of fracture, but a statistically significant result was achieved only by pooling the results for both doses (*Table 79*). It should be noted that the baseline prevalence of vertebral fracture was slightly higher

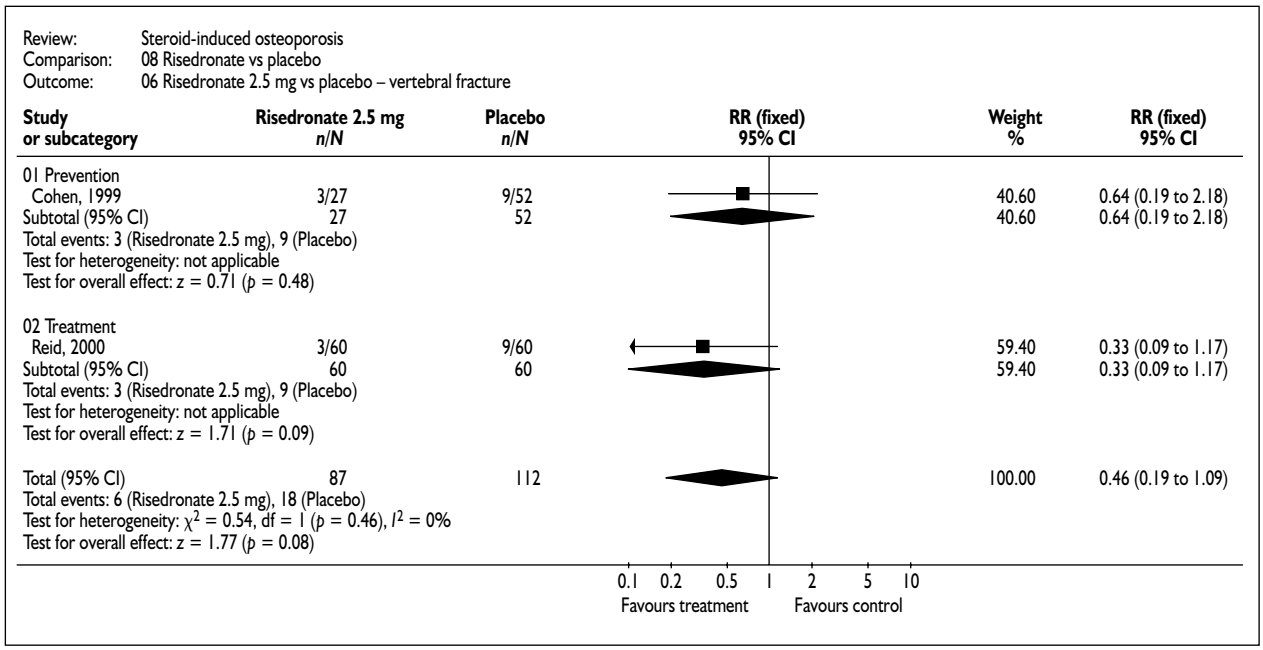

FIGURE 14 *Risedronate 2.5 mg/day: vertebral fracture data*

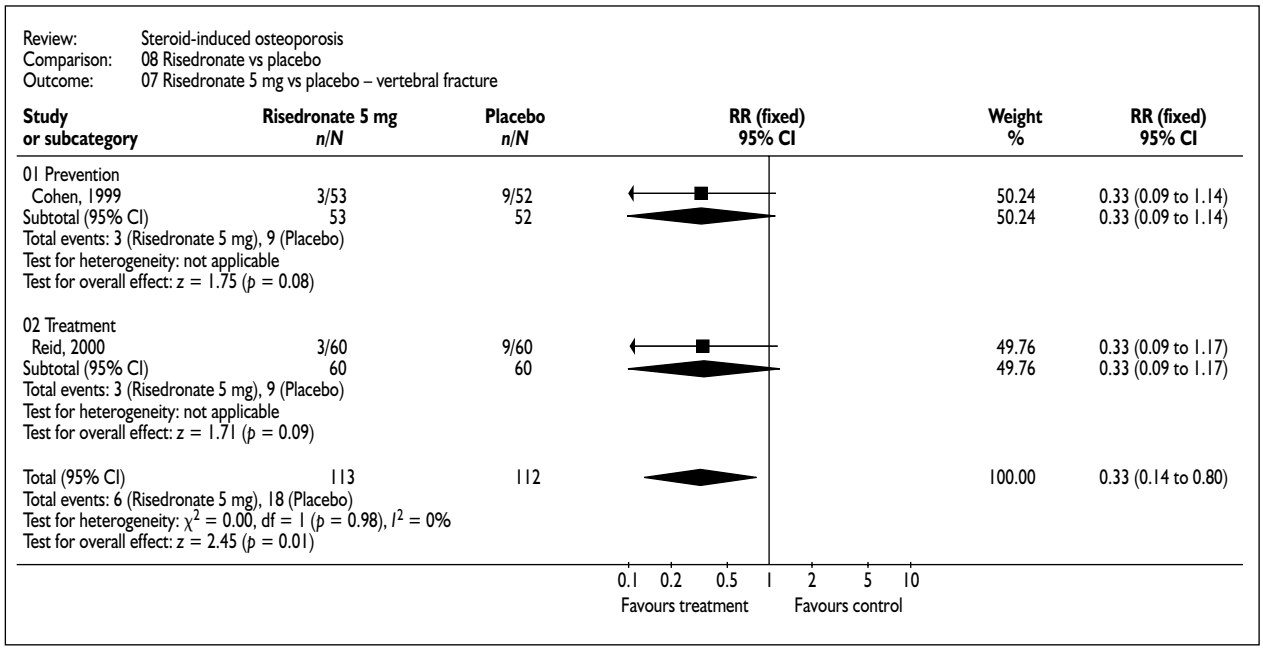

FIGURE 15 *Risedronate 5 mg/day: vertebral fracture data*

TABLE 77 *Risedronate 2.5 mg/day: vertebral fracture data by sex and menopausal status*[59]

Subgroup	Number of subjects suffering fracture		RR of fracture (95% CI)
	Risedronate 2.5 mg/day	Placebo	
Postmenopausal women	3/14	5/24	1.03 (0.29 to 3.66)
Premenopausal women	0/6	0/11	Not estimable
Men	0/7	4/17	0.25 (0.02 to 4.11)

TABLE 78 *Risedronate 5 mg/day: vertebral fracture data by sex and menopausal status*[59]

Subgroup	Number of subjects suffering fracture		RR of fracture (95% CI)
	Risedronate 5 mg/day	Placebo	
Postmenopausal women	2/24	5/24	0.40 (0.09 to 1.86)
Premenopausal women	0/10	0/11	Not estimable
Men	1/19	4/17	0.22 (0.03 to 1.81)

TABLE 79 *Risedronate: vertebral fracture data – men only*[61]

Risedronate dose	Number of subjects suffering fracture		RR of fracture (95% CI)
	Risedronate	Placebo	
2.5 mg/day	0/25	9/38	0.08 (0.00 to 1.30)
5.mg/day	3/33	9/38	0.38 (0.11 to 1.30)
Pooled risedronate	3/58	9/38	0.22 (0.06 to 0.76)

TABLE 80 *Risedronate: non-vertebral fracture data*

Study	Risedronate dose (mg/day)	Number in each group suffering non-vertebral fracture
Cohen, 1999[59]	2.5 or 5	2.5 mg: 3/75 5 mg: 3/76 Placebo: 4/77 RR 2.5 mg vs placebo 0.77 (95% CI 0.18 to 3.32) RR 5 mg vs placebo 0.76 (95% CI 0.18 to 3.28) Atraumatic fractures occurred in 3 patients in the placebo group (hip, ankle and rib), 1 in the 2.5-mg group (rib) and 2 in the 5-mg group (rib, sacrum) 1 patient in each group had a hip fracture
Reid, 2000[60]	2.5 or 5	2.5 mg: 8/92 5 mg: 8/99 Placebo: 6/94 RR 2.5 mg vs placebo 1.36 (95% CI 0.49 to 3.77) RR 5 mg vs placebo 1.27 (95% CI 0.46 to 3.51)

(46%) in the 5 mg/day group than in the other groups.

Non-vertebral fracture

Only two studies reported the number of patients who sustained non-vertebral fracture. Neither yielded a statistically significant result individually, nor did the pooled results achieve significance (*Table 80* and *Figures 16* and *17*).

Risedronate: side-effects

In two of the three studies,[59,60] adverse events, including upper GI adverse events, were evenly distributed among the treatment groups (for details, see Appendix 9, *Table 131*). In both studies back pain and arthralgia were reported by more patients in the 5-mg risedronate group than in the placebo group, but these events were mostly mild and were generally not considered to be related to the study drug. One study[59] specified that no relationship was seen between back pain and incident vertebral fracture.

In the remaining study,[7] although a similar number of patients in each group suffered either any adverse event or upper GI adverse events, the incidence of abdominal pain was higher in the risedronate groups. Such pain was mostly mild to moderate in severity, but caused three patients on cyclical risedronate to withdraw from the study. However, in each case, the event which caused withdrawal occurred during the placebo phase of the cycle; moreover, two of the three patients had a history of duodenal ulcer prior to enrolment.

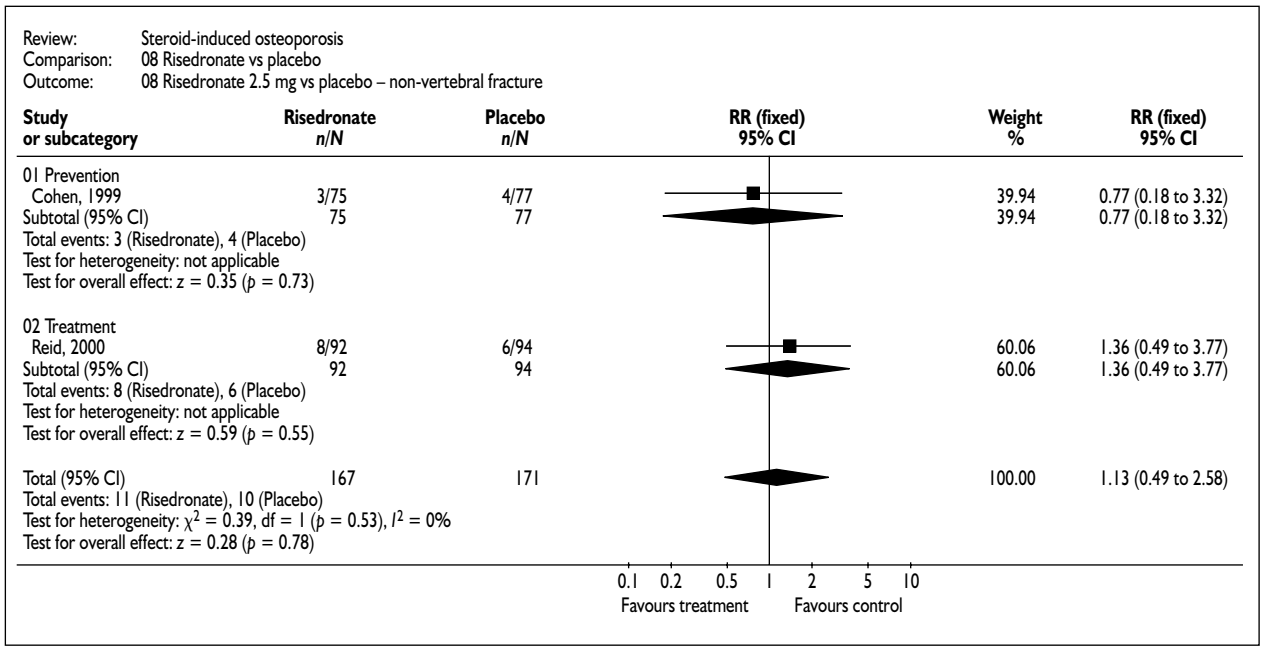

FIGURE 16 *Risedronate 2.5 mg/day: non-vertebral fracture data*

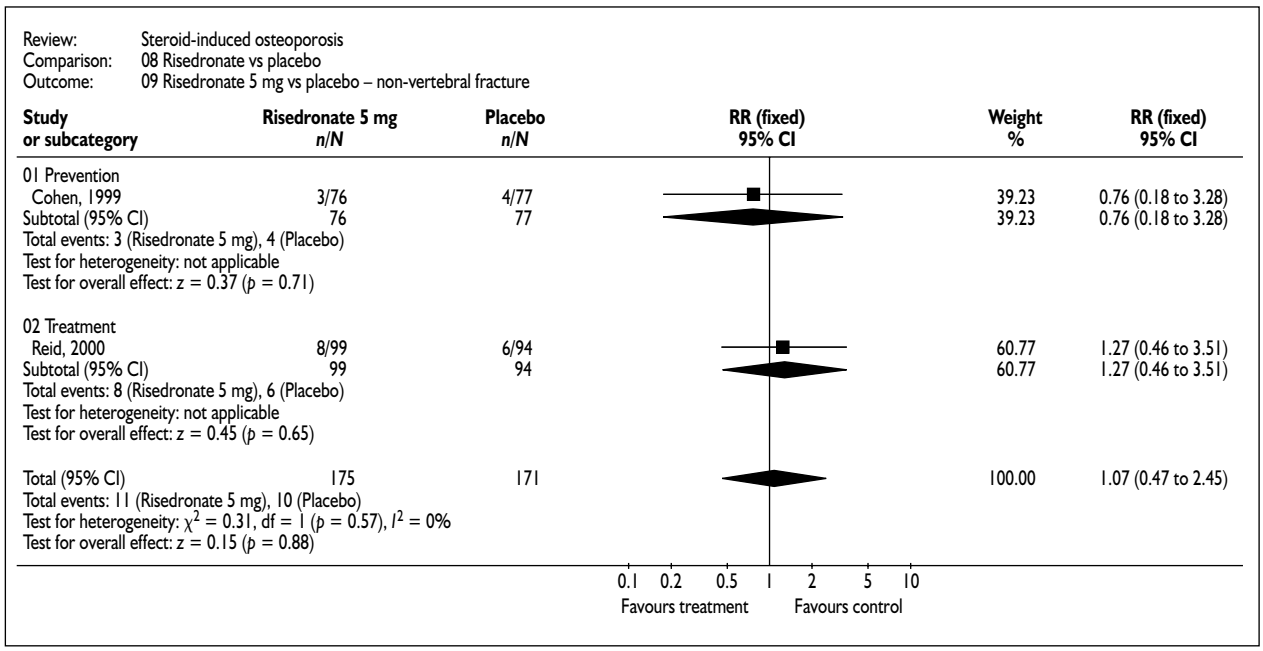

FIGURE 17 *Risedronate 5 mg/day: non-vertebral fracture data*

Two patients from the daily risedronate group, six from the cyclical risedronate group and six from the placebo group underwent upper GI endoscopy. Pathological abnormalities were found in both patients from the daily risedronate group (one patient with oesophagitis, one with oesophagitis plus gastric and duodenal ulcers), in all six in the cyclical risedronate group (two patients with duodenal ulcers, two with oesophagitis, two with gastritis) and in four of the six from the placebo group (one patient with each of the following: gastric erosion, gastritis, gastric ulcers, gastric ulcer plus oesophagitis).

Risedronate may be less toxic than alendronate. A study which compared risedronate with placebo in postmenopausal women with osteoporosis who discontinued alendronate therapy because of upper GI intolerance found that the majority were able to tolerate risedronate.[62]

TABLE 81 *Human parathyroid hormone: vertebral fracture data*

Study	hTPH dose	Fracture definition	Number in each group suffering vertebral fracture
Lane, 1998[15]	25 μg/day (400 U/day)	A decrease of 20% and at least 4 mm from baseline in any vertebral height	hPTH group: 0/26 Control group: 1/18 RR 0.23 (95% CI 0.01 to 5.45)

TABLE 82 *Human parathyroid hormone: non-vertebral fracture data*

Study	hPTH dose	Number in each group suffering non-vertebral fracture
Lane, 1998[15]	25 μg/day (400 U/day)	hPTH group: 2/28 (radius, pelvis) Control group: 2/23 (sacrum, rib) RR 0.82 (95% CI 0.13 to 5.39)

Like the other bisphosphonates, risedronate has no documented extra-skeletal benefits.

Risedronate: continuance and compliance

If allowance is made for the discontinuations made by protocol amendment in the 2.5-mg group in one study,[59] overall continuance in all studies was between 75 and 78%. However, only one study[59] provides information on continuance by treatment group; in this study, the highest proportion of study completers (82%) was in the 5-mg risedronate group (see Appendix 9, *Table 130*).

None of the studies commented specifically on compliance with treatment.

Raloxifene

Raloxifene: quantity and quality of research available

No studies were found which used raloxifene for the prevention or treatment of corticosteroid-induced osteoporosis and which reported fracture data.

Human parathyroid hormone (1–34)

Human parathyroid hormone: quantity and quality of research available

One RCT[15] was identified which compared human parathyroid hormone (1–34) (hPTH) with no treatment in osteoporotic postmenopausal women on oestrogen replacement therapy, and which reported fracture outcomes (for details, see Appendix 9, *Tables 132–134*).

All subjects were maintained on their pre-existing individual HRT regimens. They also received a calcium supplement to bring their total intake, including dietary calcium, up to 1500 mg/day, and two multivitamins per day containing 800 IU vitamin D_3.

As reported, the quality of the identified study was not high. Although randomisation appeared to have been appropriately masked, the fracture outcome assessors were not said to have been blinded to treatment allocation (see Appendix 9, *Table 135*).

Human parathyroid hormone: assessment of effectiveness

Vertebral fracture

The study did not produce a statistically significant result in relation to vertebral fracture (*Table 81*).

Non-vertebral fracture

The study did not produce a statistically significant result in relation to non-vertebral fracture (*Table 82*).

Human parathyroid hormone: side-effects

A systematic review of PTH for the treatment of osteoporosis found no published evidence that it increased the risk of cancer but suggested that it was associated with hypercalcaemia in a small proportion of patients. This hypercalcaemia occurs early in treatment, and may be dose-dependent.[63]

The study reviewed in this report stated that hPTH was well tolerated. Although many patients complained of mild headaches at the initiation of hPTH injections, these resolved after 1–2 weeks of

TABLE 83 *Vitamin D: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): vitamin D vs comparator
			Vitamin D	Comparator	
Ringe, 1999[65,66]	Alfacalcidol	Radiographic vertebral (20% definition)	Year 1: 9/42 Year 2: 5/39 Year 3: 3/35 Overall: 17/42	Year 1: 4/43 Year 2: 4/40 Year 3: 2/35 Overall: 10/43	2.30 (0.77 to 6.91) 1.28 (0.37 to 4.42) 1.50 (0.27 to 8.43) 1.74 (0.90 to 3.35)
		Non-vertebral	21/42	15/43	1.43 (0.86 to 2.38)

treatment. No patients dropped out because of discomfort caused by the injections (for details, see Appendix 9, *Table 136*).

Human parathyroid hormone: continuance and compliance

In the study reviewed above, all patients in the hPTH group appeared to complete the study. Compliance with the hPTH injections, as estimated by measuring the volume remaining in the returned medication vials at each study visit, ranged from 80 to 90% of the daily doses.

Calcium

Calcium: quantity and quality of research available

Only one study[64] was found which compared the use of calcium alone either with no treatment or with another intervention given without supplementary calcium. In this study, calcium was given to patients who had received allogeneic bone marrow transplantation for malignant blood diseases. However, this study was not truly randomised: eight participants from an earlier pilot study which used BMD as its only outcome measure were included in the untreated control group to compensate for the large number of randomised participants who had dropped out. It has therefore been excluded.

Vitamin D

Vitamin D: quantity and quality of research available

One RCT[65,66] was identified which studied the use of vitamin D for the treatment of corticosteroid-induced osteoporosis and which reported fracture data. This compared vitamin D with alfacalcidol in patients on long-term glucocorticoid therapy who had developed osteoporosis, with or without vertebral fracture. Patients in both groups received 500 mg/day calcium (for details, see Appendix 9, *Tables 137–140*).

This study did not report adequately masked allocation to treatment. However, fracture outcome assessors were said to be blinded to treatment allocation.

Vitamin D: assessment of effectiveness

Although the point estimates for both vertebral and non-vertebral fractures favour alfacalcidol, the study was not large enough to achieve statistical significance (*Table 83*). However, it also had as an outcome measure back pain, assessed at 6-monthly interviews using a simple scoring system which documented the intensity of the pain ranging from 0 (no pain) to 3 (severe pain). The average reduction in back pain over the study period was significantly higher in the alfacalcidol group than in the vitamin D group at 12 months ($p = 0.0091$), 24 months ($p = 0.0012$) and 36 months ($p = 0.0001$), supporting the possibility that alfacalcidol may be more effective than vitamin D in reducing the risk of vertebral fracture.

Vitamin D: side-effects

Excess consumption of vitamin D leads to hypercalcaemia, which may in turn lead to kidney failure caused by the deposition of the excess calcium in the blood vessels. However, there is no evidence of adverse effects with serum 25-hydroxyvitamin D concentrations as high as 140 nmol/l, which would require a total vitamin supply of 10,000 IU/day[67] (over 12 times the dose recommended for the prevention of osteoporosis). In the study reviewed above, hypercalcaemia and hypercalciuria were not reported in the vitamin D group (see Appendix 9, *Table 141*).

Vitamin D: continuance and compliance

Over 80% of patients in each arm completed the study (see Appendix 9, *Table 140*). Withdrawals were said to be largely due to discontinuation of therapy by the junior doctor, termination of

TABLE 84 *Calcium plus vitamin D: vertebral fracture data*

Study	Calcium + vitamin D dose	Fracture definition	Number in each group suffering vertebral fracture
Adachi, 1996[4]	Calcium 1000 mg/day + vitamin D 50,000 U/week	15%	Intervention group: 3/30 Placebo group: 5/31 RR 0.62 (95% CI 0.16 to 2.37)

glucocorticoid therapy or patient dropout following the disappearance of symptoms, especially in the alfacalcidol group. No withdrawals were attributed to the study therapy.[65] Compliance with the study medication was not reported.

Calcium plus vitamin D

Calcium plus vitamin D: quantity and quality of research available

One RCT[4] was identified which compared calcium plus vitamin D with placebo, and which reported fracture outcomes. This was carried out in ambulatory patients aged 18 years or over with polymyalgia rheumatica, temporal arteritis, systemic lupus erythematosus, vasculitis or asthma (for details, see Appendix 9, *Tables 142–144*).

Although subjects were not selected for low BMD, 23% had vertebral fractures at baseline.

This study did not report adequately masked allocation to treatment or blinding of fracture outcome assessors. Study allocation was undertaken using a minimisation algorithm[68] designed simultaneously to balance treatment groups with respect to age, sex, disease duration and initial prednisone dose.

Calcium plus vitamin D: assessment of effectiveness

Vertebral fractures

The study did not yield a statistically significant result in relation to vertebral fracture (*Table 84*).

Non-vertebral fractures

No non-vertebral fractures were reported in either group.

Calcium plus vitamin D: side-effects

Calcium supplementation can cause hypercalcaemia and hypercalciuria, which in turn may lead to the deposition of excess calcium in the kidneys. The risk of symptomatic nephrolithiasis has been shown to increase slightly in women taking calcium supplements, although interestingly it decreases in women with a higher **dietary** calcium intake.[69] As noted in the section 'Vitamin D: side-effects' (p. 111), excess consumption of vitamin D also leads to hypercalcaemia.

There were no episodes of hypercalcaemia in the study reviewed here. Although hypercalciuria (defined as urinary calcium excretion ≥7.0 mmol/day) occurred frequently, affecting 14 patients in the intervention group and seven in the placebo group, none developed renal stones during the course of the study (for details, see Appendix 9, *Table 146*).

Calcium plus vitamin D: continuance and compliance

Continuance in this study was low (see Appendix 9, *Table 145*). This was in part because study medication was discontinued as soon as corticosteroid therapy was discontinued: this affected nine subjects in each group (29%). In addition, eight patients in the intervention group (26%) and six in the placebo group (19%) refused follow-up because of personal preferences. Hence, although there were no withdrawals attributed to study medication, overall continuance was very low.

Compliance with the study medication was not reported.

Alfacalcidol

Alfacalcidol: quantity and quality of research available

Five RCTs[14,28,35,49,65] were identified which compared alfacalcidol with another intervention or with no treatment, and which reported fracture outcomes. One[14] compared alfacalcidol with calcium, another[49] with etidronate and a third[65,66] with vitamin D. The fourth study[35] compared alfacalcidol, either alone or with fluoride, with fluoride alone, and the fifth[28] compared alfacalcidol plus calcium, with or without trichlormethiazide, with no treatment.

TABLE 85 *Alfacalcidol: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): alfacalcidol vs comparator
			Alfacalcidol	Comparator	
Lakatos, 2000[14]	Calcium	All clinical fractures (sites unspecified)	1/21	2/20	0.48 (0.05 to 4.85)
Ringe, 1999[65,66]	Vitamin D	Radiographic vertebral (20% definition)	Year 1: 4/43 Year 2: 4/40 Year 3: 2/35 Overall: 10/43	Year 1: 9/42 Year 2: 5/39 Year 3: 3/35 Overall: 17/42	0.43 (0.14 to 1.30) 0.78 (0.23 to 2.69) 0.67 (0.12 to 3.75) 0.57 (0.30 to 1.11)
		Non-vertebral	15/43	21/42	0.70 (0.42 to 1.16)
Van Cleemput, 1996[49]	Etidronate	Symptomatic vertebral	0/22	3/19	0.12 (0.01 to 2.26)
		Radiographic vertebral (20% definition)	Year 1: 1/22 Year 2: 1/22 Overall: 2/22 (almost certainly in 2 patients, but just possibly in 1)	Year 1: 4/19 Year 2: 4/19 Overall: 5/19	0.22 (0.03 to 1.77) 0.22 (0.03 to 1.77) 0.35 (0.08 to 1.58)
		Non-vertebral	0/22	1/19	0.29 (0.01 to 6.72)
Yamada, 1989[28]	Alfacalcidol + trichlormethiazide	Vertebral	3/14	0/11	5.60 (0.32 to 98.21)

One study[49] was undertaken in transplant patients. Of the remainder, three[14,28,35] were carried out in women who were receiving corticosteroid therapy for a range of diagnoses, and the fourth[65] in men and women receiving long-term glucocorticoid therapy for chronic obstructive lung disease, rheumatoid arthritis or polymyalgia rheumatica (for details, see Appendix 9, *Tables 147–149*).

Two of the studies[14,49] were carried out in patients who had received corticosteroids for no more than 4 weeks. In two of the remaining studies, osteoporosis, whether with[35] or with or without fracture,[65] was an inclusion criterion. In one of these studies,[35] the overall mean duration of corticosteroid treatment was 14 years and in the other[65] 5 years. In the third study,[28] the patients appeared to have been treated with prednisolone for at least 12 months.

As reported, none of the studies were of high quality (see Appendix 9, *Table 150*). However, one study[28] was available in full only in Japanese. As it was not possible to obtain a translation, only data from the English abstract and tables could be used, and this may have resulted in an unfairly low quality score. Two studies[49,66] were quasi-randomised using alternate allocation; one of these[66] was the only study in which the fracture outcome assessor was blinded to treatment allocation.

Alfacalcidol: assessment of effectiveness

Comparisons with active treatment

None of the comparisons of alfacalcidol with active treatment were large enough to yield a statistically significant result in terms of vertebral or non-vertebral fracture (*Table 85*). However, as noted in the section 'Vitamin D: assessment of effectiveness' (p. 111), one study[65] found a significantly higher average reduction in back pain in patients receiving alfacalcidol than in those receiving vitamin D at 12 months ($p = 0.0091$), 24 months ($p = 0.0012$) and 36 months ($p = 0.0001$).

Comparison with no treatment: vertebral fracture

Only one study[28] compared alfacalcidol with no treatment: this only reported vertebral fractures, and again was not large enough to produce a statistically significant result (*Table 86*).

Alfacalcidol: side-effects

Like vitamin D, an excess of alfacalcidol may result in lassitude, nausea and vomiting, diarrhoea, weight loss, polyuria, sweating, headache, thirst, vertigo and raised concentrations of calcium and phosphate in plasma and urine.[70] In two of the studies reviewed above,[28,49] hypercalcaemia developed in patients receiving alfacalcidol. In addition, two studies[14,28] reported the development of renal stones in patients receiving alfacalcidol (for details, see Appendix 9, *Table 151*).

TABLE 86 *Alfacalcidol: vertebral fracture data*

Study	Alfacalcidol dose (μg/day)	Fracture definition	Number in each group suffering vertebral fracture
Yamada, 1989[28]	0.75	Not stated	Alfacalcidol group: 3/14 Control group: 2/13 RR 1.39 (95% CI 0.28 to 7.05)

Alfacalcidol: continuance and compliance

Only one study[65] reported continuance separately for both the alfacalcidol and the control groups; this was just over 80% in both groups. Withdrawals were said to be largely due to discontinuation of therapy by the junior doctor, the termination of glucocorticoid therapy or patient dropout following the disappearance of symptoms, especially in the alfacalcidol group. No withdrawals were attributed to the study therapy.

None of the studies reviewed above commented specifically on compliance with therapy.

