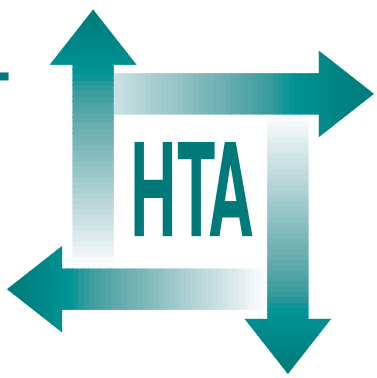
Health Technology Assessment 2002; Vol. 6: No. 29

Treatment of established osteoporosis: a systematic review and cost–utility analysis

JA Kanis
JE Brazier
M Stevenson
NW Calvert
M Lloyd Jones

Health Technology Assessment
NHS R&D HTA Programme



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Treatment of established osteoporosis: a systematic review and cost–utility analysis

JA Kanis[1*]
JE Brazier[2]
M Stevenson[2]
NW Calvert[2]
M Lloyd Jones[2]

[1] WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, UK
[2] Sheffield Centre for Health and Related Research, University of Sheffield, Sheffield, UK

[*] Corresponding author

Declared competing interests of the authors: Professor John Kanis has worked with and received funding from many pharmaceutical companies and non-governmental organisations that are involved in osteoporosis research.

Published February 2003

This report should be referenced as follows:

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).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

Related publications:
Brazier JE, Green C, Kanis JA, on behalf of the Committee of Scientific Advisors, International Osteoporosis Foundation. A systematic review of health state utility values for osteoporosis related conditions. *Osteoporos Int* 2002;**13**:768–77.

Stevenson M. Gaussian process modelling in conjunction with individual patient simulation modelling. A case study describing the calculation of cost-effectiveness ratios for the treatment of osteoporosis. *Med Decis Making* (in press).

NHS R&D HTA Programme

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Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme continues to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

The research reported in this monograph was funded as project number 95/11/04.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.

ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

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List of abbreviations

BMD	bone mineral density
CHD	coronary heart disease
CI	confidence interval
EQ-5D	EuroQol-5 dimension [scale]
FIT	Fracture Intervention Trial
GP	general practitioner
HCHS	Hospital and Community Health Services
HRT	hormone replacement therapy
HUI	Health Utility Index (-II/-III)
ITT	intention-to-treat
LOS	length of stay
MI	myocardial infarction
NNT	number needed to treat [to prevent one fracture]
NOF	National Osteoporosis Foundation (USA)
PROOF	Prevention of Osteoporotic Fractures [study]
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SERM	selective [o]estrogen receptor modulator
SF	Short Form (-36 or -6D)
SHEMO	Sheffield health economic model of osteoporosis
SG	standard gamble
SOF	Study of Osteoporotic Fractures
T-score	the deviation in units of SD of a BMD value from the mean value in premenopausal healthy women
TTO	time trade-off
Vitamin D	cholecalciferol or calciferol
Vitamin D derivatives	1-alpha hydroxylated forms of vitamin D (calcitriol, alfacalcidol, dihydrotachysterol)
Z-score	the deviation in units of SD of a BMD value from the mean value in individuals of the same age and gender

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.

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.

Osteoporosis is operationally defined by the measurement of bone mineral density (BMD) at the hip, and is diagnosed in women when BMD is 2.5 standard deviations (SDs) or more below the average for young healthy women. Established osteoporosis denotes the disease in the presence of one or more fragility fractures.

A variety of agents are available for the treatment of osteoporosis. The evidence for their efficacy is examined and their cost-effectiveness is modelled in established osteoporosis.

Methods

Therapeutic intervention

A systematic review was undertaken of all randomised controlled trials (RCTs) in which fracture was measured as an outcome. RCTs that studied fracture benefits in patients in whom osteoporosis or osteopaenia was not identified were excluded, as were epidemiological studies, although account was taken of these lower levels of evidence in the interpretation and subsequent analysis of information. The interventions reviewed were: bisphosphonates, vitamin D, 1-alpha hydroxylated derivatives of vitamin D, calcitonin, calcium, oestrogens, oestrogen-like agents, anabolic steroids, fluoride salts, thiazide diuretics, raloxifene, vitamin K_2, protein supplements and exercise.