Calcitriol

Calcitriol: quantity and quality of research available

Eight RCTs were identified which compared calcitriol with another intervention or comparator, and which reported fracture outcomes.[5,10,13,18,71–74] Two of these studies compared calcitriol with another active intervention – etidronate[10] or HRT.[13] A third study compared calcitriol, plus intranasal calcitonin for the first 3 months, with pamidronate.[5] The remainder compared calcitriol (in one case[18] with or without intranasal salmon calcitonin) with placebo (for details see Appendix 9, *Table 152*).

Five studies were carried out in patients who had undergone cardiac or lung transplantation.[5,10,72–74] The remainder were undertaken in patients with rheumatic, immunological or respiratory diseases (for details, see Appendix 9, *Tables 153* and *154*).

Two studies[13,71] were undertaken in patients with osteopenia. Low BMD was not an entry criterion for the remaining studies, most of which[5,10,18,72] recruited patients shortly after the commencement of corticosteroid therapy (see Appendix 9, *Table 153*).

The dose of calcitriol used in these studies ranged from 0.25 to 1 μg/day (for details, see Appendix 9, *Table 152*).

None of the studies reported evidence of adequately masked randomisation. Indeed, one study[5] was quasi-randomised, using alternate allocation. However, two studies[18,72] reported blinded fracture outcome assessors. A fourth study[13] stated that BMD assessors were blinded, but the status of the fracture assessors was not mentioned; however, this study seemed to report only clinical fractures.

Calcitriol: assessment of effectiveness

Comparisons with active interventions

None of the comparisons of calcitriol with other active interventions were large enough to yield statistically significant results in relation to fracture data (*Table 87*).

Comparisons with placebo or no treatment

Vertebral fracture

None of the four studies which provided information on vertebral fracture yielded a statistically significant result (*Table 88*). A fifth placebo-controlled study[71] only provided pooled information on vertebral and non-vertebral fractures; these data are discussed below under non-vertebral fractures.

It does not seem appropriate to meta-analyse together data relating to transplant patients on the one hand and to patients with rheumatic, immunological or respiratory diseases on the other. Moreover, meta-analysis of the studies in transplant patients is complicated by the fact that two of those studies[73,74] do not provide aggregate data for the whole study period; in a third study of transplant patients,[72] data are presented for the two calcitriol groups at 1 and 2 years, respectively, and for the placebo group only at 2 years. However, it seemed appropriate to pool data for the first and second years of the two studies by Stempfle and colleagues;[73,74] this yielded RRs of fracture in year 1 of 1.98 (95% CI 0.30 to 2.86) (*Figure 18*), and in year 2 of 0.87 (95% CI 0.06 to 13.54).

Non-vertebral fracture

Four studies reported non-vertebral fractures; none yielded statistically significant results

TABLE 87 *Calcitriol: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): calcitriol vs comparator
			Calcitriol	Comparator	
Bianda, 2000[5]	Pamidronate	Clinical vertebral Non-vertebral	1/12 0	0/14 0	3.46 (0.15 to 77.86) Not estimable
Kung, 1999[13]	HRT	Clinical vertebral Non-vertebral	0/15 0/15	0/13 0/13	Not estimable Not estimable
Henderson, 2001[10]	Etidronate	Clinical vertebral Non-vertebral	0/21 2/21	3/20 0/20	0.14 (0.01 to 2.48) 4.77 (0.24 to 93.67)
Sambrook, 1993[18]	Calcitriol + calcitonin	Radiographic vertebral Non-vertebral	1/34 1/34	2/29 0/29	0.43 (0.04 to 4.47) 2.57 (0.11 to 60.81)

TABLE 88 *Calcitriol: vertebral fracture data*

Study	Calcitriol dose (μg/day)	Fracture definition	Number in each group suffering vertebral fracture
Sambrook, 1993[18]	Starting dose 0.5 increasing to 1.0 (mean dose 0.59 ± 0.17)	20%	Calcitriol/calcitonin group: 2/29 Calcitriol group: 1/34 Placebo group: 2/29 RR calcitriol vs placebo 0.43 (95% CI 0.04 to 4.47) RR calcitriol/calcitonin vs placebo 1.00 (95% CI 0.15 to 6.63) All fractures occurred in the 2nd year of the study
Sambrook, 2000[72]	Starting dose 0.5 increasing to 0.75	Semiquantitative method	Calcitriol 12 months/placebo: 0 Calcitriol 24 months: 1/44 Placebo 24 months: 4/21 (data clarified by personal communication) RR calcitriol 24 months vs placebo 0.12 (95% CI 0.01 to 1.00)
Stempfle, 1999[73]	0.25	Method of Eastell *et al*.[53]	Year 1: Calcitriol group: 2/54 Placebo group: 0/47 RR 4.36 (95% CI 0.21 to 88.67) Year 2: Calcitriol group: 1/54 Placebo group: 1/47 RR 0.87 (95% CI 0.06 to 13.54) Year 3: Calcitriol group: 0/54 Placebo group: 0/47 RR not estimable All fractures were associated with acute back pain; it is not clear whether only symptomatic fractures were recorded
Stempfle, 2002[74]	0.25	A 20% decrease in any vertebral height compared with baseline	Year 1: Calcitriol group: 1/22 Placebo group: 1/18 RR 0.82 (95% CI 0.05 to 12.19) Year 2: Calcitriol group: 0/22 Placebo group: 0/18 RR not estimable All fractures were associated with acute back pain

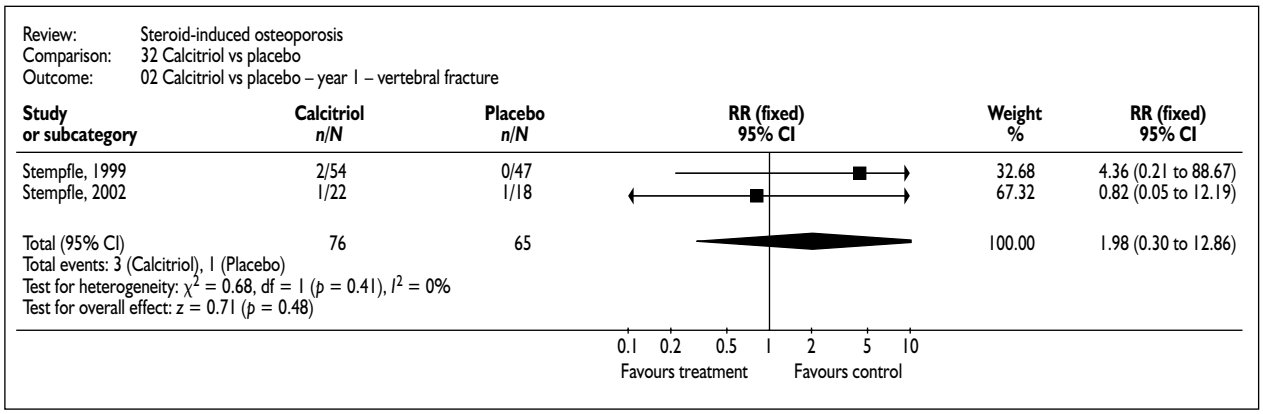

FIGURE 18 *Calcitriol versus placebo: vertebral fracture at 1 year*

TABLE 89 *Calcitriol: non-vertebral fracture data*

Study	Calcitriol dose (μg/day)	Number in each group suffering non-vertebral fracture
Dykman, 1984[71]	Mean dose at end of study 0.4	All non-traumatic fractures (including radiographic vertebral fractures): Calcitriol: 3/13 Placebo: 4/10 RR: 0.58 (95% CI 0.17 to 2.01)
Sambrook, 1993[18]	Starting dose 0.5 increasing to 1.0 (mean dose 0.59 ± 0.17)	Calcitriol/calcitonin group: 0/29 Calcitriol group: 1/34 Placebo group: 1/29 Calcitriol vs placebo: RR 0.85 (95% CI 0.06 to 13.04) Calcitriol/calcitonin vs placebo: RR 0.33 (95% CI 0.01 to 7.86) All were atraumatic rib fractures
Stempfle, 1999[73]	0.25	Calcitriol: 0/54 Placebo: 0/47 RR not estimable
Stempfle, 2002[74]	0.25	Calcitriol: 0/22 Placebo: 0/18 RR not estimable

(*Table 89*). In one case,[71] as noted above, non-vertebral fractures were only reported pooled with vertebral fractures. It was therefore not appropriate to include data from this study in a meta-analysis.

Calcitriol: side-effects

Calcitriol can cause hypercalcaemia. At the recommended dosages, this is generally mild and responds to reductions in dosage. However, because calcitriol has a narrow therapeutic window, adequate supervision, with periodic monitoring of serum calcium and creatinine levels, is necessary to avoid renal toxicity.[75]

Several of the studies reviewed above reported a higher incidence of hypercalcaemia or hypercalciuria in patients receiving calcitriol than in controls (for details, see Appendix 9, *Table 156*). In one study,[71] this was partially attributed to the investigators' attempt to increase the calcitriol dose to 1 μg/day. No patient in this study developed nephrolithiasis and there was no evidence that patients with normal renal function sustained any long-lasting complications. In another study,[18] mild hypercalcaemia occurred at a dose of 1 μg/day in some patients receiving less than 10 mg/day prednisone or prednisolone; the calcitriol dose was therefore subsequently limited to 0.5 μg/day in patients taking ≤10 mg/day of either corticosteroid.

Calcitriol: continuance and compliance

No study reported continuance separately for the treatment and control arms. Overall continuance ranged from 58% to possibly 100%, but was in most cases around 80% (for details, see Appendix 9, *Table 155*). In each of the five studies carried out

TABLE 90 *Calcidiol: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): calcidiol vs comparator
			Calcidiol	Comparator	
Garcia-Delgado, 1997[47]	Calcitonin	Vertebral	0/13	4/13	0.11 (0.01 to 1.88)
	Etidronate	Vertebral	0/13	3/14	0.15 (0.01 to 2.71)

TABLE 91 *Calcidiol: vertebral fracture data*

Study	Calcidiol dose (μg/day)	Fracture definition	Number in each group suffering vertebral fracture
Talalaj, 1996[76]	Initial dose 40, subsequently adjusted to serum calcium concentration	A 20% decrease in anterior, middle or posterior diameter of vertebral body (Talalaj M, personal communication)	Calcidiol group: 19/41 Placebo group: 30/36 (Talalaj M, personal communication) RR 0.56 (95% CI 0.39 to 0.80)

in transplant patients, some or all instances of non-completion were due to deaths or underlying illnesses not considered related to the study medication. Two of the remaining three studies[18,71] reported that 10% of patients withdrew as a result of non-compliance.

Calcidiol

Calcidiol: quantity and quality of research available

Only two studies were identified which used calcidiol and which reported fracture data. One[76] compared calcidiol plus 3 g/day calcium with no treatment in renal transplant patients aged 15–63 years. The other[47] compared calcidiol with calcitonin or etidronate in cardiac transplant patients; in this study, all patients received 1 g/day elemental calcium (for details see Appendix 9, *Tables 157–159*).

In both studies, study medication appeared to have been commenced immediately after transplantation, at the same time as the start of corticosteroid therapy.

As reported, neither study provided evidence of adequately masked randomisation or blinding of fracture outcome assessors (for details of quality, see Appendix 9, *Table 160*).

Calcidiol: assessment of effectiveness

Comparisons with active interventions

The point estimates suggest that the RR of vertebral fracture is lower in patients receiving calcidiol than in those receiving either calcitonin or etidronate; however, the study was not large enough to attain statistical significance in either case (*Table 90*). The authors noted that, although the patients were not elderly and had normal sunlight exposure and nutritional status, their baseline serum vitamin D levels had not been measured, hence a degree of vitamin D deficiency could not be excluded.[47]

Comparison with no treatment

Calcidiol plus calcium resulted in a significant decrease in the number of vertebral deformities compared with no treatment[76] (*Table 91*).

There were no non-vertebral fractures in either group.

Calcidiol: side-effects

As an intermediate metabolite of the vitamin D group, calcidiol (25-hydroxycholecalciferol), although less active than calcitriol, is similar in structure. It therefore theoretically has the potential to cause hypercalcaemia. However, this was not reported in either study.

Neither study reported any adverse events.

Calcidiol: continuance and compliance

Neither study either provided information relating to the number of subjects who completed the study protocol or commented on compliance with treatment.

TABLE 92 *Calcitonin: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): calcitonin vs comparator
			Calcitonin	Comparator	
Garcia-Delgado, 1997[47]	Calcidiol	Vertebral	4/13	0/13	9.00 (0.53 to 151.94)
	Etidronate	Vertebral	4/13	3/14	1.44 (0.39 to 5.23)

Calcitonin

Calcitonin: quantity and quality of research available

Ten studies were identified which used either subcutaneous[77–80] or intranasa[l9,12,47,81–83] calcitonin and which reported fracture data. One study[47] compared calcitonin with calcidiol and another[9] with clodronate or no treatment; the remainder compared it with placebo[77,81] or no treatment.[12,78–80,82,83]

An eleventh study,[5] in which patients receiving calcitriol were also given intranasal calcitonin for the first 3 months of an 18-month study, was discussed in the section 'Calcitriol' (p. 114).

An additional study[64] was identified in which calcium, with or without intranasal calcitonin, was given to patients who had received allogeneic bone marrow transplantation for malignant blood diseases. This was excluded because it was not truly randomised: eight participants from an earlier pilot study which used BMD as its only outcome measure were included in the untreated control group to compensate for the large number of randomised participants who had dropped out.

In seven studies, all subjects received supplementary calcium at a dose of 500,[9,12] 1000[47,77,82] or 1500[78,79] mg/day; in two studies,[77,79] they also received supplementary vitamin D, whereas in a third study[78] vitamin D was given only to those patients who met specific criteria (for further details, see Appendix 9, *Table 162*). In one study,[83] supplementary calcium was only given to the calcitonin group; in another,[81] neither group received supplementary calcium or vitamin D (Grøvle L, personal communication).

Three studies[47,77,83] were carried out in cardiac transplant patients and a fourth[78] in liver transplant recipients. The remainder were carried out in patients with rheumatoid arthritis,[12,81] newly diagnosed polymyalgia rheumatica, temporal arteritis and other vasculitides,[79] asthma[82] or obstructive lung disease.[80]

Only one study[80] stipulated that participants should display incipient to severe signs of osteoporosis. In a second study,[47] 40% of patients had osteoporosis at study entry and in a third[83] 37% had osteopenia. In a fourth,[78] 75% of patients had low BMD at study entry,and 13% had already suffered vertebral fractures; in two other studies,[79,82] 17 and 18% of subjects, respectively, had vertebral fractures at study entry.

Only one study[77] provided evidence of adequately masked randomisation. Three stated that fracture outcome assessors had been blinded to treatment allocation.[79,81,82]

One study was available only in abstract form[81] and as a conference poster.[84]

Calcitonin: assessment of effectiveness

Comparisons with active treatment

Neither of the comparisons of calcitonin with an active intervention yielded a statistically significant result (*Table 92*).

Comparisons with placebo or no treatment

Vertebral fracture

None of the studies which reported vertebral fracture data yielded a statistically significant result (*Table 93*).

Of the five studies which presented usable data, two used calcitonin for the prevention[78,79] and the other three[12,80,82] for the treatment of corticosteroid-induced osteoporosis. Pooling of the data from the treatment studies did not produce a statistically significant result, nor was this achieved with the inclusion of the non-transplant prevention study (*Figure 19*). It should be noted that two of the pooled studies[12,82] used intranasal rather than subcutaneous calcitonin; however, it is not apparent that this affected the efficacy of treatment.

Non-vertebral fracture

Five studies reported non-vertebral fractures; none produced a statistically significant result (*Table 94*).

TABLE 93 *Calcitonin: vertebral fracture data*

Study	Calcitonin dose	Fracture definition	Number in each group suffering vertebral fracture
Cremer, 1999[77]	Injected: 40 MRC standard units Monday–Friday for 2 weeks followed by 2 calcitonin-free weeks	Clinical only	None in either group
Grøvle, 1996[81,84]	Intranasal: 200 IU/day for 1 month followed by 100 IU/day for 11 months	Modified vertebral deformity index	Not stated. Vertebral deformity is said to have increased more in the placebo group than in the calcitonin group at all vertebral levels except T8; the changes were significantly different at T12 ($p = 0.04$), L1 ($p = 0.02$) and L2 ($p = 0.009$)
Hay, 2001[78]	Subcutaneous; 100 MRC units/day	None given	Calcitonin group: 10/29 Placebo group: 16/34 RR 0.73 (95% CI 0.40 to 1.36) (these figures seem to include fractures present at baseline)
Healey, 1996[79]	Subcutaneous: 100 IU three times per week	A decrease of 15% in at least one of the three heights within a vertebra between any two examinations	Year 1: Calcitonin group: 1/20 Placebo group: 3/22 RR 0.37 (95% CI 0.04 to 3.25) Year 2: Calcitonin group: 1/19 Placebo group: 0/21 RR 3.30 (95% CI 0.14 to 76.46) Overall: Calcitonin group: 2/19 Placebo group: 3/21 RR 0.74 (95% CI 0.14 to 3.95)
Kotaniemi, 1996[12]	Intranasal: 100 IU/day	None given; probably clinical fractures only	Calcitonin group: 0/32 Control group: 1/31 (this patient was subsequently treated with calcitonin, and defined as a dropout due to protocol violation) RR 0.32 (95% CI 0.01 to 7.65)
Luengo, 1994[82]	Intranasal: 200 IU/day	A reduction of 25% or more in anterior or posterior vertebral height	Calcitonin group: 2/22 Control group: 2/22 RR 1.00 (95% CI 0.15 to 6.48)
Ringe, 1987[80]	Subcutaneous: 100 IU on alternate days	Clinical only	Calcitonin group: 0/18 Control group: 3/18 RR 0.14 (95% CI 0.01 to 2.58) Number of patients showing a deterioration in radiological score: Calcitonin group: 1/18 Control group: 4/18 RR 0.25 (95% CI 0.03 to 2.02)
Välimäki, 1999[83]	Intranasal: 400 IU/day for 1 month followed by 200 IU/day for 11 months	At least 20% decrease in anterior, central or posterior vertebral height	Calcitonin + calcium: 2 Calcium alone: 4 No treatment: 1 RR not calculable as denominators not available 2 patients had a single fracture and 5 had multiple (≥3) fractures. Only 1 had symptomatic fractures

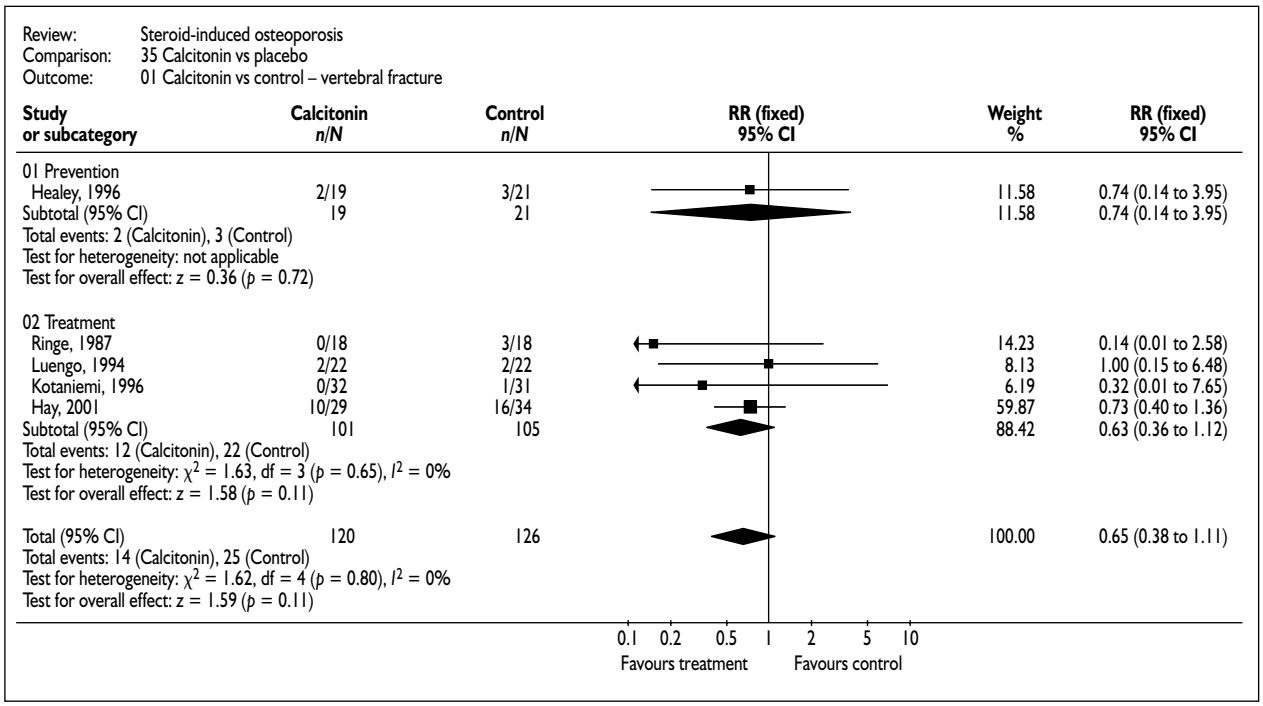

FIGURE 19 *Calcitonin versus control: vertebral fracture*

TABLE 94 *Calcitonin: non-vertebral fracture data*

Study	Calcitonin dose	Number in each group suffering non-vertebral fracture
Cremer, 1999[77]	40 MRC standard units Monday–Friday for 2 weeks followed by 2 injection-free weeks	None in either group
Grøvle, 1996[81]	Intranasal: 200 IU/day for 1 month followed by 100 IU/day for 11 months	None in either group
Kotaniemi, 1996[12]	Intranasal: 100 IU/day	Calcitonin group: 1/32 (metatarsal) Control group: 0/31 RR 2.91 (95% CI 0.12 to 68.81)
Luengo, 1994[82]	Intranasal: 200 IU/day	Calcitonin group: 1/22 (sternum) Control group: 1/22 (femoral) RR 1.00 (95% CI 0.07 to 15.00)
Ringe, 1987[80]	Subcutaneous: 100 IU on alternate days	Calcitonin group: 1/18 (rib) Control group: 2/18 (rib) RR 0.50 (95% CI 0.05 to 5.04)

Again, when pooled, the results still failed to achieve statistical significance (*Figure 20*).

Calcitonin: side-effects

The side-effects most commonly associated with subcutaneous calcitonin are GI side-effects (including nausea) and vascular phenomena such as hot flushes. Dermatological side-effects include local rash at the injection site, generalised rash and pruritus. True allergic reactions (urticaria and anaphylaxis) are rare.[85]

Similar side-effects are found with intranasal calcitonin, but are less common. Local skin reactions do not occur, and anaphylaxis has not been reported. However, nasal irritation may occur.[85]

Only one of the studies of subcutaneous calcitonin reviewed in this report reported side-effects: three of 18 patients in the calcitonin group reported nausea and three hot flushes, particularly facial flushing. In one patient, the nausea was severe enough to lead to discontinuation of treatment.[80]

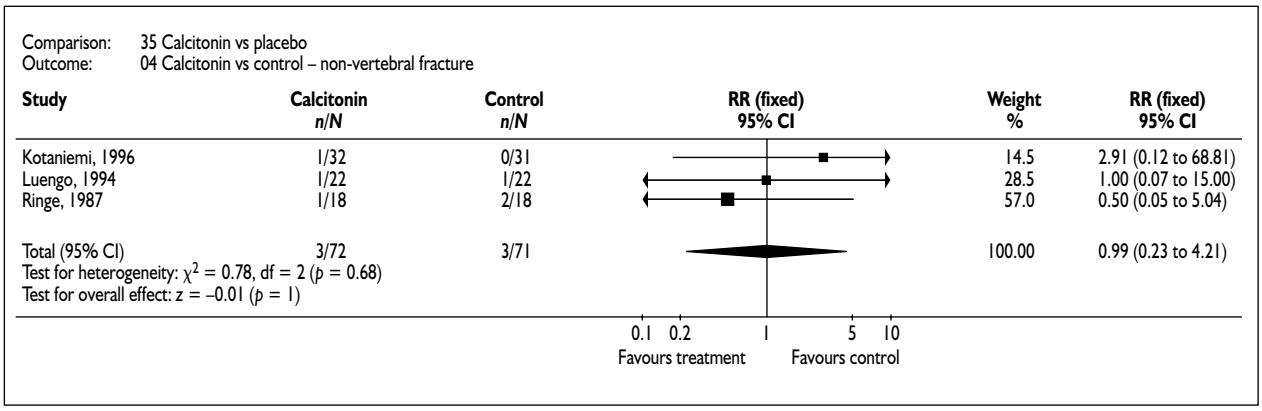

FIGURE 20 *Calcitonin versus control: non-vertebral fracture*

In two of the studies of intranasal calcitonin,[12,82] patients in the calcitonin group reported facial flushing or nausea. In one,[82] some patients reported rhinorrhea and one reported pruritus. In a third study,[9] one patient in the calcitonin group reported heat sensation, one a skin rash and a third arthralgia (for further details, see Appendix 9, *Table 166*).

Several placebo-controlled studies have shown that intranasal[86,87] or injected[88] calcitonin significantly reduces the pain associated with recent osteoporotic vertebral fractures. It has also been found to be associated with significant reductions in intensity of pain, limitation of action by pain and analgesic use in women with established postmenopausal osteoporosis who had not been specifically selected for recent fracture.[89] One of the studies[80] reviewed in this section had pain as an outcome measure; it found that calcitonin was associated with a statistically significant decrease in mean pain intensity in patients with incipient to severe signs of osteoporosis.

Calcitonin: compliance and continuance

Some of the studies reviewed here only provided overall information on the number of study completers: two[47,77] appeared to achieve 100% continuance; continuance was 92% in a third[81] and 80% in the fourth.[83]

Of the studies which provided separate information, two[80,82] reported equal continuance in the calcitonin and control groups, two[9,12] observed higher continuance in the calcitonin group and two[78,79] in the control group (for details, see Appendix 9, *Table 165*).

One study of injected calcitonin[79] assessed compliance with study medication by regular pill, vial and syringe counts and by previews of patients' medication diaries. Over the 2-year period, patients took 80% or more of the prescribed injections and 90% or more of the prescribed calcium and vitamin D_3 supplements. However, this was a self-selected population: 25 of the 100 patients who met the study eligibility criteria refused to participate because of unwillingness to undergo injections. Another study[78] reported that four patients (14%) in the treatment group did not comply with the full 6 months of therapy.

Oestrogen

Oestrogen: quantity and quality of research available

One RCT[13] was identified which studied oestrogen in women receiving corticosteroid therapy and which reported fracture outcomes. This compared cyclical oestrogen and progesterone with calcitriol in osteopenic hypogonadal young women receiving chronic steroid therapy for Systemic lupus erythematosus (SLE). All patients received 1 g/day calcium (for details see Appendix 9, *Tables 167–169*).

This study did not report evidence of adequately masked randomisation. Although the BMD assessors were said to be blinded, the status of the fracture assessors was not mentioned; however, apparently only clinical fractures were reported.

Oestrogen: assessment of effectiveness

This was a very small study, which did not demonstrate a difference in efficacy between HRT and calcitriol in preventing either vertebral or non-vertebral fractures (*Table 95*).

TABLE 95 *HRT: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): HRT vs comparator
			HRT	Comparator	
Kung, 1999[13]	Calcitriol	Clinical vertebral	0/13	0/15	Not assessable
		Non-vertebral	0/13	0/15	Not assessable

Oestrogen: side-effects

Oestrogen therapy has both beneficial and detrimental effects on health. In terms of benefits, the pooled results of four major placebo-controlled RCTs indicate that it offers protection against colorectal cancer (RR 0.64; 95% CI 0.45 to 0.92).[90] It also reduces the frequency and severity of menopausal hot flushes and night sweats.[91] In addition, a large cross-sectional study[92] found that, after adjusting for relevant variables, elderly women receiving unopposed oestrogen were at reduced risk of reporting six or more depressive symptoms (odds ratio 0.6; 95% CI 0.4 to 0.9), an effect which disappeared with the addition of a progestin (odds ratio 0.8; 95% CI 0.5 to 1.4).

In terms of detriments, the pooled results of the four RCTs indicate that HRT increases the risk of breast cancer (RR 1.27; 95% CI 1.02 to 1.56), stroke (RR 1.27; 95% CI 1.06 to 1.51) and pulmonary embolism (RR 2.16; 95% CI 1.47 to 3.18).[90] The Million Women Study,[93] an extremely large cohort study of British women, found an RR of breast cancer of 1.66 (95% CI 1.58 to 1.75) and of death from breast cancer of 1.22 (95% CI 1.00 to 1.48) in current users of HRT, although past users were not at increased risk. The increase in risk of cancer was particularly high for users of combined oestrogen–progestogen therapy (RR 2.00; 95% CI 1.88 to 2.12).

HRT also appears to increase the risk of gall-bladder disease.[94] In addition, in unhysterectomised women, oestrogen unopposed by progestogen increases the risk of endometrial cancer.[95,96] However, the risk appears to be countered by the addition of progestogen: the pooled results of three RCTs which used combined oestrogen–progestogen and one which used oestrogen alone found no significant effect on endometrial cancer (RR 0.76; 95% CI = 0.45 to 1.31).[90]

The pooled results of four major RCTs do not demonstrate a significant effect in relation to coronary heart disease (RR 1.11; 95% CI 0.96 to 1.30).[90] Existing trials are too small to provide information relating to other important, but rarer, conditions such as ovarian cancer.[90] Although HRT may possibly offer protection against Alzheimer's disease,[97,98] it does not appear either to slow its progress or to improve cognitive or functional outcomes in women with the disease.[99]

HRT is associated with a number of side-effects which reduce the quality of life: these include vaginal bleeding, breast tenderness, headaches, weight gain, mood change and nausea. Some of these may be attributed to the progestogen rather than the oestrogen component of HRT. Thus, a large study reported that breast discomfort was significantly more common in women receiving combination treatment than in those receiving either placebo or unopposed oestrogens.[100]

Kung and colleagues[13] did not report any side-effects associated with HRT.

Oestrogen: continuance and compliance

Kung and colleagues[13] did not comment on either continuance or compliance, implying that all subjects continued to take the study medications for the whole of the study period. This may indeed have been so in this small study. However, there is evidence that, generally, continuance with HRT may be poor, because of both fears over its long-term effects and the impact of side-effects on quality of life. A retrospective study[101] found that only 28% of members of a large health maintenance organisation (the Kaiser Foundation Health Plan) who had been prescribed oestrogens, for whatever reason, remained on treatment at 24 months. A Spanish RCT[102] in women who had requested HRT following surgical menopause caused by hysterectomy and bilateral oophorectomy for benign disease randomised them to either continuous oestrogen or transdermal oestradiol. A high rate of continuance might have been expected in these patients, who would not have experienced the vaginal bleeding and other side-effects associated with progestogen use, yet at 5 years only 47% of the oral oestrogen group and 20% of the transdermal oestradiol

group remained on treatment. Fear of cancer was a major reason for withdrawal, affecting 18–22% in each group; 22% of the transdermal oestradiol group withdrew because of erythema in the patch application area.

As initial compliance with HRT is likely to be higher in women with menopausal symptoms than in those without, compliance cannot be extrapolated from women prescribed HRT for the relief of menopausal symptoms to asymptomatic women prescribed it for osteoporosis prevention.[103] Three UK studies looked specifically at continuance in patients prescribed HRT for postmenopausal osteoporosis. Whereas in one study 61% remained on treatment at 6 months,[104] in the others only 49%[105] to 36%[106] remained on treatment at 1 year.

Oestrogen-like molecules

Oestrogen-like molecules: quantity and quality of research available

No RCTs were identified which studied the use of oestrogen-like molecules in women receiving corticosteroid therapy and which reported fracture outcomes.

Fluoride

Fluoride: quantity and quality of research available

Five RCTs[20,35,107–110] were identified which studied fluoride in patients receiving corticosteroid therapy and which reported fracture outcomes. One study compared fluoride plus etidronate with placebo plus etidronate,[108] another compared fluoride, with or without alfacalcidol, with alfacalcidol alone[35] and the remainder compared fluoride with placebo[107,109] or no treatment[20] (for details, see Appendix 9, *Tables 172–174*).

One study was carried out in patients with active Crohn's disease[20] and one in patients with respiratory diseases.[107] The remainder recruited patients who were taking corticosteroids for a range of conditions.

Two studies were carried out in patients with established osteoporosis.[35,108] In one of these,[108] lumbar spine BMD was significantly lower in the fluoride than in the control group, leading to an approximate doubling of the risk of fracture in the intervention group.

In all studies but one,[35] all subjects received supplementary calcium. In one study,[20] all subjects also received supplementary vitamin D_3; in two other studies,[108,109] vitamin D was given only to those whose serum 25-hydroxyvitamin D concentration was below 10 μg/l in winter and 15 μg/l in summer (for details, see Appendix 9, *Table 172*). In another study,[107] subjects were specifically not permitted to take vitamin D during the study period.

None of the studies report adequately masked randomisation and none stated that the fracture outcome assessors were blinded to treatment allocation (see Appendix 9, *Table 175*). One study[35] was available only in abstract form.

Fluoride: assessment of effectiveness

Comparisons with active treatment

The study which compared fluoride with alfacalcidol[35] only provided pooled data from subjects receiving fluoride with or without alfacalcidol. Comparison of these data with those for patients receiving alfacalcidol alone did not yield a statistically significant result (*Table 96*).

Comparisons with placebo or no treatment

Vertebral fracture

Four studies reported vertebral fracture data. Two did not provide data in a form which allowed the calculation of RRs. In one of these studies,[108] more patients in the fluoride group than in the placebo group suffered vertebral fractures; although the difference was not statistically significant, the authors suggested that it was

TABLE 96 *Fluoride: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): fluoride vs comparator
			Fluoride with or without alfacalcidol	Comparator	
Rozhinskaya, 1999[35]	Alfacalcidol alone	Vertebral	2/12	2/10	0.83 (0.14 to 4.90)

TABLE 97 *Fluoride: vertebral fracture data*

Study	Fluoride dose (mg/day)	Fracture definition	Number in each group suffering vertebral fracture
Guaydier-Souquières, 1996[107]	200 sodium monofluorophosphate (= 26.4 fluoride)	A 25% reduction in anterior or middle height relative to posterior height, or a 25% reduction in vertebral height relative to adjacent vertebrae	Fluoride group: 2/15 Placebo group: 0/13 RR 4.37 (95% CI 0.23 to 83.63)
Lems, 1997a[108]	50	15%	Year 1: Fluoride group: 4 Placebo group: 4 Year 2: Fluoride group: 3 Placebo group: 0 RRs not calculable as denominators not available
Lems, 1997b[109]	50	15%	There were 3 fractures in the placebo group and 1 in the fluoride group. The number of patients suffering these fractures was not stated
Von Tirpitz, 2000[20]	75 retarded-release sodium fluoride (= 33.9 fluoride)	Assumed clinical only	Fluoride: 0/18 Control: 0/15 RR: not estimable

probably related to the between-group difference in baseline BMD noted above.

Neither of the remaining studies yielded a statistically significant result, either individually or collectively, in terms of vertebral fracture (*Table 97*).

One study[35] assessed back pain, measured on a scale of 0–4. Mean back pain was significantly reduced in the groups receiving fluoride alone (from 2.78 to 1.3) or with alfacalcidol (from 2.86 to 1.12), whereas the reduction in the alfacalcidol group (from 2.68 to 1.53) was not statistically significant.

Non-vertebral fracture

None of the five studies which reported non-vertebral fracture data produced a statistically significant result (*Table 98*).

Fluoride: side-effects

Fluoride has been associated with lower extremity pain syndrome and with an increase in GI complaints. In one of the studies reviewed above,[108] lower extremity pain syndrome was only reported by patients receiving fluoride. The studies either did not report GI adverse events or found that they were not significantly higher in patients receiving fluoride (see Appendix 9, *Table 176*).

Fluoride: continuance and compliance

In the studies reviewed above, the proportion of patients receiving fluoride who completed the study ranged from 73 to 92% (see Appendix 9, *Table 175*).

None of the studies provided data relating to compliance.

Thiazide diuretics

Thiazide diuretics: quantity and quality of research available

One RCT[28] was identified which studied the use of thiazide diuretics in patients receiving corticosteroid therapy and which reported fracture outcomes. This compared alfacalcidol plus calcium, with or without trichlormethiazide, with no treatment in premenopausal women with collagen diseases who appeared to have been treated with prednisolone for at least 12 months (for details, see Appendix 9, *Tables 177–179*).

This study was available in full only in Japanese. In the absence of a translation, only data from the English abstract and tables could be used; as a result, the quality score may be unfairly low (see Appendix 9, *Table 180*).

TABLE 98 *Fluoride: non-vertebral fracture data*

Study	Fluoride dose (mg/day)	Number in each group suffering non-vertebral fracture
Guaydier-Souquières, 1996[107]	200 sodium monofluorophosphate (= 26.4 fluoride)	Fluoride: 0/15 Placebo: 0/13 RR: not estimable
Lems, 1997a[108]	50 sodium fluoride	Year 1: number of patients in each group suffering non-vertebral fracture: Fluoride group: 4/23 (2 ankle, 2 proximal tibia) Placebo group: 1/24 (wrist) RR 4.17 (95% CI 0.50 to 34.61) Year 2: number of non-vertebral fractures in each group: Fluoride group: 4/23 (3 hip, 1 distal tibia) Placebo group: 4/24 (2 hip, 2 ankle) RR 1.04 (95% CI 0.30 to 3.69)
Lems, 1997b[109]	50 sodium fluoride	Fluoride: 0/20 Placebo: 0/24 RR: not estimable
Von Tirpitz, 2000[20]	75 retarded-release sodium fluoride (= 33.9 fluoride)	Fluoride: 0/18 Control: 0/15 RR: not estimable

TABLE 99 *Trichlormethiazide: comparisons with active treatment*

Study	Comparator	Type of fracture	Number of subjects suffering fracture		RR of fracture (95% CI): trichlormethiazide + alfacalcidol vs comparator
			Trichlormethiazide + alfacalcidol	Comparator	
Yamada, 1989[28]	Alfacalcidol alone	Vertebral	0/11	3/14	0.18 (0.01 to 3.13)
	No treatment	Vertebral	0/11	2/13	0.23 (0.01 to 4.40)

Thiazide diuretics: assessment of effectiveness

Although the point estimates suggest that trichlormethiazide plus alfacalcidol may be more effective in preventing vertebral fracture than either alfacalcidol alone or no treatment, neither result was statistically significant (*Table 99*).

Non-vertebral fracture outcomes were not reported.

Thiazide diuretics: side-effects

In the study reviewed above, patients receiving alfacalcidol alone experienced hypercalciuria and renal stones; these were not seen either in those receiving alfacalcidol plus trichlormethiazide or in untreated controls (see Appendix 9, *Table 181* for details).

Thiazide diuretics: continuance and compliance

No data were available regarding continuance and compliance.

Anabolic steroids

Anabolic steroids: quantity and quality of research available

No RCTs were identified which studied the use of anabolic steroids in patients receiving corticosteroid therapy and which reported fracture outcomes.

Conclusions

The data reviewed in the previous 20 sections highlight the inadequacy of the evidence for the

TABLE 100 *Comparison of interventions with placebo or no treatment: RR of vertebral fracture (95% CI)*

Intervention	Transplant patients	Patients receiving corticosteroids for other diagnoses
Alendronate	No data	0.60 (0.19 to 1.94)[a]
Clodronate	Not estimable	No data
Etidronate	No data	0.55 (0.28 to 1.08)
Ibandronate	1.00 (0.07 to 15.38)	No data
Pamidronate	3.38 (0.39 to 29.28)	Not estimable
Risedronate 5 mg/day	No data	0.33 (0.14 to 0.80)
Raloxifene	No data	No data
Teriparatide	No data	0.23 (0.01 to 5.45)
Calcium	No data	No data
Vitamin D	No data	No data
Calcium + vitamin D	No data	0.62 (0.16 to 2.37)
Alfacalcidol	No data	1.39 (0.28 to 7.05)
Calcitriol	1.98 (0.30 to 12.86)[b]	0.43 (0.04 to 4.47)
Calcidiol	0.56 (0.39 to 0.80)	No data
Calcitonin	Not estimable	0.65 (0.38 to 1.11)
HRT	No data	No data
Oestrogen-like molecules	No data	No data
Fluoride	No data	4.37 (0.23 to 83.63)
Thiazide diuretics	No data	0.23 (0.01 to 4.40)
Anabolic steroids	No data	No data

[a] At 48 weeks.
[b] At 1 year.

TABLE 101 *Comparison of interventions with placebo or no treatment: RR of non-vertebral fracture*

Intervention	Transplant patients	Patients receiving corticosteroids for other diagnoses
Alendronate	No data	Identical in both groups[a]
Clodronate	0.33 (0.01 to 7.58)	No data
Etidronate	No data	0.38 (0.10 to 1.38)
Ibandronate	1.00 (0.07 to 15.38)	No data
Pamidronate	0.56 (0.17 to 1.89)	Not estimable
Risedronate 5 mg/day	No data	1.07 (0.47 to 2.48)
Raloxifene	No data	No data
Teriparatide	No data	0.82 (0.13 to 5.39)
Calcium	No data	No data
Vitamin D	No data	No data
Calcium + vitamin D	No data	Not estimable
Alfacalcidol	No data	No data
Calcitriol	Not estimable	0.85 (0.06 to 13.04)
Calcidiol	Not estimable	No data
Calcitonin	Not estimable	0.99 (0.23 to 4.21)
HRT	No data	No data
Oestrogen-like molecules	No data	No data
Fluoride	No data	4.17 (0.50 to 34.61)[b]
Thiazide diuretics	No data	No data
Anabolic steroids	No data	No data

[a] At 48 weeks.
[b] At 1 year.

impact of current treatments on osteoporotic fracture in patients receiving long-term corticosteroids. For some interventions (raloxifene, anabolic steroids), no RCTs were identified which reported fracture outcomes. For the remaining interventions, the studies were too small to demonstrate an effect on fracture, and in only one case (risedronate) was statistical significance achieved when the data from all relevant studies were pooled.

The evidence for the impact of the various interventions on vertebral and non-vertebral fracture is summarised in the next two subsections.

Impact of interventions on vertebral fracture

Data relating to the efficacy of the interventions reviewed above in preventing vertebral fracture are summarised in *Table 100*. As can be seen, the only treatments which could be shown to have a statistically significant effect, relative to placebo or no treatment, were calcidiol in renal transplant patients and risedronate, at a dose of 5 mg/day, in patients receiving corticosteroid therapy for reasons other than organ transplantation.

No intervention was demonstrated to be more effective than any other active intervention in preventing vertebral fracture.

Impact of interventions on non-vertebral fracture

Data relating to the efficacy of the interventions reviewed above in preventing non-vertebral fracture are summarised in *Table 101*. As can be seen, no intervention was demonstrated to be beneficial, relative to placebo or no treatment, in preventing non-vertebral fracture.

Again, no intervention was demonstrated to be more effective than any other active intervention in preventing non-vertebral fracture.

Impact of interventions on hip fracture

Hip fracture is arguably the most important osteoporotic fracture in terms of its health impact. However, the studies reviewed in this report were neither large nor long enough to yield useful data relating to the efficacy of the interventions in preventing hip fracture.

Appendix 2

Electronic bibliographic databases searched

1 BIOSIS Previews
2 CCTR (Cochrane Controlled Trials Register)
3 CDSR (Cochrane Database of Systematic Reviews)
4 CINAHL
5 EMB Reviews – AJP Journal Club
6 EMBASE
7 HEED (Health Economic Evaluations Database)
8 MEDLINE
9 NHS DARE (Database of Assessments of Reviews of Effectiveness)
10 NHS EED (Economic Evaluations Database)
11 NHS HTA (Health Technology Assessment)
12 PreMEDLINE
13 Science Citation Index
14 Social Sciences Citation Index

Appendix 3

Other sources searched

1 AHRQ (Agency for Healthcare Research and Quality), USA
2 Bandolier
3 British Geriatrics Society – Gastro Special Interests Group
4 British Oncological Association
5 CCOHTA (Canadian Coordinating Office for Health Technology Assessment)
6 CenterWatch
7 CHE (Centre for Health Economics), York
8 Clinical Evidence
9 CliniWeb
10 COIN (Department of Health)
11 CriB (Current Research in Britain)
12 DES Reports (West Midlands Health Technology Assessment Collaboration)
13 Department of Health
14 eBNF (electronic British National Formulary)
15 eGuidelines
16 Health Evidence Bulletin, Wales
17 HSRU (Health Services Research Unit), Aberdeen
18 INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
19 MRC Trials Register
20 National Osteoporosis Society
21 The National Osteoporosis Foundation, USA
22 National Guidelines Clearinghouse
23 NCCHTA (National Coordinating Centre for Health Technology Assessment)
24 POINT (Department of Health)
25 Royal College of General Practitioners
26 Royal College of Nursing
27 Royal College of Physicians
28 Royal College of Radiologists
29 Royal College of Surgeons
30 Royal Pharmaceutical Society
31 ScHARR (School of Health and Related Research, University of Sheffield) Library Catalogue
32 SIGN (Scottish Intercollegiate Guidelines Network)
33 Trent Working Group on Acute Purchasing Reports
34 Wessex DEC (Development and Evaluation Committee) Reports
35 WHO

Appendix 4

MEDLINE search strategies used

MEDLINE 1966–2002 – Ovid Biomed
Search undertaken May and September 2002

#1 Exp osteoporosis/
#2 Osteoporo$.tw
#3 Bone diseases, metabolic/
#4 or/1-3
#5 (Bone adj6 densit$).tw
#6 Bone density/
#7 (Bone or bones).mp
#8 Exp densitometry/
#9 Tomography, x-ray computed/
#10 Densit$.tw
#11 9 and 10
#12 8 or 11
#13 7 and 12
#14 5 or 6 or 13
#15 Colles' fracture/
#16 Exp hip fractures/
#17 Spinal fractures/
#18 15 or 16 or 17
#19 Fractures/
#20 Colles$.tw
#21 (Hip or hips).tw
#22 (Femur adj6 neck).tw
#23 (Femoral adj6 neck).tw
#24 (Spine or spinal).tw
#25 Vertebra$.tw
#26 Lumbar vertebrae/
#27 Or/20-26
#28 19 and 27
#29 Fractur$.tw
#30 ((Fractur$ adj6 colles$) or (hip or hips) or (femur adj6 neck) or (femoral adj6 neck) or (spine or spinal) or vertebra$).tw
#31 29 or 30
#32 14 or 18 or 28 or 31
#33 4 and 32

Appendix 5

Methodological search filters used in Ovid MEDLINE

Systematic reviews/meta-analyses

#1. Meta-analysis/
#2. Exp review literature/
#3. (Meta-analy$ or meta analy$ or metaanaly$).tw
#4. Meta analysis.pt
#5. Review academic.pt
#6. Review literature.pt
#7. Letter.pt
#8. Review of reported cases.pt
#9. Historical article.pt
#10. Review multicase.pt
#11. or/1-6
#12. or/7-10
#13. 11 not 12

Randomised controlled trials

#1. Randomized controlled trial.pt
#2. Controlled clinical trial.pt
#3. Randomized controlled trials/
#4. Random allocation/
#5. Double blind method/
#6. Single blind method/
#7. or/1-6
#8. Clinical trial.pt
#9. Exp clinical trials/
#10. ((Clin$) adj25 (trial$)).ti,ab
#11. ((Singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
#12. Placebos/
#13. Placebos.ti,ab
#14. Random.ti,ab
#15. Research design/
#16. or/8-15
#17. Comparative study/
#18. Exp evaluation studies/
#19. Follow up studies/
#20. (Control$ or prospectiv$ or volunteer$).ti,ab
#21. Prospective studies/
#22. or/17-21
#23. 7 or 16 or 22

Economic and quality of life evaluations

#1. Economics/
#2. Exp "costs and cost analysis"/
#3. Economic value of life/
#4. Exp economics, hospital/
#5. Exp economics, medical/
#6. Economics, nursing/
#7. Economics, pharmaceutical/
#8. Exp models, economic/
#9. Exp "fees and charges"/
#10. Exp budgets/
#11. Ec.fs.
#12. (Cost or costs or costed or costly or costing$).tw
#13. (Economic$ or pharmacoeconomic$ or price$ or pricing).tw
#14. Quality-adjusted life years/
#15. "Economic burden".tw
#16. Cost of illness/
#17. Exp quality of life/
#18. Quality of life.tw
#19. Life quality.tw
#20. Hql.tw
#21. Sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
#22. Qol.tw
#23. (Euroqol or eq5d or eq 5d).tw
#24. Qaly$.tw
#25. Quality adjusted life year$.tw
#26. Hye$.tw
#27. Health$ year$ equivalent$.tw
#28. Health utilit$.tw
#29. HUI.tw
#30. Quality of wellbeing$.tw
#31. Qwb.tw
#32. Quality of well being.tw
#33. (Qald$ or qale$ or qtime$).tw
#34. or/1-33

Appendix 6

Quality assessment tool

	Score
Was randomisation to the study groups blinded?	
Not randomised	0
States random but no description or quasi-randomised (*i.e. allocation by date of birth, hospital record no., admission dates, alternately, etc.*)	1
Small but real chance of disclosure of assignment (*e.g. sealed envelopes*)	2
Method does not allow disclosure of assignment (*e.g. assigned by telephone communication or by indistinguishable drug treatments randomly precoded by centralised pharmacy*)	3
Were assessors of outcome blinded to treatment status?	
Not mentioned	1
Moderate chance of unblinding of assessors	2
Action taken to blind assessors or outcomes such that bias is unlikely	3
Were the outcomes of patients who withdrew described and included in the analysis?	
Not mentioned or states number of withdrawals only	1
States numbers and reasons for withdrawal, but analysis unmodified	2
Primary analysis based on all cases as randomised	3
Comparability of treatment and control groups at entry	
Large potential for confounding or not discussed	1
Confounding small; mentioned but not adjusted for	2
Unconfounded; good comparability of groups or confounding adjusted for	3
For hip or other appendicular skeleton fracture	
Not applicable	0
No confirmation of diagnosis	1
X-ray confirmation of diagnosis	3
For vertebral fracture	
Not applicable	0
Inadequately described method	1
Radiological method: uses anterior/posterior height ratio	2
Radiological method: uses anterior, middle and posterior height in criteria *or* reports radiologically confirmed clinical events only	3
Total methodology score (actual score as % of possible score)	

Appendix 7

Trials meeting the inclusion criteria for review

Asterisks indicate the major publication for the study.

Adachi, 1996
*Adachi JD, Bensen WG, Bianchi F, Cividino A, Pillersdorf S, Sebaldt RJ, *et al*. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year followup. *J Rheumatol* 1996;**23**:995–1000.

Adachi, 1997
*Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R, *et al*. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;**337**:382–7.

Olszynski WP, Adachi JD, Chines AA. Intermittent cyclical therapy with etidronate in the prevention of corticosteroid-induced osteoporosis. *Osteoporos Int* 1997; **7** Suppl 2:17.

Aris, 2000
*Aris RM, Lester GE, Renner JB, Winders A, Denene BA, Lark RK, *et al*. Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. *Am J Respir Crit Care Med* 2000; **162**:941–6.

Bianda, 2000
*Bianda T, Linka A, Junga G, Brunner H, Steinert H, Kiowski W, *et al*. Prevention of osteoporosis in heart transplant recipients: a comparison of calcitriol with calcitonin and pamidronate. *Calcif Tissue Int* 2000; **67**:116–21.

Boutsen, 2001
*Boutsen Y, Jamart J, Esselinckx W, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. *J Bone Miner Res* 2001;**16**:104–12.

Cohen, 1999
*Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, *et al*. Risedronate therapy prevents corticosteroid-induced bone loss – a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 1999; **42**:2309–18.

Cohen S, Levy R, Keller M, Sewell KL, Boling E, Eusebio R, Sod E, Chines A. Risedronate prevents corticosteroid-induced bone loss and decreases the risk of vertebral fractures. *Arthritis Rheum* 1998;**41**(9) Suppl: S137.

Reid D, Cohen S, Pack S, Chines A, Ethgen D. Risedronate reduces the incidence of vertebral fractures in patients on chronic corticosteroid therapy. *Arthritis Rheum* 1998;**41**(9) Suppl:S136.

Wallach S, Cohen S, Reid DM, Hughes, RA, Hosking DJ, Laan RF, *et al*. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int* 2000;**67**:277–85.

Cortet, 1999
*Cortet B, Hachulla E, Barton I, Bonvoisin B, Roux C. Evaluation of the efficacy of etidronate therapy in preventing glucocorticoid-induced bone loss in patients with inflammatory rheumatic diseases. A randomized study. *Rev Rhum (Engl Ed)* 1999;**66**:214–19.

Cremer, 1999
*Cremer J, Struber M, Wagenbreth I, Nischelsky J, Demertzis S, Graeter T, *et al*. Progression of steroid-associated osteoporosis after heart transplantation. *Ann Thorac Surg* 1999;**67**:130–3.

Dykman, 1984
*Dykman R, Haralson KM, Gluck OS, Murphy WA, Teitelbaum SL, Hahn TJ, *et al*. Effect of oral 1,25-dihydroxyvitamin D and calcium on glucocorticoid-induced osteopenia in patients with rheumatic diseases. *Arthritis Rheum* 1984;**27**:1336–43.

Eastell, 2000
*Eastell R, Devogelaer JP, Peel NF, Chines AA, Bax DE, Sacco-Gibson N, *et al*. Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. *Osteoporos Int* 2000;**11**:331–7.

Garcia-Delgado, 1997
*Garcia-Delgado I, Prieto S, Gil-Fraguas L, Robles E, Rufilanchas JJ, Hawkins F. Calcitonin, etidronate, and calcidiol treatment in bone loss after cardiac transplantation. *Calcif Tissue Int* 1997;**60**:155–9.

Geusens, 1998
*Geusens P, Dequeker J, Vanhoof J, Stalmans R, Boonen S, Joly J, *et al*. Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study. *Ann Rheum Dis* 1998;**57**:724–7.

Grotz, 1998
*Grotz WH, Rump LC, Niessen A, Schmidt-Gayk H, Reichelt A, Kirste G, *et al*. Treatment of osteopenia and osteoporosis after kidney transplantation. *Transplantation* 1998;**66**:1004–8.

Grotz, 2001
*Grotz W, Nagel C, Poeschel D, Cybulla M, Petersen KG, Uhl M, *et al*. Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 2001;**12**:1530–7.

Grøvle, 1996
*Grøvle L, Angelskar S, Whist JE, Johannesen A. Effect of nasal calcitonin on bone density and vertebral deformity in rheumatoid arthritis patients treated with steroids. *Osteoporos Int* 1996;**6**:244.

Grovle L, Angelskar S, Whist JE, Johannesen A. Nasal calcitonin reduces vertebral deformation in rheumatoid arthritis patients treated with steroids. Poster presented at the World Congress of Osteoporosis, Amsterdam, 1996.

Guaydier-Souquières, 1996
*Guaydier-Souquières G, Kotzki PO, Sabatier JP, Basse-Cathalinat B, Loeb G. In corticosteroid-treated respiratory diseases, monofluorophosphate increases lumbar bone density: a double-masked randomized study. *Osteoporos Int* 1996;**6**:171–7.

Healey, 1996
*Healey JH, Paget SA, Williams-Russo P, Szatrowski TP, Schneider R, Spiera H, *et al*. A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. *Calcif Tissue Int* 1996;**58**:73–80.

Henderson, 2001
*Henderson K, Eisman J, Keogh A, MacDonald P, Glanville A, Spratt P, *et al*. Protective effect of short-term calcitriol or cyclical etidronate on bone loss after cardiac or lung transplantation. *J Bone Miner Res* 2001; **16**:565–71.

Jenkins, 1999
*Jenkins EA, Walker-Bone KE, Wood A, McCrae FC, Cooper C, Cawley MI. The prevention of corticosteroid-induced bone loss with intermittent cyclical etidronate. *Scand J Rheumatol* 1999;**28**:152–6.

Jinnouchi, 2000
*Jinnouchi Y. Efficacy of intermittent etidronate therapy for corticosteroid-induced osteoporosis in patients with diffuse connective tissue disease. *Kurume Med J* 2000; **47**:219–24.

Kotaniemi, 1996
*Kotaniemi A, Piirainen H, Paimela L, Leirisalo-Repo M, Uoti-Reilama K, Lahdentausta P, *et al*. Is continuous intranasal salmon calcitonin effective in treating axial bone loss in patients with active rheumatoid arthritis receiving low dose glucocorticoid therapy? *J Rheumatol* 1996;**23**:1875–9.

Kung, 1999
*Kung AW, Chan TM, Lau CS, Wong RW, Yeung SS. Osteopenia in young hypogonadal women with systemic lupus erythematosus receiving chronic steroid therapy: a randomized controlled trial comparing calcitriol and hormonal replacement therapy. *Rheumatology* 1999; **38**:1239–44.

Lakatos, 2000
*Lakatos P, Nagy Z, Kiss L, Horvath C, Takacs I, Foldes J, *et al*. Prevention of corticosteroid-induced osteoporosis by alfacalcidol. *Z Rheumatol* 2000; **59** Suppl 1:48–52.

Lane, 1988
*Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. *J Clin Invest* 1998; **102**:1627–33.

Lems, 1997a
*Lems WF, Jacobs JW, Bijlsma JW, van Veen GJ, Houben HH, Haanen HC, *et al*. Is addition of sodium fluoride to cyclical etidronate beneficial in the treatment of corticosteroid induced osteoporosis? *Ann Rheum Dis* 1997;**56**:357–63.

Lems, 1997b
*Lems WF, Jacobs WG, Bijlsma JW, Croone A, Haanen HC, Houben HH, *et al*. Effect of sodium fluoride on the prevention of corticosteroid-induced osteoporosis. *Osteoporos Int* 1997;**7**:575–82.

Luengo, 1994
*Luengo M, Pons F, Martinez de Osaba MJ, Picado C. Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy for asthma: a two year follow up study. *Thorax* 1994; **49**:1099–102.

Pitt, 1998
*Pitt P, Li F, Todd P, Webber D, Pack S, Moniz C. A double blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long-term oral corticosteroid treatment. *Thorax* 1998;**53**:351–6.