Epidemiology, costs and utilities

The annual risk of osteoporotic fracture was characterised for women from the UK. Fractures of the hip, spine, distal forearm and humerus were designated as being osteoporotic. Collectively, they account for approximately 70% of osteoporotic fractures in postmenopausal women and more than 70% of the morbidity.

The risk of osteoporotic fractures in women at the threshold for osteoporosis was determined from a published meta-analysis of the relationship between BMD and fracture risk. The risk of such a 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 consequences of fracture on mortality were assessed for each fracture type. The annual risk of breast cancer, coronary heart disease (CHD) and mortality were reviewed so that extraskeletal risks and benefits of hormone replacement therapy (HRT) and raloxifene could be modelled.

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

Health economics model

A model was developed comprising an individual patient-based approach that simulated whether or not events occurred in each subsequent year for each patient.

Transition states included fracture states (hip, wrist, vertebral and proximal humerus), death from hip fracture, nursing home admission owing to the hip fracture, fatal and non-fatal CHD, fatal and non-fatal breast cancer, and death from other causes.

The model simulated cohorts at fixed ages (50, 60, 70 and 80 years) with established osteoporosis. The proportions of the population with different fracture types were simulated from the known distribution of these fractures at different ages.

Effectiveness was populated from the systematic review of interventions in osteoporosis. Treatments were given for 5 years using a 5-year offset time, except for calcium and calcitonin for which a

3-year offset time was used (in this context, offset time is the duration for which an effect persists after the treatment stops). The analytic framework was set at 10 years. Because of the many uncertainties, particularly for hip fracture and extra-skeletal risks and benefits, extensive sensitivity analyses were undertaken for each agent.

Results

The results of the systematic review of RCTs indicated that bisphosphonates, calcitonin, calcium, fluoride salts and raloxifene reduced the incidence of vertebral fracture. The bisphosphonate, alendronate, also decreased non-vertebral fracture, including hip fracture.

For several agents, failure to demonstrate efficacy, particularly for hip fracture, was largely due to the lack of appropriate RCTs. Epidemiological evidence suggested that treatment with calcium, calcitonin, HRT, thiazide diuretics, etidronate and anabolic steroids decreased hip fracture risk. There was also RCT evidence that calcium plus vitamin D decreased fracture risk in patients for whom BMD was not known.

The results for each agent at each age are 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 90% confidence interval representing the range of cost–utility that was incurred by 90% of the combinations of relative risks (RRs) for efficacy.

Cost-effectiveness was graded A–D from the range of cost-effectiveness ratios using a threshold value of £30,000/QALY gained to denote good cost-effectiveness.

Only those agents that RCT data showed to have significant effectiveness for at least one fracture outcome were tested – raloxifene, HRT, calcium (with and without vitamin D), calcitonin, alendronate, other bisphosphonates, fluoride and alfacalcidol.

It was not cost-effective to treat established osteoporosis with raloxifene in the time frame modelled. If cardiovascular benefits were assumed, treatment was only cost-effective compared with no intervention at ages of at least 70 years.

HRT was not cost-effective except below the age of 60 years. However, treatment became cost-effective from the age of 50 years if the effects on appendicular fractures reported in epidemiological studies were included. Additional benefits from reductions in CHD, with additional risks from an increased incidence of breast cancer, did not markedly change the conclusions on cost-effectiveness.

Treatment with calcium alone was cost-effective compared with no intervention from age 60 years, assuming an effect only on vertebral fracture risk. Treatment was cost-effective at all ages if effects on appendicular fractures were included, as shown by the RCT data for calcium with vitamin D.

Treatment with calcitonin was not cost-effective at any age largely because of its high costs. Treatment with alendronate was only cost-effective from age 70 years onwards.

Since no difference in efficacy between the bisphosphonates could be shown, a pooled analysis was undertaken using the cost of intervention equivalent to etidronate. 'Bisphosphonate' treatment was cost-effective from age 60 years solely because its therapeutic cost was lower than that for alendronate.

Using the meta-analysis of RCTs, treatment with fluoride was not cost-effective, largely because of a high point estimate for hip fracture risk (RR = 1.78). If no adverse effect on hip fracture was assumed, then treatment became cost-effective from age 60 years.