Reid, 2000
*Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, *et al*. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. *J Bone Miner Res* 2000;**15**:1006–13.

Reid D, Devogelaer JP, Hughes R, Laan R, Adami S, Sacco-Gibson N, *et al*. Risedronate is effective and well-tolerated in treating corticosteroid-induced osteoporosis. *Arthritis Rheum* 1998;**41**(9) Suppl:S303.

Reid D, Cohen S, Pack S, Chines A, Ethgen D. Risedronate reduces the incidence of vertebral fractures in patients on chronic corticosteroid therapy. *Arthritis Rheum* 1998;**41**(9) Suppl:S136.

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Appendix 8

Studies excluded from the review of clinical effectiveness

Study	Reason for exclusion
Compston, 1999[111]	Not original study; commentary on Saag *et al.*[36]
Rizzoli, 1995[110]	Although 33 of the 48 subjects were said to be enrolled in a double-masked trial, which implies randomisation, the remaining 15, who were followed in an open protocol, were not randomised to treatment (Rizzoli R, personal communication). The study was excluded as only combined results for all 48 subjects are presented
Välimäki, 1999[64]	Not a true RCT: included 8 participants from an earlier pilot study to compensate for the large number of dropouts amongst randomised participants
Wallach, 2000[112]	Not a primary report of RCT; summarises data from included studies by the groups of Cohen[59] and Reid[60]

Appendix 9
Study details

TABLE 102 *Alendronate in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Saag, 1998;[36] Adachi, 2001[37]	Multinational	Originally 48 weeks; 12-month extension	Difference between groups in % change in lumbar spine BMD	Men and women aged 17–83 years with underlying rheumatological, pulmonary, dermatological, GI or other diseases requiring long-term (at least 1 year) oral glucocorticoid therapy with at least 7.5 mg prednisone or its equivalent	55	Varied from <4 months to >1 year	Median baseline dose of prednisone or its equivalent: 5-mg group: 10 10-mg group: 10 Placebo group: 11 Overall range 5–135 mg/day 67% of subjects were still receiving at least 7.5 mg/day prednisone at week 48	Alendronate 2.5, 5 or 10 mg/day All subjects received 800–1000 mg/day calcium and 250–500 IU/day vitamin D	Placebo + 800–1000 mg/day calcium and 250–500 IU/day vitamin D

TABLE 103 *Alendronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Saag, 1998;[36] Adachi, 2001[37]	Men and women aged 17–83 years with underlying rheumatological, pulmonary, dermatological, GI or other diseases requiring long-term (at least 1 year) oral glucocorticoid therapy with at least 7.5 mg prednisone or its equivalent	Evidence of metabolic bone disease (other than glucocorticoid-induced or postmenopausal osteoporosis), serum 25-hydroxyvitamin D concentration <10 ng (25 nmol) per litre, concomitant therapy with drugs which affect bone turnover (e.g. bisphosphonates, calcitonin, fluoride), pregnancy or lactation, renal insufficiency (creatinine clearance rate <35 ml/minute), severe cardiac disease, history of recent (within 1 year) major upper GI disease	Comparable	Decreases of ≥20% and ≥4 mm between baseline and follow-up in anterior, middle or posterior vertebral body height; or an increase in at least 1 grade using a semiquantitative visual assessment[38]	Reports the combined results of 1 US and 1 multinational study of nearly identical design. Data relating to the 83 subjects randomised to alendronate 2.5 mg/day were not included in the analysis or the description of baseline characteristics Randomisation was stratified by duration of previous glucocorticoid therapy (<4, 4–12, >12 months). At baseline, 34% had been treated with glucocorticoids for <4 months, 21% for 4–12 months and 45% for >12 months Low BMD was not an inclusion criterion. At baseline, 43% had a lumbar spine *T*-score of +1 to –1 and 32% had a *T*-score of –2 or below 34% of postmenopausal women in the study were taking HRT; they continued taking the same dose throughout the study. In the original 48-week study, over 96% of subjects maintained a calcium intake (including supplements) of at least 1000 mg/day (median 1584 mg/day) during the study period[36] Only 389 subjects were eligible (in terms of glucocorticoid therapy) for inclusion in the 12-month extension study; of these, 208 agreed to participate. They continued to receive their original study medication, except for those originally assigned to 2.5 mg, who were blindedly switched to 10 mg (also, 2 patients receiving placebo and 1 receiving 2.5 mg were classified fast bone losers and switched to 10 mg open-label alendronate)

TABLE 104 *Alendronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Year 1[36]	Alendronate 5 mg/day ($n = 161$)	Not stated	0.92 ± 0.17	(15)	Men	45 (28)	Rheumatological[a]	116 (72)
					Premenopausal women	34 (21)	Pulmonary[b]	18 (11)
					Postmenopausal women	82 (51)	Dermatological (pemphigus)	15 (9)
							Myasthenia/myasthenia gravis	2 (1)
							GI[c]	6 (4)
							Renal[d]	4 (2)
	Alendronate 10 mg/day ($n = 157$)	Not stated	0.93 ± 0.16		Men	44 (28)	Rheumatological[a]	106 (68)
					Premenopausal women	30 (19)	Pulmonary[b]	23 (15)
					Postmenopausal women	83 (53)	Dermatological (pemphigus)	10 (6)
							Myasthenia/myasthenia gravis	1 (1)
							GI[c]	10 (6)
							Renal[d]	7 (4)
	Placebo ($n = 159$)	Not stated	0.95 ± 0.16	(17)	Men	52 (33)	Rheumatological[a]	102 (64)
					Premenopausal women	40 (25)	Pulmonary[b]	23 (14)
					Postmenopausal women	67 (42)	Dermatological (pemphigus)	12 (8)
							Myasthenia/myasthenia gravis	12 (8)
							GI[c]	8 (5)
							Renal[d]	2 (1)
Year 2[37]	Alendronate 5 mg/day ($n = 63$)	−1.24 ± 1.59	0.92 ± 0.17	7 (11)	Men	18 (29)	Rheumatological	45 (71)
					Premenopausal women	16 (25)	Pulmonary	3 (5)
					Postmenopausal women	29 (46)	Dermatological	8 (13)
							Myasthenia/myasthenia gravis	1 (2)
							GI[c]	2 (3)
							Renal	4 (6)
	Alendronate 10 mg/day ($n = 55$)	−1.14 ± 1.41	0.93 ± 0.15	9 (16)	Men	15 (27)	Rheumatological	37 (67)
					Premenopausal women	14 (25)	Pulmonary	8 (15)
					Postmenopausal women	26 (47)	Dermatological	5 (9)
							Myasthenia/myasthenia gravis	0
							GI[c]	0
							Renal	5 (9)

continued

TABLE 104 *Alendronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors (cont'd)*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
	Alendronate 2.5/10 mg/day ($n = 29$)	−1.66 ± 1.43	0.89 ± 0.16	3 (10)	Men Premenopausal women Postmenopausal women	14 (48) 5 (17) 10 (34)	Rheumatological Pulmonary Dermatological Myasthenia/myasthenia gravis GI[a] Renal	21 (72) 1 (3) 4 (14) 1 (3) 0 2 (7)
	Placebo ($n = 61$)	−1.18 ± 1.31	0.93 ± 0.15	7 (11)	Men Premenopausal women Postmenopausal women	19 (31) 17 (28) 25 (41)	Rheumatological Pulmonary Dermatological Myasthenia/myasthenia gravis GI[c] Renal	42 (69) 3 (5) 5 (8) 9 (15) 1 (2) 1 (2)

COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
[a] RA, polymyalgia rheumatica, SLE, inflammatory myopathy, giant-cell arteritis.
[b] Asthma, COPD, sarcoidosis.
[c] Inflammatory bowel disease.
[d] Nephrotic syndrome.

TABLE 105 *Alendronate in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Saag, 1998;[36] Adachi, 2001[37]	1	3	3	3	1	3	14/18 (78)	560	At 48 weeks: Alendronate 5 mg: 136/161 (84) Alendronate 10 mg: 137/157 (87) Placebo: 133/159 (84) At 2 years: Alendronate 5 mg: 48/63 (76) Alendronate 10 mg: 45/55 (82) Alendronate 2.5/10 mg: 23/29 (79) Placebo: 50/61 (82) (Data provided by Anastasia Daifotis)	Merck & Co. National Institutes of Health

TABLE 106 *Alendronate: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Saag, 1998;[36] Adachi, 2001[37]	At 48 weeks: Alendronate 5 mg: 30/161 (19%) Alendronate 10 mg: 40/157 (25%) Placebo: 26/159 (16%) ($p < 0.05$) At 2 years: Alendronate 2.5/10 mg: 5/29 (17%) Alendronate 5 mg: 13/63 (21%) Alendronate 10 mg: 17/55 (31%) Placebo: 19/61 (31%)	At 48 weeks: Musculoskeletal pain: Alendronate 5 mg: 14% Alendronate 10 mg: 16% Placebo: 16% Upper respiratory infection: Alendronate 5 mg: 12% Alendronate 10 mg: 13% Placebo: 9% Headache: Alendronate 5 mg: 8% Alendronate 10 mg: 8% Placebo: 6% Urinary tract infection: Alendronate 5 mg: 10% Alendronate 10 mg: 6% Placebo: 8% At 2 years: all adverse events (including upper GI): Alendronate 2.5/10 mg: 26/29 (90%) Alendronate 5 mg: 59/63 (94%) Alendronate 10 mg: 51/55 (93%) Placebo: 55/61 (90%)	At 48 weeks: Alendronate 5 mg: 8/161 (5%) Alendronate 10 mg: 6/157 (4%) Placebo: 8/159 (5%) At 2 years: Alendronate 2.5/10 mg: 1/29 (3%) Alendronate 5 mg: 2/63 (3%) Alendronate 10 mg: 3/55 (6%) Placebo: 3/61 (5%)

TABLE 107 *Clodronate in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/dose	Comparison(s)
Grotz, 1998[9]	Germany	1 year	Change in BMD at 12 months	Patients who had received renal allografts more than 6 months previously and had a BMD 1.5 SD below normal	45	Presumably at least 6 months; mean time since transplantation (months): Clodronate group: 44 ± 30 Calcitonin group: 54 ± 47 Control group: 72 ± 59 (NS)	Baseline prednisone dose (mg/day): Clodronate group: 8.8 ± 2.8 Calcitonin group: 9.6 ± 5.1 Control group: 8.4 ± 4.9 (NS)	Clodronate 800 mg/day vs intranasal calcitonin 100 IU twice a day, in both cases taken for 14 days followed by 75 days without treatment Both groups received 500 mg/day calcium gluconate throughout the study period	500 mg/day calcium gluconate

NS, not significant.

TABLE 108 *Clodronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Grotz, 1998[9]	Patients who had received renal allografts more than 6 months previously at the University of Freiburg and had a BMD of –1.5 SD or below	None specified	Although the groups were comparable in most respects, there was an imbalance in the distribution of menopausal women (6 in the calcitonin group, 2 in the clodronate group and none in the control group ($p = 0.043$))	Reduction of central or anterior vertebral height in excess of 15% of the maximum distance between the end-points of the posterior edges	During the observation period, participants received no fluorides or vitamin D 1 of the postmenopausal women (in the clodronate group) had received HRT for several years; this was continued through the study period 2 patients did not receive corticosteroids for immunosuppression Allocation to treatment was by block randomisation using sealed envelopes Although it is not stated, the study appears to have been open-label

TABLE 109 *Clodronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Grotz, 1998[9]	Clodronate (n = 15)	Not stated	0.871 ± 0.083	4 (9)	Men Premenopausal women Postmenopausal women	10 (67) 3 (20) 2 (13)	Renal transplant	15 (100)
	Calcitonin (n = 16)	Not stated	0.874 ± 0.082		Men Premenopausal women Postmenopausal women	7 (44) 3 (19) 6 (38)	Renal transplant	16 (100)
	Control (n = 15)	Not stated	0.929 ± 0.063		Men Premenopausal women Postmenopausal women	12 (80) 3 (20) 0 (0)	Renal transplant	15 (100)

TABLE 110 *Clodronate in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Grotz, 1998[9]	2	1	3	3	1	3	13/18 (72)	46	Clodronate: 15/15 (100) Calcitonin: 16/16 (100) Control: 14/15 (93)	Not stated

TABLE 111 *Clodronate: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Grotz, 1998[9]	Clodronate group: 2/15 Calcitonin group: 0/16 Control group: 1/15	Clodronate group: 0/15 Calcitonin group: 3/16 (heat sensation, skin rash, arthralgia) Control group: 0/15	1 patient in the untreated control group died of coronary heart disease

TABLE 112 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
General studies									
Adachi, 1997[45,113]	Canada	1 year	Difference between groups in mean % change from baseline in lumbar spine BMD	Ambulatory patients aged 18–90 years who had started high-dose therapy with prednisone or its equivalent within the previous 100 days and were expected to continue treatment for at least 1 year at a mean daily dose of 7.5 mg/day or greater for 90 days, with subsequent ongoing treatment at a mean daily dose of 2.5 mg or more	61 (19–87)	Maximum of 100 days	Mean daily dose at baseline (mg): Etidronate group: 21 ± 22 Placebo group: 23 ± 22 Mean daily dose at 26 weeks (mg): Etidronate group: 13 ± 10 Placebo group: 14 ± 12 Mean daily dose at 52 weeks (mg): Etidronate group: 11 ± 8 Placebo group: 11 ± 9	Etidronate 400 mg/day for 14 days followed for 76 days by 500 mg/day elemental calcium	Placebo for 14 days followed for 76 days by 500 mg/day elemental calcium
Cortet, 1999[46]	France	1 year	Change in lumbar BMD between baseline and treatment completion	Patients receiving long-term glucocorticoid therapy for an anticipated duration of more than 1 year for inflammatory rheumatic diseases (RA, polymyalgia rheumatica or giant cell arteritis)	62	No more than 90 days	In each group, the mean daily dose was 12.5 mg at baseline	Etidronate 400 mg/day for 14 days followed for 76 days by 500 mg/day elemental calcium	Placebo for 14 days followed for 76 days by 500 mg/day elemental calcium
Geusens, 1998[8]	Belgium and The Netherlands	2 years	% change from baseline in spinal BMD	Postmenopausal women receiving long-term corticosteroid treatment mainly for rheumatological conditions	64	More than 3 months (median 45 months, range 3–503) in the etidronate group and 31 months (range 3–108) in the placebo group)	Mean prestudy dose (mg/day): etidronate group: 6.3 placebo group: 6.4 Mean dose during the study (mg/day): etidronate group: 5.5 placebo group: 4.7 (NS)	Etidronate 400 mg/day for 2 weeks followed for 11 weeks by 500 mg/day calcium	Placebo for 2 weeks followed for 11 weeks by 500 mg/day calcium

continued

TABLE 112 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Jenkins, 1999[11]	England	1 year	% change from baseline in BMD at lumbar spine and proximal femur	Patients aged 18 years and over with either polymyalgia rheumatica or RA in whom there was a clinical indication to commence corticosteroids, at low to moderate doses, for the first time	67	None prior to commencement of study medication	Prednisolone 15 mg/day for 1 month, 12.5 mg/day for the 2nd month, 10 mg/day for the 3rd month and dosage altered thereafter according to clinical response. Median daily dose: All patients: 9 mg Etidronate group: 10.0 mg Placebo group: 8.75 mg	Etidronate 400 mg/day for 2 weeks followed for 11 weeks by 500 mg/day calcium	Placebo for 2 weeks followed for 11 weeks by 500 mg/day calcium
Jinnouchi, 2000[48]	Japan	1 year	Biochemical markers	Patients aged 20 years or over with diffuse connective tissue disease who developed corticosteroid-induced osteoporosis were selected from patients given steroids at a mean daily dose of 5 mg or more for at least 6 months	59	At least 6 months (mean in etidronate group ~32 months, in control group ~23 months)	Mean daily dose of prednisolone equivalent (mg/day): Etidronate group: 14.11 ± 8.21 Control group: 11.46 ± 7.49	Etidronate 200 mg/day for 14 consecutive days every 3 months + 1 μg/day vitamin D_3 throughout	1 μg/day vitamin D_3
Pitt, 1998[16]	England	2 years	% change from baseline in lumbar BMD at week 104	Ambulatory Caucasian patients aged 30 years or over with normal BMD suffering from a variety of disorders and being treated with high-dose corticosteroids	59	At least 6 months. Estimated mean pretrial exposure ~8.5 years (range 6 months–35 years)	Mean daily dose Etidronate group: 8 mg Placebo group: 7 mg	Etidronate 400 mg/day for 14 days followed for 76 days by calcium (equivalent to 97 mg/day elemental calcium) with 400 IU/day vitamin D	Placebo for 14 days followed for 76 days by calcium (equivalent to 97 mg/day elemental calcium) with 400 IU/day vitamin D

continued

TABLE 112 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Roux, 1998[17]	Western Europe	1 year	BMD	Patients with a variety of conditions who had recently initiated high-dose oral corticosteroid therapy which was expected to continue for at least 12 months, with a mean daily dose, for the initial 90 days in the study, of at least 7.5 mg prednisone or its equivalent, and with subsequent ongoing treatment at a mean cumulative dose of at least 2.5 mg/day	59	No more than 90 days	Mean daily dose: Etidronate group: 10.89 ± 6.34 mg Placebo group: 11.19 ± 7.17 mg	Etidronate 400 mg/day for 14 days followed by 76 days of 500 mg/day elemental calcium	Placebo for 14 days followed by 76 days of 500 mg/day elemental calcium
Skingle, 1997[19]	England	2 years	BMD at spine and hip	Ambulatory patients with a variety of diseases who had received a minimum of 5 mg prednisolone per day for at least a month	61 (patients completing year 1, *n* = 38)	At least 1 month	Mean daily dose of prednisolone in patients who completed year 1 (*n* = 38): Etidronate: 8.4 mg Control: 8.9 mg Year 2 completers (*n* = 21): Etidronate: 6.6 mg Control: 6.9 mg	Calcium 1000 mg/day plus etidronate 400 mg/day taken for 2 weeks within a 15-week cycle	Calcium 1000 mg/day
Worth, 1994[50]	Germany	6 months	Lumbar BMD	Adult clinically stable asthmatics without hypoxaemia who received more than 10 mg prednisone or equivalent for more than 9 months	57	Mean 7 years	Mean dose (mg/day prednisone equivalent) in study completers: Baseline: Etidronate: 27 Control: 28 6 months: Etidronate: 28 Control: 28	Etidronate 7.5 mg/kg, vitamin D 1000 IU/day, calcium 1 g/day	Calcium 1 g/day

continued

TABLE 112 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Transplant studies									
Garcia-Delgado, 1997[47]	Spain	18 months	Vertebral BMD	Ambulatory patients with normal mobilisation and diet who had undergone cardiac transplantation in Madrid University Hospital between 1991 and 1994	53	Randomisation took place immediately after transplantation and the start of corticosteroid therapy	Starting dose of 1 mg/kg/day prednisone reduced to 0.2 mg/kg/day after 6 weeks	Etidronate 400 mg/day for 14 days every 2.5 months	Calcidiol 32,000 IU/week Intranasal calcitonin 100 IU/day
Henderson, 2001[10]	Australia	6 months	BMD	Patients undergoing cardiac or lung transplantation	49	Very short (corticosteroids were commenced perioperatively and patients were recruited within 1 week of transplant)	2 g i.v. methylprednisolone perioperatively, followed by 125 mg every 8 h for 3 doses, and then oral prednisolone at 1 mg/kg/day reducing to 0.15–0.18 mg/kg/day by day 14 and 0.10–0.15 mg/kg/day by 6 months. Larger amounts were given during periods of rejection	Etidronate 400 mg/day for 14 days followed by 1.25 g/day calcium carbonate for 76 days	Calcitriol 0.5 μg/day
Van Cleemput, 1996[49]	Belgium	2 years	BMD	Cardiac transplant recipients aged 25 years or over	53	Less than 1 month	Cumulative prednisone intake (g): Year 1: Etidronate: 4.9 ± 1.8 Alfacalcidol: 5.3 ± 1.8 Year 2: Etidronate: 1.6 ± 0.5 Alfacalcidol: 1.5 ± 0.4	Cyclical etidronate (calcium carbonate 1.25 g/day for 11 weeks followed by etidronate 400 mg/day for 2 weeks)	Calcium carbonate 1.25 g/day plus an incremental dose of alfacalcidol (starting dose 0.25 μg/day, to a maximum of 1 μg/day)

TABLE 113 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
General studies					
Adachi, 1997[45]	Ambulatory patients aged 18–90 years who had started high-dose therapy with prednisone or its equivalent within the previous 100 days and were expected to continue treatment for at least 1 year at a mean daily dose of 7.5 mg/day or greater for 90 days, with subsequent ongoing treatment at a mean daily dose of 2.5 mg or more	Abnormalities on spinal radiographs that precluded accurate DXA measurements of the lumbar spine; diseases or medications within the previous year known to affect bone metabolism	The authors claim that the groups were comparable at baseline. However, this has been queried on the grounds that baseline lumbar BMD was about 1 SD lower in the control group, which might be expected to double the fracture risk, while the etidronate group included a significantly higher number of patients with RA (RA being an independent risk factor for osteoporotic fracture).[114] It should be noted that these factors pull in opposite directions	Any increase in the vertebral deformity score (where grade 0 = normal, grade 1 = a 20–25% reduction in anterior, middle or posterior vertebral height relative to adjacent vertebrae, grade 2 a 26–40% reduction, and grade 3 a >40% reduction)	Randomisation was stratified by sex and menopausal status None of the subjects had previously taken corticosteroids
Cortet, 1999[46]	Patients receiving long-term glucocorticoid therapy (starting dose greater than 7.5 mg/day administered for at least 3 months, followed by a maintenance dose of at least 2.5 mg/day) for an anticipated duration of more than 1 year for inflammatory rheumatic diseases (RA, polymyalgia rheumatica or giant cell arteritis)	Medications known to modify bone metabolism or the metabolism of calcium and phosphate; bisphosphonates, fluoride, oestrogens and/or progestogens within the last year; calcitonin or vitamin D derivatives within the last 6 months; pregnancy	Comparable	Only radiographically confirmed symptomatic fractures were recorded	Vitamin D supplementation of no more than 1000 IU/day was permitted
Geusens, 1998[8]	Postmenopausal women receiving long-term corticosteroid treatment (equivalent to 5–20 mg/day prednisolone) mainly for rheumatological conditions	None stated	Comparable	Only radiographically confirmed symptomatic fractures were recorded	Randomisation was by blocks of 2 within each centre No subjects were receiving HRT

continued

TABLE 113 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Jenkins, 1999[11]	Patients aged 18 years and over with either polymyalgia rheumatica or RA in whom there was a clinical indication to commence corticosteroids, at low to moderate doses, for the first time	Coexistent diseases likely to impair interpretation of the results; concomitant medication known to influence bone mineral metabolism	Generally comparable. However, because the placebo group contained more men, the mean height and lumbar spine BMD of the placebo group were significantly greater than those of the etidronate group	Clinically diagnosed fractures only	Baseline and 12-month radiographs were only available for 13 patients, 6 in the etidronate group and 7 in the placebo group
Jinnouchi, 2000[48]	Patients aged 20 years or over with diffuse connective tissue disease (e.g. systemic lupus erythematosis, dermatomyositis, polymyositis, interstitial pneumonitis or RA) who developed corticosteroid-induced osteoporosis (diagnosed using the Japanese Society for Bone and Mineral Research's 1996 criteria for primary osteoporosis) were selected from patients given steroids at a mean daily dose of 5 mg or more for at least 6 months	Physical inability in conducting activities of daily living; renal or thyroid disorders; pregnancy or lactation; RA patients with severe inflammation	Comparable (but no information was provided regarding the number of women who were pre- and postmenopausal)	Not clear	
Pitt, 1998[16]	Ambulatory, Caucasian, aged 30 years or over, being treated with high-dose corticosteroids (equivalent to 5–20 mg prednisolone/day, or 20 mg or more on an alternate day schedule) for at least 6 months at study entry, with a lumbar-spine Z-score ±1. All asthmatics had to receive the maximum dose of inhaled corticosteroids in addition to oral therapy	Premenopausal (unless hysterectomised or sterilised); with generalised bone disease (including RA); previously treated with bone-active agents; having inflammatory bowel disease	Comparable	Method of Genant *et al.*[52]	

continued

TABLE 113 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Roux, 1998[17]	Patients with a variety of conditions who had initiated high-dose oral corticosteroid therapy within 90 days of study entry which was expected to continue for at least 12 months, with a mean daily dose, for the initial 90 days in the study, of at least 7.5 mg prednisone or its equivalent, and with subsequent ongoing treatment at a mean cumulative oral dose of at least 2.5 mg/day (inhaled, topical and intravenous steroids were permitted but not included in calculating the mean dose, and prednisone at a dose <7.5 mg/day was allowed in the year before study entry) 24% of the placebo group and 25% of the etidronate group were osteoporotic at baseline; 1 patient in the placebo group and 2 in the etidronate group had baseline vertebral fractures	Medications or diseases affecting bone or calcium metabolism (in particular, treatment within 1 year with bisphosphonates, fluoride, oestrogen, progestogen or oestrogen-like compounds, or within 6 months with calcitonin or supplemental vitamin D); pregnancy	Comparable	Qualitative assessment	Use of inhaled, topical or intravenous steroids was allowed but was not included in the calculation of the mean cumulative oral steroid dose Patients were allowed to receive up to 1000 IU/day vitamin D; during the study, 2 patients in the etidronate group and 4 in the placebo group took supplements up to 800 IU/day 24% of the placebo group and 25% of the etidronate group were osteoporotic at baseline
Skingle, 1997[19]	Ambulatory patients with a variety of diseases who had received a minimum of 5 mg prednisolone per day for at least 1 month. Although low BMD or prior fracture was not a requirement, the great majority had suffered at least 1 vertebral fracture	Patients taking medication which might interfere with bone metabolism (e.g. HRT, calcium and vitamin D supplements, thiazide diuretics, anticonvulsants, anticoagulants)	Subjects completing year 1 were comparable in terms of mean age and prednisone dose; no other information given, and details relating to all subjects randomised to treatment not given	Method of Eastell *et al*.[53]	It was decided from the outset to withdraw all patients whose prednisone dose fell below 5 mg/day Although 38 patients completed 1 year, and 21 2 years, only 23 sets of paired radiographs were available for analysis at 1 year and 12 at 2 years

continued

TABLE 113 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Worth, 1994[50]	Adult clinically stable asthmatics without hypoxaemia who received more than 10 mg prednisone or equivalent for more than 9 months	Disorders of bone and mineral metabolism other than osteoporosis; disorders of liver or renal function; taking drugs other than corticosteroids which might affect bone metabolism	Baseline data were only provided for study completers. In relation to these patients, the groups were comparable at baseline in terms of age, sex, average steroid intake, vitamin D status and bone mass	A reduction of at least 15% in anterior, middle or posterior vertebral height	Inhaled corticosteroids were allowed in doses of 1 mg budenoside or flunisolide 11 patients in the treatment group and 14 in the control group had osteopenia at baseline
Transplant studies					
Garcia-Delgado, 1997[47]	Ambulatory patients with normal mobilisation and diet who had undergone cardiac transplantation in Madrid University Hospital between 1991 and 1994	Taking other drugs known to interfere with calcium metabolism; if male, symptoms of hypogonadism	Comparable	Method of Eastell *et al*.[53]	
Henderson, 2001[10]	Patients undergoing cardiac or lung transplantation	Pre-existing diseases known to affect bone and mineral metabolism; significant renal impairment or liver disease; prior treatment with chronic corticosteroids, calcitonin, calcitriol, fluoride or vitamin D >50,000 U/week	Comparable	Radiographically confirmed symptomatic fractures only	Randomisation was stratified by age (≤40 or >40 years), sex and type of transplant The groups did not differ in baseline dietary calcium intake, assessed by food frequency questionnaire The calcitriol group did not receive supplemental calcium
Van Cleemput, 1996[49]	Recipients of heart transplants within the University Hospital Gasthuisberg, Leuven	Aged under 25 years at the time of transplantation; previous renal transplant	Patients receiving alfacalcidol were on average 8 years older than the etidronate group ($p = 0.02$) and received a slightly higher cumulative dose of steroids in the first postoperative year (p = NS)	A reduction of at least 20% in anterior, middle or posterior vertebral height	'Randomisation' was by alternate allocation

TABLE 114 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
General studies								
Adachi, 1997[45,113]	Etidronate ($n = 67$)	Not stated	0.94 ± 0.14	30 (45)	Men Premenopausal women Postmenopausal women	26 (39) 8 (12) 33 (49)	Rheumatological[a] Pulmonary[b] Dermatological Myasthenia/myasthenia gravis Chronic active hepatitis	62 (93) 2 (3) 0 (0) 1 (1) 2 (3)
	Placebo ($n = 74$)	Not stated	0.90 ± 0.18	36 (49)	Men Premenopausal women Postmenopausal women	28 (38) 9 (12) 37 (50)	Rheumatological[a] Pulmonary[b] Dermatological Myasthenia/myasthenia gravis Chronic active hepatitis	61 (82) 3 (4) 2 (3) 2 (3) 6 (8)
Cortet, 1999[46]	Etidronate ($n = 44$)	–1.82 ± 1.12	Not stated	Not stated	Men Premenopausal women Postmenopausal women	15 (34) 6 (14) 23 (52)	Rheumatological (RA, polymyalgia rheumatica or giant cell arteritis)	44 (100)
	Placebo ($n = 39$)	–1.48 ± 1.39	Not stated	Not stated	Men Premenopausal women Postmenopausal women	13 (33) 3 (8) 23 (59)	Rheumatological (RA, polymyalgia rheumatica or giant cell arteritis)	39 (100)
Geusens, 1998[8]	Etidronate ($n = 18$)	–2.82 (1.12) ($n = 17$)	Not stated	Not stated	Postmenopausal women	18 (100)	'Mainly rheumatological conditions'	
	Placebo ($n = 19$)	–2.47 (0.60) ($n = 18$)	Not stated	Not stated	Postmenopausal women	19 (100)		
Jenkins, 1999[11]	Etidronate ($n = 15$)	Not stated	1.219 ± 0.206	Not stated	Men Women	3 (20) 12 (80)	Rheumatological (RA or polymyalgia rheumatica)	15 (100)
	Placebo ($n = 13$)	Not stated	1.065 ± 0.169	Not stated	Men Women	8 (62) 5 (38)	Rheumatological (RA or polymyalgia rheumatica)	13 (100)
Jinnouchi, 2000[48]	Etidronate ($n = 16$)	Not stated	Not stated	5 (31)	Men Women	3 (19) 13 (81)	Diffuse connective tissue disease (e.g. RA, SLE, dermatomyosotis, polymyosotis, interstitial pneumonitis)	25 (100)
	Control ($n = 9$)	Not stated	Not stated	2 (22)	Men Women	3 (33) 6 (67)		

continued

TABLE 114 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors (cont'd)*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Pitt, 1998[16]	Etidronate (n = 26)	–2.50 ± 0.77 (n = 25)	0.74 ± 0.12 (n = 25)	Not stated	Men Women	10 (38) 16 (62)	Rheumatological[c] Pulmonary[d] Dermatological (fasciitis)	14 (54) 11 (42) 1 (4)
	Placebo (n = 23)	–2.42 ± 0.83 (n = 21)	0.76 ± 0.11 (n = 21)	Not stated	Men Women	9 (39) 14 (61)	Rheumatological[c] Pulmonary[d] Dermatological (fasciitis)	9 (39) 14 (60) 0 (0)
Roux, 1998[17]	Etidronate (n = 59)	–1.61 ± 1.33	0.897 ± 0.158	2 (3)	Men Premenopausal women Postmenopausal women	22 (37) 10 (17) 27 (46)	Rheumatological[e] Pulmonary[f] Dermatological	57 (97) 2 (3) 0 (0)
	Placebo (n = 58)	–1.45 ± 1.38	0.924 ± 0.156	1 (2)	Men Premenopausal women Postmenopausal women	20 (34) 8 (14) 30 (52)	Rheumatological[e] Pulmonary[f] Dermatological	55 (95) 2 (3) 1 (2)
Skingle, 1997[19]	Etidronate (n not clear)	Not stated	Median (range) 0.927 (0.666–1.337)	N=13 10 (77)	Patients completing year 1 only (n = 20): Men Premenopausal women Postmenopausal women	 5 (25) 1 (5) 14 (70)	Patients completing year 1 only (n = 20): Rheumatological[g] Pulmonary (asthma) Dermatological (pemphigus) Renal transplant	 10 (50) 8 (40) 1 (5) 1 (5)
	Control (n not clear)	Not stated	Median (range) 0.977 (0.788–1.232)	N=10 9 (90)	Patients completing year 1 only (n = 18): Men Premenopausal women Postmenopausal women	 4 (22) 2 (11) 12 (67)	Patients completing year 1 only (n = 18): Rheumatological[g] Pulmonary (asthma) Dermatological (pemphigus) Renal transplant	 11 (61) 6 (33) 0 (0) 1 (6)
Worth, 1994[50]	Etidronate (n = 14)	Not stated	0.72 ± 0.022	Not stated	Men Premenopausal women Postmenopausal women	3 (21) 3 (21) 8 (57)	Asthma	14 (100)
	Control (n = 19)	Not stated	0.76 ± 0.03	Not stated	Men Premenopausal women Postmenopausal women	9 (47) 2 (11) 8 (42)	Asthma	19 (100)

continued

TABLE 114 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors (cont'd)*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Transplant studies								
Garcia-Delgado, 1997[47]	Etidronate ($n = 14$)	Not stated *Z*-score: –1.47 ± 0.27	0.871 ± 0.091	Not stated	Men Women	14 (100) 0 (0)	Cardiac Transplant	14 (100)
	Calcitonin ($n = 13$)	Not stated *Z*-score: –1.65 ± 0.41	0.854 ± 0.069	Not stated	Men Women	13 (100) 0 (0)	Cardiac Transplant	13 (100)
	Calcidiol ($n = 13$)	Not stated *Z*-score: –0.99 ± 0.39	0.905 ± 0.043	Not stated	Men Women	11 (85) 2 (15)	Cardiac Transplant	13 (100)
Henderson, 2001[10]	Etidronate ($n = 20$)	Not stated	1.09 ± 0.13	Not stated	Men Women	15 (75) 5 (25)	Cardiac transplant Lung transplant	15[h] 6[h]
	Calcitriol ($n = 21$)	Not stated	1.14 ± 0.20	Not stated	Men Women	15 (71) 6 (29)	Cardiac transplant Lung transplant	16[h] 4[h]
Van Cleemput, 1996[49]	Etidronate ($n = 19$)	Not stated	gHA/cm^2[i] 944 ± 181	0 (0)	Men Women	15 (79) 4 (21)	Cardiac Transplant	19 (100)
	Alfacalcidol ($n = 22$)	Not stated	gHA/cm^2[i] 967 ± 163	2 (9)	Men Women	19 (86) 3 (14)	Cardiac Transplant	22 (100)

[a] RA, polymyalgia rheumatica, ankylosing spondylitis, dermatomyosotis, SLE, polymyosotis, temporal arteritis, vasculitis.
[b] Chronic interstitial lung disease.
[c] Polymyalgia rheumatica, SLE, giant cell arteritis, polyarteritis nodosa, scleroderma.
[d] Asthma, emphysema, bronchiectasis, fibrosing alveolitis.
[e] RA, polymyalgia rheumatica, temporal arteritis, SLE, dermatomyosotis, polymyosotis, vasculitis.
[f] Asthma, chronic interstitial lung disease.
[g] Polymyalgia rheumatica, temporal arteritis, SLE, RA, polyarteritis nodosa.
[h] *Sic*. Presumably these figures were transposed in the original publication.
[i] Grams of hydroxyapatite.

TABLE 115 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
General studies										
Adachi, 1997[45]	1	3	3	3	0	3	13/15 (87)	141 (54 men, 17 premenopausal women, 70 post-menopausal women)	Etidronate: 54/67 (81) Placebo: 63/74 (85)	Procter & Gamble Pharmaceuticals, Canada
Cortet, 1999[46]	1	1	3	3	3	3	14/18 (78)	83 (28 men, 9 premenopausal women, 46 post-menopausal women)	Etidronate: 43/44 (98) Placebo: 33/39 (85)	Not stated
Geusens, 1998[8]	3	1	3	3	3	3	16/18 (89)	37 (all post-menopausal women)	Etidronate: 13/18 (72) Placebo: 13/19 (68)	Procter & Gamble Pharmaceuticals, UK
Jenkins, 1999[11]	1	1	3	3	0	3	11/15 (73)	28 (11 men, 17 women)	Etidronate: 13/15 (87) Placebo: 12/13 (92)	Southampton Rheumatology Trust Wessex Regional Health Authority Procter & Gamble (drugs only)
Jinnouchi, 2000[48]	1	1	3	3	0	1	9/15 (60)	25 (6 men, 19 women)	Apparently 100% in each arm	Not stated
Pitt, 1998[16]	1	3	3	3	0	3	13/15 (87)	49 (19 men, 30 women)	Etidronate: 22/26 (85) Placebo: 19/23 (83)	Procter & Gamble

continued

TABLE 115 *Etidronate in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality (cont'd)*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Roux, 1998[17]	1	1	3	3	1	1	10/18 (56)	117 (42 men, 18 premenopausal women, 57 postmenopausal women)	Etidronate: 52/59 (88) Placebo: 55/58 (95)	Not stated
Skingle, 1997[19]	1	3	3	1	0	?		55 (year 1 completers were 9 men, 3 premenopausal women and 26 postmenopausal women)	Overall: 21/55 (38) (most withdrawals were due to reductions in prednisone dose)	Procter & Gamble
Worth, 1994[50]	1	1	2	3	0	3	10/15 (67)	40 (the study completers were 12 men, 5 premenopausal women, 16 postmenopausal women)	Etidronate: 14/20 (70) Control: 19/20 (95)	Not stated
Transplant studies										
Garcia-Delgado, 1997[47]	1	1	3	3	0	3	11/15 (73)	40 (38 men, 2 women)	Apparently 100%	Not stated
Henderson, 2001[10]	1	1	3	3	3	3	14/18 (78)	41 (30 men, 11 women)	Overall: 33/41 (80)	Roche Australia Pharmacia & Upjohn Pty Ltd Procter & Gamble, Australia Pty Ltd (all medications only)
Van Cleemput, 1996[49]	1	1	2	1	0	3	8/15 (53)	48 (the study completers were 34 men and 7 women)	Overall: 40/48 (83)	Not stated

TABLE 116 *Etidronate: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
General studies			
Adachi, 1997[45]	All adverse events (mostly mild, transient GI events): Etidronate group: 12/74 (16%) Placebo group: 13/67 (19%)	None specified	None
Cortet, 1999[46]	Etidronate group: 32% Placebo group: 31%	All adverse events: Etidronate group: 84% Placebo group: 87%	5 – none treatment-related (sudden death $n = 2$, myocardial infarction $n = 1$, congestive heart failure $n = 1$, lung cancer $n = 1$)
Geusens, 1998[8]	Etidronate group: 4/18 (22%) Placebo group: 3/19 (16%)	Said to be comparable in both groups	Etidronate group: 1/18 (ruptured aortic aneurysm) Placebo group: 2/19 (anaphylactic shock, shoulder fracture)
Jenkins, 1999[11]	No data	No data	1 death in the placebo group (not treatment-related)
Jinnouchi, 2000[48]	No data	No data	None reported
Pitt, 1998[16]	Number of patients reporting mild to severe upper GI adverse events: Etidronate group: 2/26 (8%) Placebo group: 0/23 (0%)	All adverse events: Etidronate group: 17/26 (65%) Placebo group: 19/23 (83%) The most common adverse events were respiratory infections, back pain and accidental injury. Most adverse events were mild or moderate in severity Serious adverse events: Etidronate group: 5/26 (19%) Placebo group: 8/23 (35%) None of these were thought to be related to study treatment	Etidronate group: 3/26 (12%) (myocardial infarction, death due to respiratory failure, death due to adenocarcinoma of lung) Placebo group: 1/23 (4%) (death due to perforated bowel)
Roux, 1998[17]	Proportion of patients reporting upper GI adverse events (all moderate in severity): Etidronate group: 12% Placebo group: 5% ($p = 0.32$)	Proportion of patients reporting any adverse event: Etidronate group: 86% Placebo group: 88%	Etidronate group: 5/58 (9%) Placebo group: 1/59 (2%) None of the withdrawals were attributed to etidronate
Skingle, 1997[19]	No data	No data	None reported

continued

TABLE 116 *Etidronate: details of included studies – toxicity (cont'd)*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Worth, 1994[50]	No data	No data	3 patients were withdrawn from the treatment group because of side-effects (nausea). 1 patient was excluded from the control group because of exacerbation of his underlying illness
Transplant studies			
Garcia-Delgado, 1997[47]	No data	No data	None reported
Henderson, 2001[10]	No data	No data	None reported
Van Cleemput, 1996[49]	None reported	3/22 patients in the alfacalcidol group developed asymptomatic hypercalcaemia necessitating a dose reduction	Etidronate group: 2/19 (severe intercurrent illness not attributed to study medication) Alfacalcidol group: 0/22

TABLE 117 *Ibandronate in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Grotz, 2001[54]	Germany	1 year	Change in BMD after 12 months	Male and female renal allograft recipients aged 20–60 years	43 (n = 72)	Apparently commenced at same time as ibandronate therapy	Prednisone 100 mg for 5 days, 50 mg for 5 days, 25 mg for 10 days and tapered to 5 mg after 1 year	Bolus injections of ibandronate (1 mg immediately before and 2 mg at 3, 6 and 9 months after, transplantation)	No treatment

TABLE 118 *Ibandronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Grotz, 2001[54]	Men and women aged 20–60 years undergoing kidney transplantation at the University Hospital of Freiburg	Combined kidney and pancreas grafts	Baseline data provided for study completers only. These were comparable in both groups	Reduction of the anterior or posterior height >20% compared with adjacent vertebrae	Patients had diet counselling to achieve an intake of at least 1000 mg/day calcium. Patients with an intolerance to dairy products were supplemented with 500 mg/day calcium Patients with initial vitamin D deficiency below 15 ng/ml (11 in the ibandronate group and 8 in the control group) were supplemented with a single dose of 10,000 U cholecalciferol Patients who were already on HRT (one postmenopausal woman in each group) continued on it during the study

TABLE 119 *Ibandronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Grotz, 2001[54]	Ibandronate ($n = 36$; study completers only)	Not stated	1.137 ± 0.168	3 (8)	Men Premenopausal women Postmenopausal women	25 (69) 6 (17) 5 (14)	Renal transplant	36 (100)
	Control ($n = 36$; study completers only)	Not stated	1.147 ± 0.166	4 (11)	Men Premenopausal women Postmenopausal women	23 (64) 7 (19) 6 (17)	Renal transplant	36 (100)

TABLE 120 *Ibandronate in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Grotz, 2001[54]	1	3	2	3	1	3	13/18 (72)	80 (study completers were 48 men, 24 women)	Ibandronate: 36/40 (90) Control: 36/40 (90)	Not stated

TABLE 121 *Ibandronate: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Grotz, 2001[54]	No data	3/40 patients in the ibandronate group reported side-effects in temporal relation to ibandronate administration (bone pain, flatulence). No side-effects were reported in the control group	Ibandronate group: 4/40 (2 early graft loss, 2 deaths as a result of infectious complications) Control group: 3/40 (3 deaths as a result of infectious complications) No withdrawals in either group were due to side-effects

TABLE 122 *Pamidronate in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Aris, 2000[55]	USA	2 years	Spine BMD	Ambulatory white adults with cystic fibrosis who had received lung transplants	28	As patients were recruited 1–12 months after transplantation, this was presumably the duration of steroid treatment. Mean months post-transplant in each group: Pamidronate: 4.0 ± 4.1 Control: 4.2 ± 3.4	Mean prednisone dose during the study (mg/day): Pamidronate: 14.7 ± 4.5 Control: 15.1 ± 6.3 Mean methylprednisolone dose during the study (mg/day): Pamidronate: 4.8 ± 3.1 Control: 4.5 ± 3.6	Pamidronate 30 mg i.v. every 3 months + calcium carbonate 1 g/day and ergocalciferol 800 IU/day	Calcium carbonate 1 g/day and ergocalciferol 800 IU/day

continued

TABLE 122 *Pamidronate in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Bianda, 2000[5]	Switzerland	18 months	BMD	Patients who had undergone cardiac transplantation at the University Hospital of Zurich no more than 2 weeks previously	53	Presumably no more than 2 weeks	Cumulative prednisone intake at 12 months (g): Calcitriol group: 14.8 ± 1.2 Pamidronate group: 13.8 ± 1.7	Intermittent intravenous pamidronate (0.5 mg/kg every 3rd month) + 1 g/day calcium carbonate	Oral calcitriol (starting dose 0.25 μg/day, maximum dose 0.5 μg/day) + intranasal calcitonin 200 U/day for the first 3 months + 1 g/day calcium carbonate
Boutsen, 2001[6]	Belgium	1 year	BMD	In- or outpatients aged over 18 years requiring first-time glucocorticoid therapy, who were expected to require a dose of at least 10 mg/day prednisolone for at least 3 months	57	Commenced simultaneously with study medication	All patients received at least 10 mg/day prednisolone during the first 3 months. Mean initial daily dose in mg (median): Pamidronate single infusion: 28 ± 25 (15) Pamidronate 3-monthly: 25 ± 23 (15) Control: 19 ± 16 (15) Mean cumulative dose at 12 months (mg): Pamidronate single infusion: 3993 ± 2787 (2891) Pamidronate 3-monthly: 4962 ± 3300 (3180) Control: 3233 ± 1401 (3300)	Pamidronate i.v. given as a single initial infusion of 90 mg in 500 ml of 0.9% NaCl, over 2 h, with or without subsequent infusions of 30 mg every 3 months Both groups received 800 mg/day elemental calcium (given as calcium carbonate)	800 mg/day elemental calcium (given as calcium carbonate)

continued

TABLE 122 *Pamidronate in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Ninkovic, 2002[56]	UK	1 year	Incident vertebral fracture	Consecutive consenting adult patients with chronic liver disease undergoing orthotopic liver transplantation	51 (19–68)	None	Oral prednisolone either 20 mg/day (n = 52) or 1 mg/kg (n = 27); this was reduced to zero by 3 months in 64%, with a mean daily dose in the remainder of 8 mg	Pamidronate i.v. given as a single infusion of 60 mg in 500 ml 5% dextrose over 6–8 h prior to liver transplantation	No treatment

TABLE 123 *Pamidronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Aris, 2000[55]	Ambulatory white adults with cystic fibrosis who had received lung transplants at the University of Carolina 1–12 months previously	Primary graft failure or other postoperative morbidities that precluded long-term survival; renal insufficiency (serum creatinine >3.0 mg/dl); pregnancy	Comparable	'Determined by measuring anterior and posterior vertebral body height and expressing the difference divided by the posterior height as a percentage'	Open-label study Randomisation was stratified by gender and by severity of osteoporosis, using a spine T-score of –3.0 as the cut-point between groups, and then done in a blocks-of-4 design 13 patients in the pamidronate arm and 12 in the control arm were osteoporotic by the WHO definition (T-score <–2.5)

continued

TABLE 123 *Pamidronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Bianda, 2000[5]	Consecutive recipients of heart transplants at the University Hospital of Zurich who had undergone transplantation no more than 2 weeks previously	None stated	Baseline characteristics were only given for the 26 study completers; in these terms, there were said to be no significant differences between the groups at baseline. However, there does seem to be a difference in terms of *T*-score, which was –1.51 ± 0.32 in the calcitriol group and only –0.80 ± 0.30 in the pamidronate group	Clinical fractures only	Treatment allocation was by alternate allocation The authors stated that they collected 'historic information on atraumatic fractures'. It is not clear whether this means that radiological confirmation of diagnosis was required Baseline data are only provided for study completers, and it is not even stated to which groups the non-completers were assigned. Hence it is not clear what the denominator should be in relation to the vertebral fracture
Boutsen, 2001[6]	In- or outpatients aged over 18 years requiring first-time glucocorticoid therapy, who were expected to require a dose of at least 10 mg/day prednisolone for at least 3 months	Previous treatment with glucocorticoids, fluoride or bisphosphonates; renal disease, urolithiasis, hyperparathyroidism, malignancy or liver or thyroid disease; prevalent vertebral fracture	Baseline characteristics were presented only for the 27 patients in the matched groups who completed the study (see comments). In terms of these 27, the groups were comparable at baseline	Minne *et al.*'s method[57]	Most of the patients suffered from various inflammatory rheumatic diseases Allocation to treatment took into account the starting dose of steroid (daily prednisolone dosage 10–20, 20–40 or >40 mg), sex, and pre- or postmenopausal status, with or without HRT, as follows: for every combination of these 4 parameters which was not yet observed, the patient was randomly allocated to treatment. If this combination was already present in 1 patient, the new patient was randomly allocated to one of the other 2 groups. If the combination was present in 2 subjects, the new patient received the treatment which was not given to the 2 previously enrolled subjects 30 patients were matched; the additional 2 were assigned to the 3-monthly pamidronate group One patient dropped out of the 3-monthly pamidronate group because she unexpectedly no longer required glucocorticoids after 2 months. As a result, only 27 patients remained available for BMD analysis in matched groups

continued

TABLE 123 *Pamidronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Ninkovic, 2002[56]	Consecutive consenting adult patients with chronic liver disease undergoing orthotopic liver transplantation	Undergoing re-transplantation; prior bisphosphonate treatment; significant renal impairment (creatinine clearance <35 ml/minute)	Comparable	A reduction of more than 20% in anterior, middle or posterior vertebral height	At enrolment, few patients were receiving any bone-specific treatment: 5 were taking calcium + vitamin D and one woman was taking HRT which was continued during the first year after transplantation. No women started HRT after transplantation Randomisation was by sealed envelopes Pamidronate was given at admission or listing for transplantation. 81% received it within 4 weeks, 88% within 8 weeks and 95% within 12 weeks of transplantation

TABLE 124 *Pamidronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Aris, 2000[55]	Pamidronate (n = 16)	–3.00 ± 1.00	0.732 ± 0.120	4 (25)	Men Women	9 (56) 7 (44)	Cystic fibrosis + lung transplant	16 (100)
	Control (n = 18)	–2.78 ± 1.05	0.768 ± 0.120	7 (39)	Men Women	8 (44) 10 (56)	Cystic fibrosis + lung transplant	18 (100)
Bianda, 2000[5]	Pamidronate (n = 14)	–0.80 ± 0.30	1.01 ± 0.03	No data	Men Women	13 (93) 1 (7)	Cardiac transplant	14 (100)
	Calcitriol (n = 12)	–1.51 ± 0.32	0.97 ± 0.04	No data	Men Women	11 (92) 1 (8)	Cardiac transplant	12 (100)
Boutsen, 2001[6]	Pamidronate single infusion (n = 9)	Not stated	0.965 ± 0.161	No data	Men Premenopausal women Postmenopausal women	4 (44) 1 (11) 4 (44)	Rheumatic[a] Pulmonary (asthma) GI[b]	7 (78) 0 (0) 2 (22)
	Pamidronate 3 monthly (n = 9)	Not stated	0.874 ± 0.130	No data	Men Premenopausal women Postmenopausal women	4 (44) 1 (11) 4 (44)	Rheumatic[a] Pulmonary (asthma) GI[b]	9 (100) 0 (0) 0 (0)
	Control (n = 9)	Not stated	0.963 ± 0.173	No data	Men Premenopausal women Postmenopausal women	4 (44) 1 (11) 4 (44)	Rheumatic[a] Pulmonary (asthma) GI[b]	6 (67) 1 (11) 2 (22)
Ninkovic, 2002[56]	Pamidronate (n = 45)	Not stated	0.93 ± 0.187 (n = 41)	2/42 evaluable patients (5)	Men Premenopausal women Postmenopausal women	22 (49) 5 (11) 18 (40)	Viral Alcohol PBC/PSC[c] Other	10 (22) 10 (22) 18 (40) 7 (16)
	Control (n = 54)	Not stated	0.89 ± 0.187 (n = 48)	4/49 evaluable patients (8)	Men Premenopausal women Postmenopausal women	28 (52) 8 (15) 18 (33)	Viral Alcohol PBC/PSC[c] Other	20 (37) 8 (15) 12 (22) 14 (26)

[a] Polymyalgia rheumatica, temporal arteritis, RA, reactive arthritis.
[b] Inflammatory bowel disease.
[c] Primary biliary cirrhosis/primary sclerosing cholargitis.

TABLE 125 *Pamidronate in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Aris, 2000[55]	1	1 (although BMD outcome assessors were said to be blinded)	3	3	3	2	13/18 (72)	37 (study completers were 17 men, 17 women)	Overall: 34/37 (92)	Cystic Fibrosis Foundation Verne S Caviness General Center for Clinical Research (NIH RR00046)
Bianda, 2000[5]	1	1	2	1	1	1	7/18 (39)	31 (29 men, 2 women)	84% overall	Not stated
Boutsen, 2001[6]	1	1	2	3	1	3	11/18 (61)	32 (data presented only relating to 12 men, 3 premenopausal women, 12 post-menopausal women)	Pamidronate single infusion: 9/9 (100) Pamidronate repeated infusions: 8/9 (89) Control: 9/9 (100)	Not stated
Ninkovic, 2002[56]	2	3	3	3	3	3	17/18 (94)	99 (50 men, 49 women)	Pamidronate: 33/45 (73) Control: (70)	Wellcome Trust

TABLE 126 *Pamidronate: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Aris, 2000[55]	None reported	3 episodes of mild hypervitaminosis D occurred during the study; these were not attributed to treatment group and all resolved spontaneously	There were 3 deaths during the course of the study; these were not attributed to treatment group
Bianda, 2000[5]	None in any group	None in any group	5 patients died within 12 months of transplantation; they were not attributed to study group. All the remaining patients completed the study
Boutsen, 2001[6]	None reported	None reported	None
Ninkovic, 2002[56]	None reported	Pamidronate group: symptomatic fever (n = 3), diarrhoea (n = 1), osteolysis due to immunosuppression with rapamycin and requiring i.v. pamidronate (n = 1) Control group: osteolysis due to immunosuppression with rapamycin and requiring i.v. pamidronate (n = 1), symptomatic hypercalcaemia (n = 1)	1 patient randomised to pamidronate died prior to, and 4 within 12 months of, transplantation; 3 patients in the control group died before, and 8 within 12 months of, transplantation 1 patient withdrew from the pamidronate group because of psychosis

TABLE 127 *Risedronate in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Cohen, 1999[59,61]	USA	1 year	Difference between treatment groups in % change in lumbar spine BMD at 12 months	Ambulatory patients aged 18–85 years with a variety of rheumatological, pulmonary and skin conditions, who had initiated moderate to high doses of corticosteroids (mean dose of prednisone or prednisone equivalent ≥7.5 mg/day) within the previous 3 months and were expected to continue treatment for another 12 months	60	No more than 3 months	Mean daily dose of prednisone (or equivalent) at baseline (mg): 2.5-mg group: 21.4 ± 2.6 5-mg group: 20.4 ± 1.9 Placebo group: 21.7 ± 2.0 Mean daily dose of prednisone (or equivalent) during the study (mg): 2.5-mg group: 10.9 ± 0.9 5-mg group: 11.2 ± 1.0 Placebo group: 11.1 ± 0.8	Risedronate 2.5 or 5 mg/day All subjects received 500 mg/day elemental calcium as calcium carbonate	Placebo + 500 mg/day elemental calcium as calcium carbonate
Eastell, 2000[7]	England and Belgium	96 weeks + 48 weeks of non-treatment follow-up	Mean % change in lumbar spine BMD from baseline at week 97	Postmenopausal women with rheumatoid arthritis who required long-term (>6 months) treatment with oral glucocorticoids at an average daily dose of at least 2.5 mg prednisolone	64	Median duration of previous prednisolone treatment (years): Daily risedronate: 13.5 Cyclical risedronate: 14.6 Placebo: 16.6	All but 3 patients (1 in each group) received at least 2.5 mg/day prednisolone in the 5 years before study entry Mean daily prednisolone dose during the study (mg): Daily risedronate: 5.5 Cyclical risedronate: 5.1 Placebo: 5.5 Overall, mean daily dose <5 mg in 58%, 5–7.5 mg in 20%, ≥7.5 mg in 23%	Group 1: Risedronate daily (2.5 mg/day) Group 2: Risedronate cyclically (15 mg/day for 2 weeks followed by placebo daily for 10 weeks)	Placebo

continued

TABLE 127 *Risedronate in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Reid, 2000[60,61]	Europe (23 centres)	1 year	Mean % change from baseline lumbar spine BMD at month 12	Ambulatory men and women aged 18–85 years who had been receiving moderate to high doses of oral corticosteroid therapy (≥7.5 mg/day prednisone or equivalent) for a range of diseases for at least 6 months and who were expected to continue corticosteroid therapy for at least 12 months. Premenopausal women had to be surgically sterile or using an acceptable form of birth control	59	At least 6 months; mean duration of previous prednisolone treatment (months): 2.5 mg/day: 56 ± 56 5 mg/day: 57 ± 58 Placebo: 62 ± 72	Mean daily corticosteroid dose (mg/day): before enrolment: 2.5 mg/day: 15 ± 13 5 mg/day: 15 ± 12 Placebo: 15 ± 13 during study: 2.5 mg/day: 12 ± 11 5 mg/day: 15 ± 18 Placebo: 13 ± 13	Risedronate 2.5 or 5 mg/day All subjects received 400 IU/day vitamin D + 1 g/day elemental calcium as calcium carbonate	Placebo + 400 IU/day vitamin D + 1 g/day elemental calcium as calcium carbonate

TABLE 128 *Risedronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Cohen, 1999[59]	Ambulatory patients aged 18–85 years with a variety of rheumatological, pulmonary and skin conditions, who had initiated moderate to high doses of corticosteroids (mean dose of prednisone or prednisone equivalent ≥7.5 mg/day) within the previous 3 months and were expected to continue treatment for another 12 months; female patients were postmenopausal, surgically sterile or using birth control methods	Conditions that would interfere with the evaluation of lumbar BMD (e.g. severe scoliosis, osteophytosis or spinal fusion); having taken in the previous year any drugs known to affect bone metabolism (e.g. bisphosphonates, oestrogen or oestrogen-related drugs, or vitamin D >500 IU/day), including any treatment with corticosteroids prior to the current therapy (low-dose vaginal oestrogen, intra-articular steroids, topical hydrocortisone and inhaled beclomethasone or budesonide (≤400 μg/day) were allowed)	The groups were comparable at baseline except that the mean age in the 5-mg group was greater than in the other 2 groups ($p = 0.02$)	A decrease of ≥15% for vertebrae intact at baseline, or of ≥4 mm in vertebrae fractured at baseline, in anterior, middle or posterior height	Randomisation was stratified by sex and menopausal status Vitamin D supplementation (up to 500 IU/day) was recommended for patients whose baseline serum levels of 25-hydroxyvitamin D_3 were below the lower limit of the normal range (i19 in all, 6 in the 2.5-mg group, 4 in the 5-mg group and 9 in the placebo group) During the course of the study, data became available indicating that the 5-mg dose of risedronate was more effective than 2.5-mg. As a result, the 2.5-mg group was discontinued, but the blind was maintained for the other 2 groups. However, since fewer than 1/3 of patients in the 2.5-mg group were discontinued per amendment (mostly after 6 months), the data for that group were included in the report
Eastell, 2000[7]	Postmenopausal women with rheumatoid arthritis who required long-term (>6 months) treatment with oral glucocorticoids at an average daily dose of at least 2.5 mg prednisolone	Metabolic bone disease other than glucocorticoid-induced osteoporosis; any significant organic disease that could affect participation or interfere with the interpretation of the data; treatment with androgens, oestrogens, or calcitonin for >3 months, or with vitamin D (>800 IU/day) or fluoride for ≥1 month, within 6 months of enrolment	Although the cyclical risedronate group was younger and nearer to the menopause than the other groups, and had fewer patients with prevalent vertebral fractures (35 vs 44% in the daily risedronate group and 40% in the placebo group), there were no statistically significant differences between the groups at baseline	A decrease of ≥15% for vertebrae intact at baseline, or of ≥4 mm in vertebrae fractured at baseline, in anterior, middle or posterior height	Vertebral fracture data were not available for the untreated follow-up period

continued

TABLE 128 *Risedronate in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Reid, 2000[60]	Ambulatory men and women aged 18–85 years who had been receiving moderate to high doses of oral corticosteroid therapy (≥7.5 mg/day prednisone or equivalent) for a range of diseases for at least 6 months and who were expected to continue corticosteroid therapy for at least 12 months. Premenopausal women had to be surgically sterile or using an acceptable form of birth control	Conditions that might interfere with the evaluation of spinal osteoporosis; history of hyperparathyroidism, hyperthyroidism or osteomalacia within 1 year before the study; history of sarcoidosis or cancer; taking or having taken (within 6–12 months, depending on the medication) medication known to affect bone metabolism, including HRT excluding low-dose vaginal oestrogen (17β-estradiol ≤0.2 mg/day; estropitate ≤ 1.5 mg/day)	Comparable	Reduction of ≥ 15% in vertebral height in a previously intact vertebra or of ≥4 mm in a previously fractured vertebra	Randomisation was stratified by gender and menopausal status Analysis was by intention-to-treat, including all patients who were randomised and received at least 1 dose of study medication. No explanation is given as to why vertebral fracture data are available for only 180 of the 222 patients who completed the study

TABLE 129 *Risedronate in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Cohen, 1999[59]	Risedronate 2.5 mg ($n = 75$)	–0.96 ± 0.22	1032 ± 25	19 (26)	Men Premenopausal women Postmenopausal women	25 (33) 17 (23) 33 (44)	Rheumatic[a] Pulmonary[b]	69 (92) 6 (8)
	Risedronate 5 mg ($n = 76$)	–0.40 ± 0.20	1082 ± 26	27 (36)	Men Premenopausal women Postmenopausal women	27 (36) 14 (18) 35 (46)	Rheumatic[a] Pulmonary[b]	73 (96) 3 (4)
	Placebo ($n = 77$)	–0.70 ± 0.20	1066 ± 22	22 (29)	Men Premenopausal women Postmenopausal women	25 (33) 15 (20) 37 (48)	Rheumatic[a] Pulmonary[b]	76 (99) 1 (1)
Eastell, 2000[7]	Risedronate daily ($n = 40$)	Not given	0.80 ± 0.13	(44)	Postmenopausal women	40 (100)	Rheumatoid arthritis	40 (100)
	Risedronate cyclical ($n = 40$)	Not given	0.81 ± 0.15	(35)	Postmenopausal women	40 (100)	Rheumatoid arthritis	40 (100)
	Placebo ($n = 40$)	Not given	0.76 ± 0.13	(40)	Postmenopausal women	40 (100)	Rheumatoid arthritis	40 (100)
Reid, 2000[60]	Risedronate 2.5 mg ($n = 94$)	–1.4 ± 1.2	960 ± 140	30 (32)	Men Premenopausal women Postmenopausal women	37 (39) 9 (10) 48 (51)	Rheumatic[c] Pulmonary[d] Other[e]	70 (74) 19 (20) 5 (5)
	Risedronate 5 mg ($n = 100$)	–1.7 ± 1.6	940 ± 180	34 (35)	Men Premenopausal women Postmenopausal women	36 (36) 9 (9) 55 (55)	Rheumatic[c] Pulmonary[d] Other[e]	75 (75) 22 (22) 3 (3)
	Placebo ($n = 96$)	–1.7 ± 1.5	930 ± 170	35 (37)	Men Premenopausal women Postmenopausal women	36 (38) 7 (7) 53 (55)	Rheumatic[c] Pulmonary[d] Other[e]	69 (72) 22 (23) 5 (5)

[a] RA, polymyalgia rheumatica, SLE, temporal arteritis, vasculitis, polymyositis, dermatomyosotis.
[b] Asthma, chronic interstitial lung disease.
[c] RA, polymyalgia rheumatica, SLE, temporal arteritis, vasculitis, polymyositis.
[d] Asthma, chronic interstitial lung disease, COPD.
[e] Pemphigoid, pemphigus, psoriasis, Behçet's disease, dermatomyosotis, eczema.

TABLE 130 *Risedronate in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Cohen, 1999[59]	1	3	3	2	1	3	13/18 (72)	228 (77 men, 46 premenopausal women, 105 post-menopausal women)	Group 1: 31/75 (41) Group 2: 62/76 (82) Control: 57/77 (74) 23 discontinuations in the 2.5-mg group were per protocol amendment	Procter & Gamble Pharmaceuticals, Cincinnatti, OH Hoechst Marion Roussel, Kansas City, MO NIH General Clinical Research Center Grant
Eastell, 2000[7]	1	1	3	3	0	3	11/15 (73)	120 (all post-menopausal women)	Not clear. vertebral fracture data were only available for 94/120 (78)	Procter & Gamble Pharmaceuticals
Reid, 2000[60]	1	1	3	3	1	1	11/18 (61)	290 (109 men, 25 premenopausal women, 156 post-menopausal women)	77% overall	Procter & Gamble Pharmaceuticals Hoechst Marion Roussel

TABLE 131 *Risedronate: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Cohen, 1999[59]	Risedronate 2.5 mg: 15/73 (21%) Risedronate 5 mg: 11/75 (15%) Placebo: 13/76 (17%)	Serious adverse events: Risedronate 2.5 mg: 15/73 (21%) Risedronate 5 mg: 17/75 (23%) Placebo: 20/76 (26%) All musculoskeletal adverse events: Risedronate 2.5 mg: 34/73 (47%) Risedronate 5 mg: 37/75 (49%) Placebo: 37/76 (49%) Back pain: Risedronate 2.5 mg: no data Risedronate 5 mg: 12% Placebo: 8% Arthralgia: Risedronate 2.5 mg: no data Risedronate 5 mg: 25% Placebo: 15% Back pain and arthralgia were mostly mild and were not considered drug-related; they did not cause any withdrawals	Risedronate 2.5 mg: 5/73 (7%) Risedronate 5 mg: 3/75 (4%) Placebo: 4/76 (5%)
Eastell, 2000[7]	Daily risedronate: 15/40 (38%) Cyclical risedronate: 21/40 (53%) Placebo: 22/40 (55%)	Serious adverse events: Daily risedronate: 25/40 (63%) Cyclical risedronate: 19/40 (48%) Placebo: 21/40 (53%)	Daily risedronate: 6/40 (15%) Cyclical risedronate: 9/40 (23%) Placebo: 6/40 (15%)
Reid, 2000[60]	Risedronate 2.5 mg: 14/92 (15%) Risedronate 5 mg: 25/99 (25%) Placebo: 21/94 (22%)	Serious adverse events: Risedronate 2.5 mg: 32/92 (35%) Risedronate 5 mg: 37/99 (37%) Placebo: 37/94 (39%) Back pain: Risedronate 2.5 mg: no data Risedronate 5 mg: 23% Placebo: 10% Arthralgia: Risedronate 2.5 mg: no data Risedronate 5 mg: 24% Placebo: 16% Back pain and arthralgia were mostly mild and were generally not considered drug-related; they did not cause any withdrawals	Due to any adverse event: Risedronate 2.5 mg: 11/92 (12%) Risedronate 5 mg: 11/99 (11%) Placebo: 11/94 (12%) Due to adverse events possibly or probably related to the study drug: Risedronate 2.5 mg: 3/92 (3%) Risedronate 5 mg: 5/99 (5%) Placebo: 6/94 (6%)

TABLE 132 *Human parathyroid hormone 1–34 in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Lane, 1998[15]	USA	1 year	BMD	Postmenopausal women aged 50–82 years with chronic non-infectious inflammatory diseases and osteoporosis, treated with HRT and corticosteroids	63	Mean duration at baseline (years): hPTH group: 12.4 ± 13.3 Control group: 14.9 ± 10.3	Mean dose of prednisone or equivalent at baseline (mg/day): hPTH group: 8.0 ± 3.8 Control group: 9.4 ± 4.5	Subcutaneous hPTH 25 μg/day (400 IU/day) + HRT + calcium supplementation to bring total intake, including dietary calcium, up to 1500 mg/day + 800 IU/day vitamin D_3	HRT + calcium supplementation to bring total intake, including dietary calcium, up to 1500 mg/day + 800 IU/day vitamin D_3

TABLE 133 *Human parathyroid hormone 1–34 in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Lane, 1998[15]	Postmenopausal women aged 50–82 years with chronic non-infectious inflammatory diseases and osteoporosis (*T*-score >2.5 at lumbar spine or femoral neck), menopausal for ≥3 years, treated with HRT (Premarin 0.625 mg/day or equivalent) for ≥1 year, and with prednisone or equivalent for the previous 12 months at a mean daily dose of 5–20 mg, who were expected to continue corticosteroid treatment for at least 1 year	Secondary osteoporosis other than from rheumatic disease and corticosteroids; renal or hepatic dysfunction; abnormalities on spinal radiograph that precluded accurate measurements of the lumbar spine by quantitative computed tomography or DXA	Comparable	A decrease of 20% and at least 4 mm from baseline in any vertebral height	Randomisation was by a computer-generated table If urinary calcium excretion exceeded 400 mg/day, calcium supplementation was decreased by 30% If serum calcium concentration exceeded 10.5 mg/dl, the hPTH dose and the calcium supplementation were both decreased by 30% Treatment was discontinued if significant hypercalcaemia occurred (calcium ≥10.5 mg/dl) which did not respond to reducing the calcium supplement and hPTH dose

TABLE 134 *Human parathyroid hormone 1–34 in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Lane, 1998[15]	hPTH ($n = 28$)	−1.81 ± 1.15	0.85 ± 0.15	8 (29)	Postmen women	28 (100)	Rheumatic[a] Asthma Renal transplant	25 (89) 2 (7) 1 (4)
	Control ($n = 23$)	−1.48 ± 1.43	0.88 ± 0.16	6 (26)	Postmen women	23 (100)	Rheumatic[a] Asthma Renal transplant	18 (78) 5 (22) 0 (0)

[a] RA, SLE, vasculitis, polymyalgia rheumatica.

TABLE 135 *Human parathyroid hormone 1–34 in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Lane, 1998[15]	3	1	2	3	0	3	12/18 (67)	51 (all postmeno-pausal women)	hPTH group: 28/28 (100) Control group: 20/23 (87)	Public Health Service Grant 1-R01-46661 Rosalind Russell Arthritis Research Center UCSF Program in Osteoporosis and Bone Biology

TABLE 136 *Human parathyroid hormone 1–34: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Lane, 1998[15]	None reported	Many patients (number not specified) complained of mild headaches at the initiation of hPTH injections; these resolved after 1–2 weeks treatment No other information is given about adverse events	hPTH group: 0/28 (0%) Control group: 2/23 (9%)

TABLE 137 *Vitamin D in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Ringe, 1999[65,66]	Germany	3 years	BMD at lumbar spine	Patients on long-term glucocorticoid therapy for chronic obstructive lung disease, RA or polymyalgia rheumatica with osteoporosis with or without vertebral fractures	61 (37–76)	Mean 5 years	Mean dose (mg/day): Vitamin D group: 9.6 Alfacalcidol group:9.7	Vitamin D 1000 IU/day + calcium 500 mg/day	Alfacalcidol 1 μg/day + calcium 500 mg/day

TABLE 138 *Vitamin D in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Ringe, 1999[65,66]	Patients with chronic obstructive lung disease, RA or polymyalgia rheumatica, on long-term glucocorticoid therapy with osteoporosis (*T*-score of –2.5 or below) with or without vertebral fractures	Not stated	Comparable	A minimum of 20% reduction in anterior, middle or posterior height	'Randomisation' was by alternate allocation

TABLE 139 *Vitamin D in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Ringe, 1999[65,66]	Vitamin D ($n = 42$)	–3.25	Not stated	21 (50)	Men Women	15 (36) 27 (64)	Rheumatic[a] Pulmonary[b]	24 (57) 18 (43)
	Alfacalcidol ($n = 43$)	–3.28	Not stated	25 (58)	Men Women	15 (35) 28 (65)	Rheumatic[a] Pulmonary[b]	22 (51) 21 (49)

[a] RA, polymyalgia rheumatica.
[b] Chronic obstructive lung disease.

TABLE 140 *Vitamin D in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Ringe, 1999[65,66]	1	3	3	3	1	3	14/18 (78)	85 (30 men and 55 women)	Vitamin D: 35/42 (83) Alfacalcidol: 35/43 (81)	Not stated

TABLE 141 *Vitamin D: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Ringe, 1999[65,66]	Epigastric discomfort: Vitamin D: 7/42 Alfacalcidol: 7/43 Nausea: Vitamin D: 0/42 Alfacalcidol: 2/43	No. of patients with at least 1 side-effect (including upper GI adverse events): Vitamin D: 10/42 Alfacalcidol: 11/43 Number of patients with hypercalciuria: Vitamin D: 0/42 Alfacalcidol: 2/43	None

TABLE 142 *Calcium and vitamin D in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Adachi, 1996[4]	USA	3 years	Lumbar spine BMD	Ambulatory patients aged 18 years or over with PMR, TA, SLE, vasculitis or asthma who had started prednisone within 1 month of study entry at a dose greater than 10 mg/day	66	Less than 1 month	Mean prednisone dose at baseline 18.9 mg/day	Calcium 1000 mg/day + vitamin D 50,000 U/week	Placebo

PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus; TA, temporal arteritis.

TABLE 143 *Calcium and vitamin D in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Adachi, 1996[4]	Ambulatory patients aged 18 years or over with PMR, TA, SLE, vasculitis or asthma who had started prednisone within 1 month of study entry at a dose greater than 10 mg/day	Treatment with prednisone within the last 2 years of >1 month duration at doses ≥ 10 mg/day; treatment within 6 months with drugs known to affect bone metabolism (e.g. bisphosphonates, sodium fluoride, oestrogen, progesterone, calcitonin, oral phosphates or pharmacological doses of vitamin D); diseases known to affect bone metabolism (e.g. hyperthyroidism, hyperparathyroidism, osteomalacia, prior malignancy, renal failure); unstable medical conditions (e.g. uncontrolled hypertension, sarcoidosis, unstable cardiovascular disease, insulin-dependent diabetes); current or prior alcohol or drug abuse; use of an investigational drug within 4 weeks	Comparable	At least 15% reduction in vertebral height (reference to Riggs paper indicates that this reduction may occur in the anterior to posterior height ratio, the posterior to middle ratio or in total height (including posterior height) in comparison with adjacent vertebrae	Study allocation was undertaken using a minimisation algorithm[68] designed to simultaneously balance treatment groups with respect to age, sex, disease duration and initial prednisone dose Study medication was discontinued as soon as corticosteroid therapy was discontinued, and was reduced to 50% (i.e. 500 mg/day calcium + fortnightly vitamin D) in subjects with persistent hypercalciuria or hypercalcaemia. 1 subject in the intervention group required dose reduction

TABLE 144 Calcium and vitamin D in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Adachi, 1996[4]	Calcium + vitamin D ($n = 31$)	Not stated	71.9 ± 12.9	8 (26)	Men Women	9 (29) 22 (71)	Rheumatic[a] Asthma	26 (84) 5 (16)
	Placebo ($n = 31$)	Not stated	72.7 ± 15.0	6 (19)	Men Women	11 (35) 20 (65)	Rheumatic[a] Asthma	27 (87) 4 (13)

[a] RA, polymyalgia rheumatica, SLE, vasculitis.

TABLE 145 *Calcium and vitamin D in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Adachi, 1996[4]	1	1	3	3	0	3	11/15 (73)	62 (20 men, 42 women)	Calcium + vitamin D: 11/31 (35) Placebo: 12/31 (39)	Ayerst, Canada (calcium + placebo only)

TABLE 146 *Calcium and vitamin D: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Adachi, 1996[4]	None reported	Hypercalciuria: Calcium + vitamin D: 14/31 (45%) Placebo: 7/31 (23%) Only 1 subject in the intervention group had persistent hypercalciuria requiring dose reduction (i.e. 500 mg/day calcium + fortnightly vitamin D)	Calcium + vitamin D: 3/31 [deaths from heart disease ($n = 1$), malignancy ($n = 2$)] Placebo: 4/31 [deaths from heart disease ($n = 2$), malignancy ($n = 1$), respiratory failure ($n = 1$)]

TABLE 147 *Alfacalcidol in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Lakatos, 2000[14]	Hungary	3 years	Biochemical markers of bone turnover BMD of lumbar spine, femoral neck and radius midshaft	Women aged 32–52 years recently diagnosed with SLE, multiple sclerosis, RA or bronchial asthma and receiving corticosteroid treatment	44	4 weeks	5–25 mg/day prednisone; mean dose (mg/day): Alfacalcidol group: 14.7 ± 1.1 Calcium group: 14.9 ± 1.3	Alfacalcidol 0.25–1.0 μg/day (mean 0.54 ± 0.03 μg/day)	Calcium 500 mg/day
Ringe, 1999[65,66]	Germany	3 years		Patients on long-term glucocorticoid therapy for chronic obstructive lung disease, RA or polymyalgia rheumatica with osteoporosis with or without vertebral fractures	61 (37–76)	Mean 5 years	Mean dose (mg/day): Alfacalcidol group: 9.7 Vitamin D group: 9.6	Alfacalcidol 1 μg/day + calcium 500 mg/day	Vitamin D 1000 IU/day + calcium 500 mg/day
Rozhinskaya, 1999[35]	Russia	1 year	BMD	Women with established steroid-induced osteoporosis (a *T*-score of –2.5 or less at spine or femur neck + 2 or more vertebral fractures)	56.3 ± 4.5	14.6 ± 3.8 years	Mean prednisolone dose 13.6 ± 2.8 mg	0.75 μg alfacalcidol	Group 1A: 15 mg fluoride + 450 mg calcium Group 1B: 15 mg fluoride + 450 mg calcium + 0.5 μg alfacalcidol
Van Cleemput, 1996[49]	Belgium	2 years	BMD	Cardiac transplant recipients aged 25 years or over	53	Less than 1 month	Cumulative prednisone intake (g): Year 1: Alfacalcidol: 5.3 ± 1.8 Etidronate: 4.9 ± 1.8 Year 2: Alfacalcidol: 1.5 ± 0.4 Etidronate: 1.6 ± 0.5	Calcium carbonate 1.25 g/day plus an incremental dose of alfacalcidol (starting dose 0.25 μg/day, to a maximum of 1 μg/day)	Calcium carbonate 1.25 g/day for 11 weeks followed by etidronate 400 mg/day for 2 weeks
Yamada, 1989[28]	Japan	2 years	BMD Vertebral fractures	Premenopausal women with collagen diseases undergoing chronic prednisolone treatment	35	Apparently at least 12 months	Mean dose for preceding 12 months: 11 mg/day	Alfacalcidol (0.75 μg/day) + calcium (400 mg/day) with or without trichlormethiazide (4 mg/day)	No treatment

TABLE 148 *Alfacalcidol in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Lakatos, 2000[14]	Women aged 32–52 years recently diagnosed with SLE, multiple sclerosis, RA or bronchial asthma, but without other diseases, and receiving corticosteroid treatment	Medication known to influence calcium or bone metabolism; history of renal stone formation	Comparable in terms of age, steroid dosage, weight, height, calcium intake and renal function	Not applicable	No information was given regarding the comparability of groups in relation to menopausal status or diagnosis requiring corticosteroid treatment
Ringe, 1999[65,66]	Patients with chronic obstructive lung disease, RA or polymyalgia rheumatica, on long-term glucocorticoid therapy with osteoporosis (*T*-score of –2.5 or below) with or without vertebral fractures	Not stated	Comparable	A minimum of 20% reduction in anterior, middle or posterior height	'Randomisation' was by alternate allocation At baseline, 25/43 patients in the alfacalcidol group had vertebral fractures and 13/43 had peripheral fractures, compared with 21/42 and 14/42, respectively in the vitamin D group
Rozhinskaya, 1999[35]	Women with established steroid-induced osteoporosis (a *T*-score of –2.5 or less at spine or femur neck + 2 or more vertebral fractures)	Not specified	No information given	Not stated	This study was available in abstract form only This was an open-label study
Van Cleemput, 1996[49]	Recipients of heart transplants within the University Hospital Gasthuisberg, Leuven	Aged under 25 years at the time of transplantation; previous renal transplant	Patients receiving alfacalcidol were on average 8 years older than the etidronate group ($p = 0.02$) and received a slightly higher cumulative dose of steroids in the first postoperative year (p = NS)	A reduction of at least 20% in anterior, middle or posterior vertebral height	'Randomisation' was by alternate allocation
Yamada, 1989[28]	Premenopausal women with collagen diseases undergoing chronic prednisolone treatment	Not specified	All 3 groups were comparable at baseline in terms of age, underlying disease, glucocorticoid dose and indices of osteoporosis	Not given	This paper is in Japanese. As a result, only data from the English abstract and tables could be used. This may explain the low quality score

TABLE 149 *Alfacalcidol in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Lakatos, 2000[14]	Alfacalcidol (n = 21)	Not stated	Not stated	Not stated	All women aged 32–52 years; menopausal status not specified		SLE, multiple sclerosis, RA or asthma (numbers not given)	
	Calcium (n = 20)	Not stated	Not stated	Not stated	All women aged 32–52 years; menopausal status not specified			
Ringe, 1999[65,66]	Alfacalcidol (n = 43)	–3.28	Not stated	25 (58)	Men Women	15 (35) 28 (65)	Rheumatic[a] Pulmonary[b]	22 (51) 21 (49)
	Vitamin D (n = 42)	–3.25	Not stated	21 (50)	Men Women	15 (36) 27 (64)	Rheumatic[a] Pulmonary[b]	24 (57) 18 (43)
Rozhinskaya, 1999[35]	Alfacalcidol (n = 10)	<–2.5	No data	10 (100)	Women	10 (100)	Connective tissue disease Pulmonary (asthma)	12 (55) 10 (45)
	Fluoride + alfacalcidol (n = 6)	<–2.5	No data	6 (100)	Women	6 (100)		
	Fluoride (n = 6)	<–2.5	No data	6 (100)	Women	6 (100)		
Van Cleemput, 1996[49]	Alfacalcidol (n = 22)	Not stated	967 ± 163	2 (9)	Men Women	19 (86) 3 (14)	Cardiac transplant	22 (100)
	Etidronate (n = 19)	Not stated	944 ± 181	0 (0)	Men Women	15 (79) 4 (21)	Cardiac transplant	19 (100)
Yamada, 1989[28]	Alfacalcidol + trichlormethiazide (n = 11)	Not stated	Not stated	1 (9)	All premenopausal women		Collagen diseases	
	Alfacalcidol alone (n = 14)	Not stated	Not stated	1 (7)	All premenopausal women		Collagen diseases	
	Control (n = 13)	Not stated	Not stated	2 (15)	All premenopausal women		Collagen diseases	

[a] RA, polymyalgia rheumatica.
[b] Chronic obstructive lung disease.

TABLE 150 *Alfacalcidol in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Lakatos, 2000[14]	1	1	1	3	1	1	8/18 (44)	41 (all women)	Not clear. 1 was withdrawn as a result of an adverse event	Not stated
Ringe, 1999[65,66]	1	3	3	3	1	3	14/18 (78)	85 (30 men and 55 women)	Alfacalcidol: 35/43 (81) Vitamin D: 35/42 (83)	Not stated
Rozhinskaya, 1999[35]	1	1	3	1	0	1	7/15 (47)	22	Alfacalcidol: 10/10 (100) Combined fluoride groups: 11/12 (92)	Not stated
Van Cleemput, 1996[49]	1	1	2	1	0	3	8/15 (53)	48 (the study completers were 34 men and 7 women)	Overall: 40/48 (83)	Not stated
Yamada, 1989[28]	1	1	1	3	0	1	7/15 (47)	38 (all premenopausal women)	No data	Not stated

TABLE 151 *Alfacalcidol: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Lakatos, 2000[14]	None reported	The only reported adverse event was renal stone formation in 1 woman in the alfacalcidol group	Alfacalcidol: 1/21 (renal stone formation in year 3) Calcium: 0/20
Ringe, 1999[65,66]	Epigastric discomfort: Alfacalcidol: 7/43 Vitamin D: 7/42 Nausea: Alfacalcidol: 2/43 Vitamin D: 0/42	Number of patients with at least 1 side-effect (including upper GI adverse events): Alfacalcidol: 11/43 Vitamin D: 10/42 Number of patients with hypercalciuria: Alfacalcidol: 2/43 Vitamin D: 0/42	None
Rozhinskaya, 1999[35]	Not specified	No details given. All side-effects said to be mild and transient	1 patient receiving fluoride refused to continue treatment because of side-effects (nausea and arthralgia)
Van Cleemput, 1996[49]	None reported	3/22 patients in the alfacalcidol group developed asymptomatic hypercalcaemia necessitating a dose reduction	3 patients died after randomisation; their study group was not specified. 2 patients allocated to etidronate stopped their medication because of severe intercurrent illness. None of these events was attributed to the study medication
Yamada, 1989[28]	No data	Hypercalciuria: Alfacalcidol alone: 9/14 Alfacalcidol + tricholormethiazide: 0/11 Control: 0/13 Renal stones: Alfacalcidol alone: 2/14 Alfacalcidol + tricholormethiazide: 0/11 Control group: 0/13	No data

TABLE 152 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Bianda, 2000[5]	Switzerland	18 months	BMD	Patients who had undergone cardiac transplantation at the University Hospital of Zurich no more than 2 weeks previously	53	Presumably no more than 2 weeks	Cumulative prednisone intake at 12 months (g): Calcitriol group: 14.8 ± 1.2 Pamidronate group: 13.8 ± 1.7	Oral calcitriol (starting dose 0.25 μg/day, maximum 0.5 μg/day) + intranasal calcitonin 200 U/day for the first 3 months + 1 g/day calcium carbonate	Intermittent i.v. pamidronate (0.5 mg/kg every 3rd month) + 1 g/day calcium carbonate
Dykman, 1984[71]	USA	18 months	Forearm bone mass	Ambulatory patients with rheumatic diseases and glucocorticoid-induced osteopenia	49	Mean duration (years): Calcitriol group: 4.8 ± 1.6 Placebo group: 7.3 ± 1.6 ($p = 0.25$)	Mean dose at baseline (mg/day): Calcitriol group: 12.2 ± 2.6 Placebo group: 11.3 ± 4.2	Oral calcitriol (increased from 0.25 μg/day by 0.25 μg/day every 1 or 2 months as long as urinary calcium levels remained <350 mg per 24 h up to a maximum of 1.0 μg/day; mean dose at end of study 0.4 μg/day) + 500 mg/day elemental calcium (in 3 divided doses) and 400 IU/day vitamin D (the latter contained in a multivitamin tablet)	Placebo + 500 mg/day elemental calcium (in 3 divided doses) and 400 IU/day vitamin D (the latter contained in a multivitamin tablet)
Henderson, 2001[10]	Australia	6 months	BMD	Patients undergoing cardiac or lung transplantation	49	Very short (corticosteroids were commenced perioperatively, and patients were recruited within 1 week of transplant)	2 g i.v. methylprednisolone perioperatively, followed by 125 mg every 8 h for 3 doses, and then oral prednisolone at 1 mg/kg/day reducing to 0.15–0.18 mg/kg/day by day 14 and 0.10–0.15 mg/kg/day by 6 months. Larger amounts were given during periods of rejection	Calcitriol 0.5 μg/day	Etidronate 400 mg/day for 14 days followed by 1.25 g/day calcium carbonate for 76 days

continued

TABLE 152 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Kung, 1999[13]	Hong Kong	2 years	BMD	Hypogonadal young women on chronic steroid therapy for SLE, and with osteopenia	37	Mean 130 ± 22 months (range 30–240)	At least 10 mg/day prednisone	Calcitriol 0.5 μg/day + 1 g/day calcium carbonate	HRT (conjugated oestrogen 0.625 mg/day on days 1–21 + medroxyprogesterone acetate 5 mg/day on days 10–21 of a 28-day cycle) + 1 g/day calcium carbonate
Sambrook, 1993[18]	Australia	1 year treatment + 1 year follow-up	BMD	Patients with rheumatic, immunological or respiratory diseases who were starting long-term corticosteroid therapy	51 (18–79)	No more than 4 weeks	Initial mean dose of prednisone or prednisolone 25 mg/day Mean dose: year 1 13.5; year 2 7.5 mg/day	Group 1: 0.5–1.0 μg/day calcitriol + 400 IU/day intranasal salmon calcitonin Group 2: 0.5–1.0 μg/day calcitriol + placebo nasal spray (The overall mean calcitriol dose was 0.59 ± 0.17 μg/day; it was comparable in both groups) All groups received 1000 mg/day elemental calcium in the form of 5.23 g calcium lactate-gluconate + 0.8 g calcium carbonate	Placebo calcitriol + placebo nasal spray + 1000 mg elemental calcium in the form of 5.23 g calcium lactate-gluconate + 0.8 g calcium carbonate

continued

TABLE 152 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Sambrook, 2000[72]	Australia	2 years	BMD	Patients aged 20–70 years undergoing cardiac or single lung transplantation	46 (22–65)	Presumably only from transplantation on, i.e. maximum of 4 weeks	1–2 g methylprednisolone perioperatively and 125 mg every 8 h for 3 doses, followed by oral prednisolone at 1 mg/kg/day reducing to 0.15–0.18 mg/kg/day by day 14 and 0.10–0.15 mg/kg/day by 6 months	Calcitriol (starting dose 0.5 μg/day, increased in the absence of hypercalcaemia to 0.75 μg/day after 2 weeks in patients receiving <10 mg/day prednis(ol)one) for 12 months followed by placebo for 12 months, or for 24 months Both groups received 600 mg/day elemental calcium as calcium carbonate	Placebo + 600 mg/day elemental calcium as calcium carbonate
Stempfle, 1999[73]	Germany	3 years	BMD	Non-selected patients who had undergone heart transplant in 1 hospital	51 ± 10	Mean 35 ± 25 months	Prednisone 1 mg/kg/day on the first postoperative day, tapering rapidly to 7.5 mg/day within 3–4 weeks, and then being reduced to 5 mg/day at 2 years and 2.5 mg/day at 3 years	Calcitriol 0.25 μg/day + 1 g/day elemental calcium	Placebo + 1 g/day elemental calcium
Stempfle, 2002[74]	Germany	2 years	BMD	Non-selected patients who had undergone heart transplant	53 ± 11	Mean 6 ± 8 months	Prednisone 1 mg/kg/day on the first postoperative day, tapering rapidly to 7.5 mg/day within 3–4 weeks, and then being reduced to 5 mg/day within the 2nd year after transplant	Calcitriol 0.25 μg/day	Placebo

TABLE 153 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Bianda, 2000[5]	Consecutive recipients of heart transplants at the University Hospital of Zurich who had undergone transplantation no more than 2 weeks previously	None stated	Baseline characteristics were only given for the 26 study completers; in these terms, there were said to be no significant differences between the groups at baseline. However, there does seem to be a difference in terms of *T*-score (see *Table 154*)	Clinical fractures only	Treatment allocation was by alternate allocation The authors stated that they collected 'historic information on atraumatic fractures'. It is not clear whether this means that radiological confirmation of diagnosis was required Baseline data are only provided for study completers, and it is not even stated to which groups the non-completers were assigned. Hence it is not clear what the denominator should be in relation to the vertebral fracture
Dykman, 1984[71]	Ambulatory patients with rheumatic diseases and glucocorticoid-induced osteopenia as defined by a greater loss of metaphyseal than diaphyseal bone mass of the radius. Glucocorticoid dose >5 mg/day prednisone equivalents for >6 months	History of nephrolithiasis; creatinine clearance <60 cm^3/minute; evidence of liver disease or gastrointestinal malabsorption; use within the previous 6 months of medications known or suspected to alter bone mineral metabolism (anticonvulsants, cytotoxic agents, oestrogens, androgens, fluoride or vitamin D >400 IU/day)	Baseline characteristics were only given for the 23 study completers; in these terms, the groups were not significantly different at baseline, but it is not possible to assess the comparability of all groups at entry	Definition not given	
Henderson, 2001[10]	Patients undergoing cardiac or lung transplantation	Pre-existing diseases known to affect bone and mineral metabolism; significant renal impairment or liver disease; prior treatment with chronic corticosteroids, calcitonin, calcitriol, fluoride or vitamin D >50,000 U/week	Comparable	Only radiographically confirmed symptomatic fractures were recorded	Randomisation was stratified by age (≤40 or >40 years), sex and type of transplant The groups did not differ in baseline dietary calcium intake, assessed by food frequency questionnaire The calcitriol group did not receive supplemental calcium

continued

TABLE 153 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Kung, 1999[13]	Hypogonadal young women on chronic steroid therapy for SLE, who had been amenorroeic for at least 2 years and had proven ovarian failure, and who had osteopenia (lumbar *T*-score less than –1 relative to local reference values)	None stated	Comparable	Definition not given – presumably reports clinical fractures only	
Sambrook, 1993[18]	Patients with rheumatic, immunological or respiratory diseases within 4 weeks after the initiation of corticosteroid therapy which was expected to continue for at least 2 years	Previous treatment with corticosteroids, calcitonin, calcitriol, fluoride, thiazide or anticoagulant drug therapy; any diseases that might affect bone metabolism; renal impairment or calculi; GI disease; vasomotor or allergic rhinitis; acute or chronic sinusitis	Baseline characteristics were provided only for the 92 patients who had efficacy measurements after baseline. The groups were comparable in relation to these patients	A reduction of at least 20% in anterior, middle or posterior vertebral height	Randomisation was stratified by sex, age, underlying disease and initial dose of prednisone or prednisolone (considered to be equipotent) The mean cumulative corticosteroid dose was comparable in all groups in the first year, but in the second year it was significantly higher in the calcitriol/placebo group than in the calcitriol/calcitonin group ($p = 0.03$) 3 patients began oestrogen therapy during the 2nd year of the study
Sambrook, 2000[72]	Patients aged 20–70 years undergoing cardiac or single lung transplantation within the previous 4 weeks	Prior treatment with chronic corticosteroids, calcitonin, calcitriol, fluoride, vitamin D >50,000 U/week; diseases that may affect bone metabolism; significant renal impairment or liver disease	Comparable at baseline, except that lumbar BMD was significantly lower in the placebo group (see *Table 154*)	Progression to a higher grade on a semiquantitative scale [in which 0 = normal, 1 = a mild fracture with a 25% reduction in anterior, middle or posterior height (or all 3), 2 = a moderate fracture with a 25–40% reduction in any height and 3 = a severe deformity with a reduction of more than 40% in any height]	Randomisation was in a 2:1 ratio with more patients receiving calcitriol; it was stratified by age (≤40 or >40 years), sex and type of transplant 3 women commenced oestrogen therapy during the course of the study, but excluding them from the analysis made no difference to the results

continued

TABLE 153 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Stempfle, 1999[73]	Non-selected patients who had undergone heart transplant in 1 hospital	Disorders known to affect bone and mineral metabolism (e.g. thyrotoxicosis, primary hyperparathyroidism, serum creatinine above 2.5 mg/dl)	Baseline data were only provided for the 101 patients with complete datasets. For these patients, the groups were comparable at baseline	Not clear – may record only clinical fractures	To exclude bias due to primary or tertiary hypogonadism, sex hormone status was screened in all patients, and hypogonadal patients were given adequate testosterone or oestrogen before randomisation and continued on that treatment as necessary
Stempfle, 2002[74]	Non-selected patients who had undergone heart transplant	Disorders known to affect bone and mineral metabolism (e.g. thyrotoxicosis, primary hyperparathyroidism, serum creatinine above 2.5 mg/dl)	Baseline data were only provided for the 40 patients with complete datasets. For these patients, the groups were comparable at baseline except that, because the interval between transplant and baseline screening was greater in the calcitriol group, the number of rejections and the cumulative corticosteroid dose was significantly higher in this group than in the placebo group	A 20% decrease in any vertebral height compared with baseline	To exclude bias due to primary or tertiary hypogonadism, sex hormone status was screened in all patients, and hypogonadal patients were given adequate testosterone or oestrogen before randomisation and continued on that treatment as necessary

TABLE 154 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Bianda, 2000[5]	Calcitriol (n = 12)	–1.51 ± 0.32	0.97 ± 0.04	No data	Men Women	11 (92) 1 (8)	Cardiac transplant	12 (100)
	Pamidronate (n = 14)	–0.80 ± 0.30	1.01 ± 0.03	No data	Men Women	13 (93) 1 (7)	Cardiac transplant	14 (100)
Dykman, 1984[71]	Calcitriol (n = 13: study completers only)	No data	No data	No data	Men Women	3 (23) 10 (77)	Rheumatic disease	13 (100)
	Placebo (n = 10: study completers only)	No data	No data	No data	Men Women	1 (10) 9 (90)	Rheumatic disease	11 (100)
Henderson, 2001[10]	Calcitriol (n = 21)	No data	1.14 ± 0.20	No data	Men Women	15 (71) 6 (29)	Cardiac transplant Lung transplant	16[a] 4[a]
	Etidronate (n = 20)	No data	1.09 ± 0.13	No data	Men Women	15 (75) 5 (25)	Cardiac transplant Lung transplant	15[a] 6[a]
Kung, 1999[13]	Calcitriol (n = 15)	No data	Total hip: 0.73 ± 0.11	No data	Hypogonadal young women		SLE	15 (100)
	HRT (n = 13)	No data	Total hip: 0.77 ± 0.09	No data	Hypogonadal young women		SLE	13 (100)
Sambrook, 1993[18]	Calcitriol + calcitonin (n = 29: study completers only)	No data	1.13 ± 0.16	No data	Men Premenopausal women Postmenopausal women	6 (21) 10 (34) 13 (45)	Overall, for all patients randomised to treatment. Data not provided by treatment group. Rheumatic[b] Pulmonary[c] Dermatological[d] Other[e]	 86 10 3 4
	Calcitriol (n = 34: study completers only)	No data	1.18 ± 0.19	No data	Men Premenopausal women Postmenopausal women	7 (21) 15 (44) 12 (35)		
	Placebo (n = 29: study completers only)	No data	1.12 ± 0.17	No data	Men Premenopausal women Postmenopausal women	7 (24) 9 (31) 13 (45)		

continued

TABLE 154 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors (cont'd)*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Sambrook, 2000[72]	Calcitriol 12 months ($n = 22$)	No data	1.20 ± 1.17	No data	Men Women	16 (73) 6 (27)	Cardiac transplant Lung transplant	16 (73) 6 (27)
	Calcitriol 24 months ($n = 22$)	No data	1.16 ± 0.17	No data	Men Women	16 (73) 6 (27)	Cardiac transplant Lung transplant	14 (64) 6 (27)[f]
	Placebo ($n = 21$)	No data	1.08 ± 0.14	No data	Men Women	15 (71) 6 (29)	Cardiac transplant Lung transplant	14 (67) 6 (29)[f]
Stempfle, 1999[73]	Calcitriol ($n = 54$: study completers only)	No data	No data	11 (37)	Men Women	45 (83) 9 (17)	Cardiac transplant	54 (100)
	Placebo ($n = 47$: study completers only)	No data	No data		Men Women	43 (91) 4 (9)	Cardiac transplant	47 (100)
Stempfle, 2002[74]	Calcitriol ($n = 22$: study completers only)	No data	No data	3 (8)	Men Women	20 (91) 2 (9)	Cardiac transplant	22 (100)
	Placebo ($n = 18$: study completers only)	No data	No data		Men Women	18 (100) 0 (0)	Cardiac transplant	18 (100)

[a] *Sic*. Presumably these figures were transposed in the original publication.
[b] RA, polymyalgia rheumatica, temporal arteritis, SLE, dermatomyositis, polymyositis, Sjögren's syndrome, connective tissue disease, vasculitis, Wegener's granulomatosis.
[c] Interstitial lung disease, sarcoidosis.
[d] Eosinophilic fasciitis, Weber-Christian disease.
[e] Uveitis, Waldenström's macroglobulinaemia, autoimmune deafness.
[f] *Sic*. Total number of types of transplant fewer than number of patients randomised to treatment; no reason given.

TABLE 155 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Bianda, 2000[5]	1	1	2	1	1	1	7/18 (39)	31 (29 men, 2 women)	84% overall	Not stated
Dykman, 1984[71]	1	1	2	1	3	1	9/18 (50)	30 (study completers were 4 men, 19 women)	77% overall	Not stated
Henderson, 2001[10]	1	1	3	3	3	3	14/18 (78)	41 (30 men, 11 women)	Overall: 33/41 (80)	Roche Australia Pharmacia & Upjohn Pty Ltd Procter & Gamble, Australia Pty Ltd (all medications only)
Kung, 1999[13]	1	3 (BMD assessors)	1	3	3	3	14/18 (78)	28	No withdrawal mentioned	Endocrine and Osteoporosis Research Fund University of Hong Kong Roche Pharmaceuticals, Hong Kong Ltd
Sambrook, 1993[18]	1	3	3	3	0	3	13/15 (87)	103 (of the subjects who had efficacy data after baseline, there were 20 men, 34 premenopausal women, 38 postmenopausal women)	58% overall	Sandoz Pharmaceuticals, Basel, Switzerland National Health and Medical Research Council of Australia

continued

TABLE 155 *Calcitriol in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality (cont'd)*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Sambrook, 2000[72]	1	3	3	3	0	3	13/15 (87)	65 (47 men, 18 women)	83% overall	National Health and Medical Research Council of Australia Roche Australia
Stempfle, 1999[73]	1	1	2	3	0	1	8/15 (53)	132 (111 men, 21 women)	77% overall	Not stated
Stempfle, 2002[74]	1	1	2	3	0	3	10/15 (67)	53 (48 men, 5 women)	75% overall	Not stated

TABLE 156 *Calcitriol: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Bianda, 2000[5]	None in any group	None in any group	5 patients died within 12 months of transplantation; they were not attributed to study group. All the remaining patients completed the study
Dykman, 1984[71]	None reported	Hypercalciuria: Calcitriol: 8/13 Placebo: 3/10 Hypercalcaemia: Calcitriol: 4/13 Placebo: 0/10	There were 2 deaths from rheumatic disease; these were not attributed to study group
Henderson, 2001[10]	No data	No data	None reported

continued

TABLE 156 *Calcitriol: details of included studies – toxicity (cont'd)*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Kung, 1999[13]	None reported	There were 5 episodes of hypercalcaemia in the calcitriol group, but the serum calcium level returned to normal on transient withdrawal of the drug	None reported
Sambrook, 1993[18]	GI symptoms: Group 1: 7/29 Group 2: 6/34 Placebo: 1/29	Hypercalcaemia: Group 1: 8/29 Group 2: 8/34 Placebo: 1/29 Nasal symptoms: Group 1: 9/29 Group 2: 9/34 Placebo: 7/29	There were two deaths in the first year, both unrelated to study medication (1 myocardial infarction, 1 due to respiratory failure due to sarcoidosis). In addition, 5 withdrawals were due to side-effects of the study drugs (hypercalcaemia $n = 2$, headaches $n = 2$, nasal symptoms $n = 1$); these were not attributed to study group
Sambrook, 2000[72]	None reported	Mild hypercalcaemia: 12-month group: 3/22 24-month group: 5/22 Placebo group: 0/21 Hypercalciuria: 12-month group: 13/22 24-month group: 13/22 Placebo group: 2/21 Hypercalciuria usually developed between 3 and 6 months, and settled with cessation of the calcium supplement and/or reduction in the calcitriol dose	6 patients died and 5 withdrew because of underlying illnesses; these were considered unrelated to the study medication and were not attributed to study group
Stempfle, 1999[73]	None reported	Asymptomatic hypercalcaemia (serum calcium >2.6 mmol/l) necessitating a reduction in calcium dose to 500 mg/day: Calcitriol group: 4/54 Placebo group: 3/47	10 patients died in the first year after enrolment; in 5 the study medication was transiently or totally stopped because of severe intercurrent illness or non-compliance. The deaths and other withdrawals were not attributed to study group
Stempfle, 2002[74]	None reported	Asymptomatic hypercalcaemia (serum calcium >2.6 mmol/l) necessitating a reduction in calcium dose to 500 mg/day: Calcitriol group: 10/22 Placebo group: 3/18	3 patients died during the first year after enrolment; in 5 patients the study medication was transiently or totally stopped because of severe intercurrent illness, relocation or non-compliance. The deaths and other withdrawals were not attributed to study group

TABLE 157 *Calcidiol in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Garcia-Delgado, 1997[47]	Spain	18 months	Vertebral BMD	Ambulatory patients with normal mobilisation and diet who had undergone cardiac transplantation in Madrid University Hospital between 1991 and 1994	53	Randomisation took place immediately after transplantation and the start of corticosteroid therapy	Starting dose of 1 mg/kg/day prednisone reduced to 0.2 mg/kg/day after 6 weeks	Calcidiol 32,000 IU/week	Intranasal calcitonin 100 IU/day Etidronate 400 mg/day for 14 days every 2.5 months
Tałałaj, 1996[76]	Poland	1 year	BMD	Renal transplant patients aged 15–63 years	36	? commenced at same time as study treatment	Initial prednisone dose 0.5 mg/kg/day, subsequently decreased by 2.5 mg/kg/day every 2 weeks to 10 mg/day	Calcidiol (initial dose 40 μg/day, subsequently adjusted to serum calcium concentration) + calcium carbonate 3 g/day	No treatment

TABLE 158 *Calcidiol in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Garcia-Delgado, 1997[47]	Ambulatory patients with normal mobilisation and diet who had undergone cardiac transplantation in Madrid University Hospital between 1991 and 1994	Taking other drugs known to interfere with calcium metabolism; if male, symptoms of hypogonadism	Comparable	Method of Eastell *et al.*[53]	
Tałałaj, 1996[76]	Renal transplant patients aged 15–63 years	Not stated	Comparable	Reduction in the vertebral body height exceeding 20%	

TABLE 159 *Calcidiol in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Garcia-Delgado, 1997[47]	Calcidiol (n = 13)	Not stated *Z*-score: –0.99 ± 0.39	0.905 ± 0.043	Not stated	Men Women	11 (85) 2 (15)	Cardiac transplant	13 (100)
	Etidronate (n = 14)	Not stated *Z*-score: –1.47 ± 0.27	0.871 ± 0.091	Not stated	Men Women	14 (100) 0 (0)	Cardiac transplant	14 (100)
	Calcitonin (n = 13)	Not stated *Z*-score: –1.65 ± 0.41	0.854 ± 0.069	Not stated	Men Women	13 (100) 0 (0)	Cardiac transplant	13 (100)
Tałałaj, 1996[76]	Calcidiol (n = 41)	No data	No data	No data	Men Women	31 (40) 46 (60)	Renal transplant	
	Control (n = 36)	No data	No data	No data				

TABLE 160 *Calcidiol in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Garcia-Delgado, 1997[47]	1	1	3	3	0	3	11/15 (73)	40 (38 men, 2 women)	No data	Not stated
Tałałaj, 1996[76]	1	1	1	3	0	1	7/15 (47)	77 (31 men, 46 women)	Not clear	Warsaw Medical School

TABLE 161 *Calcidiol: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Garcia-Delgado, 1997[47]	None reported	None reported	None reported
Tałałaj, 1996[76]	None reported	None reported	None reported

TABLE 162 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Cremer, 1999[77]	Germany	48 weeks	Trabecular and cortical BMD	Adult heart transplant patients with an uneventful early postoperative course	47	Apparently none	Starting dose of 0.5 mg/kg/day tapered down to 0.2 mg/kg/day within the first month	Subcutaneous synthetic eel calcitonin (40 MRC standard units) Monday–Friday for 2 weeks followed by 2 injection-free weeks + 2 × 500 mg oral calcium/day and 0.25 mg oral vitamin D every other day	Placebo + 2 × 500 mg oral calcium/day and 0.25 mg oral vitamin D every other day
Garcia-Delgado, 1997[47]	Spain	18 months	Vertebral BMD	Ambulatory patients with normal mobilisation and diet who had undergone cardiac transplantation in Madrid University Hospital between 1991 and 1994	53	Randomisation took place immediately after transplantation and the start of corticosteroid therapy	Starting dose of 1 mg/kg/day prednisone reduced to 0.2 mg/kg/day after 6 weeks	Intranasal calcitonin 100 IU/day Etidronate 400 mg/day for 14 days every 2.5 months	Calcidiol (25 hydroxycholecalciferol) 32,000 IU/week

continued

TABLE 162 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Grotz, 1998[9]	Germany	1 year	Change in BMD at 12 months	Patients who had received renal allografts more than 6 months previously and had a BMD 1.5 SD below normal	45	Presumably at least 6 months; mean time since transplantation (months): Clodronate group: 44 ± 30 Calcitonin group: 54 ± 47 Control group: 72 ± 59 (NS)	Baseline prednisone dose (mg/day): Clodronate group: 8.8 ± 2.8 Calcitonin group: 9.6 ± 5.1 Control group: 8.4 ± 4.9 (NS)	Intranasal calcitonin 100 IU twice a day vs clodronate 800 mg/day, in both cases taken for 14 days followed by 75 days without treatment Both groups received 500 mg/day calcium gluconate throughout the study period	500 mg/day calcium gluconate
Grøvle, 1996[81,84]	Norway	1 year	BMD	RA patients being treated with a stable dose of prednisolone	61	Mean duration 5.3 years	Mean dose 6.8 mg/day prednisolone	Intranasal calcitonin 200 IU/day for 1 month followed by 100 IU/day for 11 months	Placebo
Hay, 2001[78]	USA	6 months	Lumbar spine BMD	Patients with PBC or PSC undergoing liver transplantation	Not stated	Therapy began within 7 days of transplant	Not stated	Subcutaneous calcitonin 100 MRC units/day starting on the 7th postoperative day + 1.5 g/day oral calcium	1.5 g/day oral calcium
Healey, 1996[79]	USA	2 years	Change in lumbar spine BMD	Patients with newly diagnosed corticosteroid-treated polymyalgia rheumatica, temporal arteritis, and other vasculitides	71.6 ± 9.0 (45–87)	Randomisation took place within 2 weeks of diagnosis and the start of corticosteroid therapy	Cumulative dose (mg prednisone equivalent): Year 1: 3428 ± 1829 (range 555–7329) Year 2: 1618 ± 1334 (range 0–4966)	Subcutaneous salmon calcitonin 100 IU three times per week + 1500 mg/day calcium carbonate in divided doses, and 400 IU/day vitamin D_3	1500 mg/day calcium carbonate in divided doses, and 400 IU/day vitamin D_3

continued

TABLE 162 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Kotaniemi, 1996[12]	Finland	1 year	Lumbar and femoral BMD	Women with active RA treated with glucocorticoids	(31–64)	At least 3 months. Median duration 2.5 years (range 0–38 years)	≥7.5 mg/day oral prednisolone. Median dose at baseline 8.7 mg/day (range 7.5–13.7 mg/day)	Intranasal salmon calcitonin 100 IU/day + calcium 500 mg/day	Calcium 500 mg/day
Luengo, 1994[82]	Spain	2 years	BMD	Adult asthmatic patients receiving long-term oral glucocorticoid therapy	58	At least 1 year (mean 10.7 years)	Mean prednisone dose (mg/day): At baseline: 10.25 At 1 year: 7.7 At 2 years: 7.8	Intranasal salmon calcitonin 200 IU/day + elemental calcium 1 g/day	Elemental calcium 1 g/day
Ringe, 1987[80]	Germany	6 months	Bone mineral content at distal radius	Patients with obstructive lung disease on chronic corticosteroid therapy with incipient to severe signs of osteoporosis	50 (25–67)	Mean 71 months (range 2–204)	Mean daily dose: In the 8 weeks prior to the study: 19.9 mg/day prednisone equivalent (range 8–60) During the study: 16.5 mg/day prednisone equivalent (range 12–32)	Subcutaneous salmon calcitonin 100 IU on alternate days	No treatment
Välimäki, 1999[83]	Finland	1 year	BMD	Patients with end-stage cardiac disease undergoing cardiac transplantation	48 (26–68)	Study medication began alongside the start of corticosteroid therapy	20 mg/day prednisone	Intranasal calcitonin (400 IU/day for 1 month followed by 200 IU/day for 11 months) + 1 g oral calcium (5.23 g calcium lactate gluconate + 0.8 g calcium carbonate) twice daily	1 g oral calcium (5.23 g calcium lactate gluconate + 0.8 g calcium carbonate) twice daily No treatment

PBC, primary biliary cirrhosis; PSC, primary sclerosing cholargitis.

TABLE 163 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Cremer, 1999[77]	Adult heart transplant patients with an uneventful early postoperative course (i.e. extubation within 3 days after transplantation and no catecholamine requirement after the 4th postoperative day)	Presence of vertebral fractures prior to transplantation	The groups were comparable in age, sex and diagnosis at baseline; no other information was given	Clinical only	
Garcia-Delgado, 1997[47]	Ambulatory patients with normal mobilisation and diet who had undergone cardiac transplantation in Madrid University Hospital between 1991 and 1994	Taking other drugs known to interfere with calcium metabolism; if male, symptoms of hypogonadism	Comparable	Method of Eastell *et al*.[53]	
Grotz, 1998[9]	Patients who had received renal allografts more than 6 months previously at the University of Freiburg and had a BMD 1.5 SD below normal	None stated	The groups were comparable in most respects. However, there were 6 menopausal women in the calcitonin group, 2 in the clodronate group and none in the control group ($p = 0.043$)	Reduction of central or anterior vertebral height in excess of 15% of the maximum distance between the endpoints of the posterior edges	During the observation period, participants received no fluorides or vitamin D 1 of the postmenopausal women (in the clodronate group) had received HRT for several years; this was continued through the study period All but 2 patients received corticosteroids for immunosuppression Allocation to treatment was by block randomisation using sealed envelopes The study appears to have been open-label, although this is not stated
Grøvle, 1996[81,84]	RA patients being treated with a stable dose of prednisolone	Previous treatment with fluorides, bisphosphonates or gonadal steroids	Comparable	Used anterior, median and posterior vertebral heights; no further information given	Study available as abstract only

continued

TABLE 163 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Hay, 2001[78]	Consecutive consenting adult patients with PBC or PSC but with normal creatinine clearance undergoing liver transplantation at the Mayo Clinic	Diseases other than PBC or PSC which affect bone metabolism; medications which affect bone (corticosteroids, hormones, anticonvulsants) in the previous 12 months	Comparable for most factors. However, 18% of the control group and only 7% of the treatment group had baseline vertebral fractures, and the difference between the groups at 1 year in terms of vertebral fracture was said to be due to the higher number of pretransplant fractures in the control group	Not given	Randomisation was by 'dynamic allocation', assuring a balance for diagnosis (PBC vs PSC), sex, BMD (above or below 0.98 g/cm^2) and menopausal status Before transplantation, and at routine intervals, each patient's dietary calcium was assessed and general dietary instructions given Vitamin D was given only if specifically required If hypercalcaemia occurred with supplementation, vitamin D and calcium were discontinued and only restarted if hypocalcaemia or secondary hyperparathyroidism occurred Calcitonin therapy was given for 6 months, but fracture results were presented at 1 year Analysis was by intention-to-treat
Healey, 1996[79]	Patients with newly diagnosed corticosteroid-treated polymyalgia rheumatica, TA and other vasculitides	Active malignancy; Cushing's disease; hyperparathyroidism; urolithiasis; osteomalacia; previous corticosteroid treatment for another diagnosis within 3 months of entry; treatment with oestrogens, progesterones, testosterone, sodium fluoride, bisphosphonates, calcitonin or antimetabolites/ immunosuppressive drugs or vitamin D metabolites	Comparable	Conformational changes	Of the 100 patients who met the eligibility criteria, 52 refused to participate. The most common reason for refusal (25/52) was unwillingness to undergo injections Randomisation was stratified according to diagnosis (TA/vasculitis versus PMR)

continued

TABLE 163 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Kotaniemi, 1996[12]	Women with active rheumatoid arthritis according to the 1987 American College of Rheumatology (ACR) criteria for RA and treated with glucocorticoids	Concomitant use of fluoride, bisphosphonates, thiazides or oestrogens; diseases affecting bone metabolism (hyperthyroidism, hyperparathyroidism, osteomalacia, Cushing's syndrome, malignancy, hepatic failure, insulin-dependent diabetes, malabsorption); history of alcohol or drug abuse; pregnancy or lactation	Comparable	None given; probably clinical fractures only	5 patients (3 in the calcitonin group and 2 in the control group) had had hip replacements At the end of the study, 9 patients (4 from the calcitonin group and 5 from the control group) were found to be taking oestrogen and were therefore excluded. In addition, 1 patient did not fulfil the ACR criteria for RA, leaving 49 'valid compliant completers' (78%), 26 in the calcitonin group and 23 in the control group
Luengo, 1994[82]	Adult asthmatic patients who had received oral glucocorticoid therapy for at least 1 year	Drugs (hormones, diuretics, vitamin D, anticonvulsants) or diseases known to affect bone metabolism	Comparable in terms of age, sex, steroid treatment and prior fracture	A reduction of 25% or more in anterior or posterior vertebral height	All patients were non-smokers who led a sedentary life and did not drink more than 20 g/day ethanol All patients were given inhaled steroids (budesonide or beclomethasone) Randomisation was stratified by age and sex No information was given about the number of women in each group who were pre- and post-menopausal
Ringe, 1987[80]	Patients with obstructive lung disease on chronic corticosteroid therapy who were expected to remain steroid dependent for the next 6 months and who exhibited incipient to severe signs of osteoporosis	None stated	Data only provided for study completers. On those terms, the groups were largely comparable. The control group was taller than the calcitonin group, and had a longer mean duration of corticosteroid therapy, although a lower pre-study dose	Not clear	
Välimäki, 1999[83]	Consecutive patients with end-stage cardiac disease undergoing cardiac transplantation	Disorders and medications known to affect bone and mineral metabolism	Comparable	At least 20% decrease in anterior, central or posterior vertebral height	

TABLE 164 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Cremer, 1999[77]	Calcitonin (n = 30)	No data	No data	0	Men Women	25 (75) 5 (25)	Cardiac transplant	30 (100)
	Placebo (n = 31)	No data	No data	0	Men Women	26 (84) 5 (16)	Cardiac transplant	31 (100)
Garcia-Delgado, 1997[47]	Calcitonin (n = 13)	Not stated *Z*-score: –1.65 ± 0.41	0.854 ± 0.069	No data	Men Women	13 (100) 0 (0)	Cardiac transplant	13 (100)
	Calcidiol (n = 13)	Not stated *Z*-score: –0.99 ± 0.39	0.905 ± 0.043	No data	Men Women	11 (85) 2 (15)	Cardiac transplant	13 (100)
	Etidronate (n = 14)	Not stated *Z*-score: –1.47 ± 0.27	0.871 ± 0.091	No data	Men Women	14 (100) 0 (0)	Cardiac transplant	14 (100)
Grotz, 1998[9]	Calcitonin (n = 16)	Not stated	0.874 ± 0.082	4 (9)	Men Premenopausal women Postmenopausal women	7 (44) 3 (19) 6 (38)	Renal transplantation	46 (100)
	Clodronate (n = 15)	Not stated	0.871 ± 0.083		Men Premenopausal women Postmenopausal women	10 (67) 3 (20) 2 (13)		
	Control (n = 15)	Not stated	0.929 ± 0.063		Men Premenopausal women Postmenopausal women	12 (80) 3 (20) 0 (0)		
Grøvle, 1996[81,84]	Calcitonin	No data	No data	No data	Men Women	11 (38) 18 (62)	Rheumatic (RA)	29 (100)
	Placebo	No data	No data	No data	Men Women	9 (30) 21 (70)	Rheumatic (RA)	30 (100)

continued

TABLE 164 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors (cont'd)*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Hay, 2001[78]	Calcitonin ($n = 29$)	No data	No data	2/29 (7)	Men Premenopausal women Postmenopausal women	11 (38) 5 (18) 13 (44)	PBC[a] PSC[b]	(38) (62)
	Control ($n = 34$)	No data	No data	6/34 (18)	Men Premenopausal women Postmenopausal women	13 (38) 6 (20) 15 (43)	PBC[a] PSC[b]	(44) (56)
Healey, 1996[79]	Calcitonin ($n = 25$)	No data	1.008	5 (20)	Men Women	9 (36) 16 (64)	Rheumatic[c]	25 (100)
	Placebo ($n = 23$)	No data	0.987	3 (13)	Men Women	3 (13) 20 (87)	Rheumatic[c]	23 (100)
Kotaniemi, 1996[12]	Calcitonin ($n = 32$)	1.036 ± 0.177	*Z*-score: –0.290 ± 1.408	No data	Men Premenopausal women Postmenopausal women	0 (0) 17 (53) 15 (47)	Rheumatic (RA)	32 (100)
	Control ($n = 31$)	1.023 ± 0.140	*Z*-score: –0.159 ± 1.116	No data	Men Premenopausal women Postmenopausal women	0 (0) 12 (39) 19 (61)	Rheumatic (RA)	31 (100)
Luengo, 1994[82]	Calcitonin ($n = 22$)	No data	No data	4 (18)	Men Women	3 (14) 19 (86)	Pulmonary (asthma)	22 (100)
	Control ($n = 22$)	No data	No data	4 (18)	Men Women	3 (14) 19 (86)	Pulmonary (asthma)	22 (100)
Ringe, 1987[80]	Calcitonin ($n = 18$: study completers only)	No data	No data		Men Women	3 (17) 15 (83)	Pulmonary[d]	18 (100)
	Control ($n = 18$: study completers only)	No data	No data		Men Women	4 (22) 14 (78)	Pulmonary[d]	18 (100)

continued

TABLE 164 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors (cont'd)*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Välimäki, 1999[83]	Calcium + calcitonin (n = 10)	Not stated	0.989 ± 0.179	3/25 assessable patients overall (12%)	Men Women	10 (100) 0 (0)	Heart transplant	10 (100)
	Calcium (n = 10)	Not stated	1.135 ± 0.141		Men Women	10 (100) 0 (0)	Heart transplant	10 (100)
	Control (n = 10)	Not stated	1.025 ± 0.200		Men Women	9 (90) 1 (10)	Heart transplant	10 (100)

[a] Primary biliary cirrhosis.
[b] Primary sclerosing cholargitis.
[c] Polymyalgia rheumatica, temporal arteritis and other vasculitides.
[d] Bronchial asthma, fibrosing alveolitis, Boeck's disease, Wegener's disease.

TABLE 165 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Cremer, 1999[77]	3	1	3	3	0	1	11/15 (73)	61 (51 men, 10 women)	Apparently 100%	Not stated
Garcia-Delgado, 1997[47]	1	1	3	3	0	3	11/15 (73)	40 (38 men, 2 women)	Apparently 100%	Not stated
Grotz, 1998[9]	2	1	3	3	1	3	13/18 (72)	46 (29 men, 9 premenopausal women, 8 postmenopausal women)	Calcitonin: 16/16 (100) Clodronate: 15/15 (100) Control: 14/15 (93)	Not stated

continued

TABLE 165 *Calcitonin in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality (cont'd)*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Grøvle, 1996[81,84]	1	3	2	3	0	3	12/15 (80)	59 (20 men, 39 women)	92% overall	Not stated
Hay, 2001[78]	1	1	3	1	0	1	7/15 (47)	63 (24 men, 11 premenopausal women, 28 postmenopausal women)	Calcitonin group: 24/29 (83%) Control group: 33/34 (97%)	Sandoz
Healey, 1996[79]	1	3	3	3	0	1	11/15 (73)	48 (12 men, 36 women)	Calcitonin group: 19/25 (76) Placebo group: 21/23 (91)	National Institutes of Health Sandoz Pharmaceuticals (drugs only)
Kotaniemi, 1996[12]	1	1	3	3	1	1	10/18 (56)	63 (29 premenopausal women, 34 postmenopausal women)	Calcitonin group: 31/32 (97) Control group: 28/31 (90)	Sandoz Oy, Helsinki, Finland
Luengo, 1994[82]	1	3	3	2	1	2	12/18 (67)	44 (6 men, 38 women)	Calcitonin group: 17/22 (77) Control group: 17/22 (77)	Not stated
Ringe, 1987[80]	1	1	3	2	1	1	9/18 (50)	38 (study completers were 7 men, 29 women)	Calcitonin group: 18/19 (95) Control group: 18/19 (95)	Not stated
Välimäki, 1999[83]	1	1	3	3	0	3	11/15 (73)	30 (29 men, 1 woman)	24/30 (80) overall	Sandoz Ltd, Basel

TABLE 166 *Calcitonin: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Cremer, 1999[77]	No data	No data	None reported
Garcia-Delgado, 1997[47]	No data	No data	None reported
Grotz, 1998[9]	Calcitonin group: 0/16 Clodronate group: 2/15 Control group: 1/15	Calcitonin group: 3/16 (heat sensation, skin rash, arthralgia) Clodronate group: 0/15 Control group: 0/15	1 patient in the control group died of coronary heart disease
Grøvle, 1996[81,84]	No data	There were no serious adverse events	None reported
Hay, 2001[78]	None reported	In the calcitonin group, 1 patient suffered transient diarrhoea attributed to therapy. 30% reported mild brief discomfort at the injection site and/or dislike of the subcutaneous injection	None attributed to the study drug
Healey, 1996[79]	None reported	Urolithiasis: Calcitonin: 1/25 Placebo: 1/23 Neither patient had evidence of hypercalciuria or hypercalcaemia; both remained on the study drug, under surveillance, for the remainder of the study	2 patients died and 5 withdrew because of adverse events; they were not attributed to treatment groups. No withdrawals were attributable to the study drug
Kotaniemi, 1996[12]	Dyspepsia: Calcitonin group: 0/32 Control group: 2/31	Facial flush: Calcitonin group: 3/32 Control group: 0/31 The following adverse effects were each reported by one patient: Calcitonin group: intranasal dryness, periorbital oedema, headache, nausea, abnormal liver function tests Control group: gingival pain, loose stools	Calcitonin group: 1/32 (cancer) Control group: 3/31 (side-effects of therapy (increased joint pain and morning stiffness) $n = 1$, hip arthroplasty $n = 1$, vertebral fracture $n = 1$)

continued

TABLE 166 *Calcitonin: details of included studies – toxicity (cont'd)*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Luengo, 1994[82]	Nausea: Calcitonin group: 4/22 Control group: none reported	Rhinorrhea: Calcitonin group: 3/22 Control group: none reported Facial redness: Calcitonin group: 2/22 Control group: none reported	Calcitonin group: 1/22 (generalised pruritus)[a] Control group: 0/22
Ringe, 1987[80]	Nausea: Calcitonin group: 3/18 Control group: none reported	Hot flushes: Calcitonin group: 3/18 Control group: none reported	Calcitonin group: 1/ (severe nausea) Control group: 1/ (died in asthmatic crisis)
Välimäki, 1999[83]	No data	No data	4 patients died and 1 withdrew because of vertebral fractures which required more effective treatment. These withdrawals were not attributed to treatment groups

[a] Since this did not completely disappear after discontinuing treatment, it is not clear whether it was actually caused by the calcitonin.

TABLE 167 *Oestrogen in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Kung, 1999[13]	Hong Kong	2 years	BMD	Hypogonadal young women on chronic steroid therapy for SLE and with osteopenia	37	Mean 130 ± 22 months (range 30–240)	At least 10 mg/day prednisone	HRT (conjugated oestrogen 0.625 mg/day on days 1–21 + medroxyprogesterone acetate 5 mg/day on days 10–21 of a 28-day cycle) + 1 g/day calcium carbonate	Calcitriol 0.5 μg/day + 1 g/day calcium carbonate

TABLE 168 *Oestrogen in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Kung, 1999[13]	Hypogonadal young women on chronic steroid therapy for SLE, who had been amenorroeic for at least 2 years and had proven ovarian failure, and who had osteopenia (lumbar *T*-score less than –1 relative to local reference values)	None stated	Comparable	Definition not given – presumably reports clinical fractures only	

TABLE 169 *Oestrogen in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)	Underlying illness: no. (%)	
Kung, 1999[13]	HRT (n = 13)	No data	Total hip: 0.77 ± 0.09	No data	Hypogonadal young women	SLE	13 (100)
	Calcitriol (n = 15)	No data	Total hip: 0.73 ± 0.11	No data	Hypogonadal young women	SLE	15 (100)

TABLE 170 *Oestrogen in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Kung, 1999[13]	1	3 (BMD assessors)	1	3	3	3	14/18 (78)	28	No withdrawal mentioned	Endocrine and Osteoporosis Research Fund, University of Hong Kong, Roche Pharma, Hong Kong Ltd

TABLE 171 *Oestrogen: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Kung, 1999[13]	None reported	There were 5 episodes of hypercalcaemia in the calcitriol group, but the serum calcium level returned to normal on transient withdrawal of the drug	None reported

TABLE 172 *Fluoride in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Guaydier-Souquières, 1996[107]	France	2 years	Lumbar BMD	Men and premenopausal women on long-term corticosteroid therapy for respiratory diseases who had not previously had a vertebral fracture	46.5 (21–65)	Mean duration in years: Fluoride group: 4.7 ± 3.3 Placebo group: 7.4 ± 7.5	Overall mean daily dose prior to study inclusion 18 mg prednisone equivalent (range 7.5–60) Fluoride group: 15.9 ± 9.4 Placebo group: 20.4 ± 16.2 Mean daily dose (prednisone equivalent) during study: Fluoride group: 15.9 ± 9.3 Placebo group: 19.1 ± 11.7	200 mg/day sodium monofluorophosphate (= 26.4 mg fluoride) + 2500 mg/day calcium carbonate (= 1000 mg elemental calcium)	Placebo + 2500 mg/day calcium carbonate (= 1000 mg elemental calcium)
Lems, 1997a[108]	The Netherlands	2 years	BMD	Patients with established osteoporosis who were using at least 7.5 mg/day prednisone at study entry and expected to remain on that medication for at least 6 months	58	Not stated	Mean prednisone dose at study entry (mg/day): Fluoride group: 10 ± 10 Control group: 9 ± 9	50 mg/day enteric-coated sodium fluoride + cyclical etidronate (400 mg/day for 2 weeks of a 13-week cycle) + 500–1000 mg/day elemental calcium	Placebo + cyclical etidronate (400 mg/day for 2 weeks of a 13-week cycle) + 500–1000 mg/day elemental calcium

continued

TABLE 172 *Fluoride in the treatment of steroid-induced osteoporosis: details of included studies – general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Lems, 1997b[109]	The Netherlands	2 years	BMD	Patients receiving 7.5 mg/day or more of prednisone, who were expected to continue this medication for at least 6 months, and who did not have established osteoporosis (i.e. without previous peripheral fractures and/or radiographic vertebral deformities)	51	14 patients (7 in each group) started corticosteroid therapy at study entry. Pretrial duration of treatment in the remaining patients was not stated	Mean baseline dose (mg/day): Fluoride group: 14.6 ± 10.5 Placebo group: 21.2 ± 17.3	Enteric-coated sodium fluoride (50 mg/day as a divided dose) + 500–1000 mg/day elemental calcium	Placebo + 500–1000 mg/day elemental calcium
Rozhinskaya, 1999[35]	Russia	1 year	BMD	Women with established steroid-induced osteoporosis (a *T*-score of –2.5 or less at spine or femur neck + 2 or more vertebral fractures)	56.3 ± 4.5	14.6 ± 3.8 years	Mean prednisolone dose 13.6 ± 2.8 mg	Group 1A: 15 mg fluoride + 450 mg calcium Group 1B: 15 mg fluoride + 450 mg calcium + 0.5 μg alfacalcidol	0.75 μg alfacalcidol
Von Tirpitz, 2000[20]	Germany and Switzerland	1 year	BMD	Patients with active Crohn's disease without pre-existing vertebral fractures who had received systemic high-dose corticosteroid therapy during the previous year	41	Not stated. Duration of disease (years): Fluoride group: 15.8+1.5 Control group: 8.8 ± 1.2 ($p < 0.001$)	Mean prednisolone dose at study entry (mg/day): Fluoride group: 9.9 ± 3.4 Control group: 17.9 ± 4.7	75 mg/day retarded-release sodium fluoride (= 33.9 mg/day fluoride) + 2500 mg/day calcium carbonate (equivalent to 1000 mg/day Ca^{2+}) and 0.025 mg/day cholecalciferol (equivalent to 1000 IU/day vitamin D_3)	2500 mg/day calcium carbonate (equivalent to 1000 mg/day Ca^{2+}) and 0.025 mg/day cholecalciferol (equivalent to 1000 IU/day vitamin D_3)

TABLE 173 *Fluoride in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Guaydier-Souquières, 1996[107]	Men aged 18–65 years and premenopausal women aged over 18 years treated with corticosteroid therapy for at least 1 year at doses greater than 7 mg/day prednisone equivalent for asthma or other respiratory diseases	Radiographic vertebral fracture; neoplastic, metabolic, endocrine or hereditary bone disease; obesity or any disease likely to interfere with the interpretation of the densitometric examination; having previously received fluoride or another treatment for osteoporosis; having a contraindication to the prescription of fluoride (in particular, osteomalacia or renal failure) or calcium; urinary calcium excretion exceeding 300 mg/day	Full details were only provided for the 28 patients who both complied with the protocol and for whom more than 1 BMD measurement was available. The 2 groups were comparable in terms of these patients. There was no statistically significant difference between the 2 groups, by intention-to-treat, in terms of baseline lumbar BMD and *T*-score or cumulative corticosteroid dose used during the study period	A 25% reduction in anterior or middle height relative to posterior height, or a 25% reduction in vertebral height relative to adjacent vertebrae	Vitamin D and other osteotropic drugs (except corticosteroids) were not permitted during the study
Lems, 1997a[108]	Patients with established osteoporosis (defined by a radiographically identified vertebral deformity or a previous peripheral fracture) who were using at least 7.5 mg/day prednisone at study entry and expected to remain on that medication for at least 6 months	Not stated	The groups were comparable, except in relation to lumbar spine BMD, which was significantly lower in the fluoride than in the control group, approximately doubling the risk of fracture in the intervention group	A decrease of 15% in anterior, middle or posterior vertebral height relative to baseline. A clinical vertebral deformity was defined as a vertebral deformity which causes clinical manifestations leading to the prescription of therapy (bed rest, analgesia or both)	All subjects received a supplement of at least 500 mg elemental calcium; those with a low dietary calcium intake (<500 mg/day) received 1000 mg/day Subjects whose serum 25-hydroxyvitamin D concentration was below 10 μg/l in winter and 15 μg/l in summer received vitamin D (0.2 mg dihydrotachysterol, half a tablet on alternate days) Randomisation was done in blocks per centre

continued

TABLE 173 *Fluoride in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Lems, 1997b[109]	Patients receiving 7.5 mg/day or more of prednisone, who were expected to continue this medication for at least 6 months, and who did not have established osteoporosis (i.e. without previous peripheral fractures and/or radiographic vertebral deformities)	Not stated	The groups were comparable at baseline, except for serum creatinine and γ-glutamyl transferase levels (the former being significantly higher, and the latter significantly lower, in the fluoride group). Although the baseline daily corticosteroid dose was higher in the placebo group, the difference was not statistically significant	A decrease of 15% in anterior, middle or posterior vertebral height compared with baseline. Clinical vertebral fractures were those in which a vertebral deformity caused clinical manifestations leading to prescription of therapy (i.e. bedrest and/or analgesics)	All subjects received a supplement of at least 500 mg elemental calcium; those with a low dietary calcium intake (<500 mg/day) received 1000 mg/day Subjects whose serum 25-hydroxyvitamin D concentration was below 10 μg/l in winter and 15 μg/l in summer received vitamin D (0.2 mg dihydrotachysterol, half a tablet on alternate days) Randomisation was done in blocks per centre
Rozhinskaya, 1999[35]	Women with established steroid-induced osteoporosis (a *T*-score of –2.5 or less at spine or femur neck + 2 or more vertebral fractures)	Not specified	No information given	Not stated	This study was available in abstract form only This was an open-label study
Von Tirpitz, 2000[20]	Diagnosis of Crohn's disease with a duration of at least 2 years and involvement of the terminal or neo-terminal ileum established by endoscopic and histomorphological criteria; treatment with high-dose corticosteroids due to disease activity (≥ 50 mg prednisolone for ≥ 2 weeks) in the previous year	Radiographic vertebral fractures; treatment with calcium, vitamin D, sodium fluoride or any other drug directly affecting bone metabolism except corticosteroids; pregnancy; primary hyperparathyroidism, hyperthyroidism or primary Cushing's disease	The groups did not differ significantly at baseline except in terms of duration of disease, which was significantly longer in the fluoride group	Not stated	This appears to have been an open-label study

TABLE 174 *Fluoride in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Guaydier-Souquières, 1996[107]	Fluoride (n = 15: eligible population, not total study population)	–1.7 ± 1.2	0.910 ± 0.155	0	Men Women	12 (80) 3 (20)	Pulmonary	15 (100)
	Placebo (n = 13: eligible population, not total study population)	–1.5 ± 1.1	0.925 ± 0.129	0	Men Women	9 (69) 4 (31)	Pulmonary	13 (100)
Lems, 1997a[108]	Fluoride + etidronate (n = 23)	No data	0.804 ± 0.142	No data	Men Premenopausal women Postmenopausal women	5 (22) 3 (13) 15 (65)	Rheumatic[a] Pulmonary (COPD) Transplant NB: authors' figures do not total 23	19 (83) 2 (9) 0
	Etidronate alone (n = 24)	No data	0.944 ± 0.167	No data	Men Premenopausal women Postmenopausal women	9 (38) 5 (21) 10 (42)	Rheumatic[a] Pulmonary (COPD) Transplant	22 (92) 1 (4) 1 (4)
Lems, 1997b[109]	Fluoride (n = 20)	–0.6 ± 1.4	1.014 ± 0.131	No data	Men Premenopausal women Postmenopausal women	7 (35) 9 (45) 4 (20)	Rheumatic[b] Pulmonary (COPD) Transplant	18 (90) 1 (5) 1 (5)
	Placebo (n = 24)	–0.3 ± 1.5	1.043 ± 0.183	No data	Men Premenopausal women Postmenopausal women	10 (42) 6 (25) 8 (33)	Rheumatic[b] Pulmonary (COPD) Transplant	23 (96) 1 (4) 0 (0)
Rozhinskaya, 1999[35]	Fluoride (n = 6)	<–2.5	No data	6 (100)	Women	6 (100)	Connective tissue disease Pulmonary (asthma)	12 (55) 10 (45)
	Fluoride + alfacalcidol (n = 6)	<–2.5	No data	6 (100)	Women	6 (100)		
	Alfacalcidol (n = 10)	<–2.5	No data	100 (100)	Women	10 (100)		

continued

TABLE 174 *Fluoride in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors (cont'd)*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)		Underlying illness: no. (%)	
Von Tirpitz, 2000[20]	Fluoride (n = 18)	−1.4 ± 0.3	0.88 ± 0.03	No data	Men Women	10 (56) 8 (44)	Crohn's disease	15 (100)
	Control (n = 15)	−1.0 ± 0.3	0.90 ± 0.03	No data	Men Women	4 (27) 11 (73)	Crohn's disease	11 (100)

[a] RA, SLE, other connective tissue disorder.
[b] RA, polymyalgia rheumatica, SLE, other connective tissue disorder.
[c] SLE, collagen diseases.
[d] Obstructive lung diseases, pulmonary fibrosis, sarcoidosis.
[e] Skin disease (1), idiopathic thrombocytopenia purpura (2), allergic rhinitis (1), myasthenia gravis (1).

TABLE 175 *Fluoride in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Guaydier-Souquières, 1996[107]	1	1	3	3	0	3	11/15 (73)	35	Fluoride: 11/15 (73) Control: 12/13 (92)	Not stated
Lems, 1997a[108]	1	1	3	1	3	3	12/18 (67)	47	Fluoride: 21/24 (88) Placebo: 19/23 (83)	Dutch League against Rheumatism Christiansen (sodium fluoride and placebo tablets only)
Lems, 1997b[109]	1	1	3	3	3	3	14/18 (78)	44	Fluoride: 17/20 (85) Placebo: 23/24 (96)	Dutch League against Rheumatism Christiansen (fluoride and placebo only)
Rozhinskaya, 1999[35]	1	1	3	1	0	1	7/15 (47)	22	Combined fluoride groups: 11/12 (92) Alfacalcidol: 10/10 (100)	Not stated
Von Tirpitz, 2000[20]	1	1	3	2	0	1	8/15 (53)	33	Fluoride: 15/18 (83) Control: 11/15 (73)	Not stated

TABLE 176 *Fluoride: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Guaydier-Souquières, 1996[107]	Fluoride: 3/17 Placebo: 2/18 (minor GI disorders such as nausea, gastric pain, diarrhoea; no ulcers or clinically significant gastroduodenal bleeding were observed)	All side-effects (including GI): Fluoride: 3/17 Placebo: 5/18 Pain in lower limbs: Fluoride: 1/17 Placebo: 3/18 (these episodes of mild pain in the heel or knees did not require interruption of medication and disappeared spontaneously before the end of the study. In these cases, there was no radiographic evidence of bone fissure) Hip pain: Fluoride: 0/17 Placebo: 2/18	None due to study medications
Lems, 1997a[108]	Fluoride: 0/23 Placebo: not stated	Lower extremity pain syndrome: Fluoride: 1/23 Placebo: 0/24	Fluoride: 2/23 (deaths from pulmonary embolism $n = 1$, incomplete fractures at the knee $n = 1$) Placebo: 2/24 (pancreatic cancer $n = 1$, encephalitis $n = 1$)
Lems, 1997b[109]	Fluoride: 0/20 Placebo: not stated	Lower extremity pain syndrome: Fluoride: 0/20 Placebo: 0/24 (the authors attribute this to the low fluoride dose used)	17/20 patients in the fluoride group and 23/24 patients in the placebo group completed the study. 1 patient in the fluoride group died, probably because of cardiac arrest, and 2 patients in the fluoride group and 1 in the placebo group withdrew because they no longer wanted to travel to Utrecht for the BMD measurements
Rozhinskaya, 1999[35]	Not specified	No details given. All side-effects said to be mild and transient.	1 patient receiving fluoride refused to continue treatment because of side-effects (nausea and arthralgia)
Von Tirpitz, 2000[20]	Not specified	Frequency of drug-related side-effects said to be similar between treatment groups. No lower extremity pain syndrome was reported	Fluoride: 2/18 (nausea and diarrhoea which were considered to be drug related) Control: 1/15 (severe diarrhoea attributed to the calcium carbonate)

TABLE 177 *Trichlormethiazide in the treatment of steroid-induced osteoporosis: details of included studies – general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Pretrial duration of steroid treatment	Steroid dose	Intervention/ dose	Comparison(s)
Yamada, 1989[28]	Japan	2 years	BMD Vertebral fractures	Premenopausal women with collagen diseases undergoing chronic prednisolone treatment	35	Apparently at least 12 months	Mean dose for preceding 12 months: 11 mg/day	Alfacalcidol (0.75 μg/day) + trichloromethiazide (4 mg/day) + calcium (400 mg/day)	Alfacalcidol (0.75 μg/day) + calcium (400 mg/day) No treatment

TABLE 178 *Trichlormethiazide in the treatment of steroid-induced osteoporosis: details of included studies – inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Yamada, 1989[28]	Premenopausal women with collagen diseases undergoing chronic prednisolone treatment	Not specified	All 3 groups were comparable at baseline in terms of age, underlying disease, glucocorticoid dose and indices of osteoporosis	Not given	This paper is in Japanese. As a result, only data from the English abstract and tables could be used. This may explain the low quality score

TABLE 179 *Trichlormethiazide in the treatment of steroid-induced osteoporosis: details of included studies – potential prognostic factors*

Study	Group	Mean baseline *T*-score	Mean BMD at lumbar spine (g/cm^2)	Subjects with vertebral fracture at baseline: no. (%)	Sex and menopausal status: no. (%)	Underlying illness: no. (%)
Yamada, 1989[28]	Alfacalcidol + trichlormethiazide (n = 11)	Not stated	Not stated	1 (9)	All premenopausal women	Collagen diseases
	Alfacalcidol alone (n = 14)	Not stated	Not stated	1 (7)	All premenopausal women	Collagen diseases
	Control (n = 13)	Not stated	Not stated	2 (15)	All premenopausal women	Collagen diseases

TABLE 180 *Trichlormethiazide in the treatment of steroid-induced osteoporosis: details of included studies – methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	No. of subjects in each arm completing study protocol (%)	Source of funding
Yamada, 1989[28]	1	1	1	3	0	1	7/15 (47)	38 (all premenopausal women)	No data	Not stated

TABLE 181 *Trichlormethiazide: details of included studies – toxicity*

Study	No. of patients suffering upper GI adverse events	No. of patients suffering other adverse events	No. of patients withdrawing/discontinuing study medication due to adverse events
Yamada, 1989[28]	No data	Hypercalciuria: Tricholormethiazide + alfacalcidol: 0/11 Alfacalcidol alone: 9/14 Control: 0/13 Renal stones: Tricholormethiazide + alfacalcidol: 0/11 Alfacalcidol alone: 2/14 Control group: 0/13	No data

Appendix 10

Appendices references

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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