Compared with no treatment, it was not cost-effective to treat established osteoporosis with alfacalcidol except at ages of 70 years or more.

Further sensitivity analyses were undertaken, focussing on those agents with cost-effectiveness grades A or B.

Age and cost of intervention were important determinants of cost-effectiveness. Cost-effectiveness ratios were sensitive to changes in discount rates for benefits and in the assumption relating to offset of effect (offset time). Cost-effectiveness was markedly improved when women with T-scores under –2.5 SD were selected.

The results were not markedly affected by the threshold used for cost-effectiveness, poor compliance, variations in the assumptions about mortality after hip fracture, duration of treatment and duration of analysis. The inclusion of costs for added years of life had little effect in the elderly

but improved cost-effectiveness in women aged up to 60 years. In contrast, the inclusion of all vertebral fractures (in addition to clinically overt fractures) had a marked effect on improving cost-effectiveness.

Conclusions

Cost-effective scenarios for several interventions in the management of established osteoporosis were identified. Cost-effectiveness ratios decrease with age. At age 50 years, only HRT and calcium plus vitamin D were cost-effective (assuming that the agent would decrease the risk of appendicular fractures at this age). At age 80 years, HRT, calcium with or without vitamin D, alfacalcidol, alendronate and bisphosphonate were all cost-effective.

The conclusions derived are conservative, mainly because of the assumptions made in the absence of sufficient data. The conservative assumptions included the following:

(i) not all osteoporotic fractures are included
(ii) not all vertebral fractures are included
(iii) base-case scenarios are modelled at the threshold for osteoporosis
(iv) risks of re-fracture in the few years after a fracture are likely to be underestimated
(v) vertebral fracture incurs no reversible mortality
(vi) long-term effects of osteoporotic fractures on utilities are ignored.

Thus conclusions that treatments are cost-effective are reasonably secure. In contrast, scenarios shown to be cost-ineffective are less secure. As information in these areas becomes available, the implications on cost-effectiveness of interventions should be reappraised.

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 economics 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 should be undertaken to more closely evaluate the impact of vertebral deformities (rather than clinically overt vertebral fractures) on cost-effectiveness.

Chapter 1
Introduction

There is an increasing need for osteoporosis management strategies to be placed in an appropriate health economics perspective. Until recently, most economics studies of prevention and treatment of osteoporosis focussed upon the use of hormone replacement therapy (HRT) at the menopause.[1–8] Limited analyses are available for the use of non-HRT interventions[9–11] but only one placed this in a UK setting.[11] Moreover, little or no work has been undertaken to assess the value of agents on hip fracture – the complication of osteoporosis that carries the highest consequence for health. There are now many agents available for the treatment of osteoporosis with widely different apparent efficacies and costs. The aim of this study was to examine the cost-effectiveness of treatments available in the UK, specifically in patients with established osteoporosis.

Established osteoporosis

The internationally agreed definition of osteoporosis is:

- 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.[12]

This definition of osteoporosis captures the notion that low bone mass is an important component of the risk of fracture but that other abnormalities occur in the skeleton, and that non-skeletal factors such as falls are also important. Nevertheless, it is only bone mass measured as bone mineral that can be presently measured with precision and accuracy, and this measurement forms the basis for the diagnosis of osteoporosis.

For diagnostic purposes two thresholds of bone mineral density (BMD) have been proposed for Caucasian women based on the T-score.[13,14] The first defines the majority of individuals who will sustain a fracture in the future (osteoporosis) and the second, higher threshold may be more appropriate for investigating the impact of strategies to prevent bone loss in women at the menopause (low bone mass/osteopaenia). Osteoporosis is denoted by a BMD value that is at least 2.5 standard deviations (SDs) below the young adult mean value (T-score < –2.5 SD). Osteopaenia is denoted by a T-score that lies between –1 SD and –2.5 SD.

Severe or 'established' osteoporosis is as defined above in the presence of one or more documented fragility fractures, usually of the wrist, spine or hip.

In a young, healthy population, 15% of women will have a T-score of less than –1 SD and, thus, have osteopaenia. Approximately 0.5% will already have osteoporosis. However, these thresholds apply to women only and suitable diagnostic cut-off values for men are less secure. It has been suggested that a similar **absolute** value of BMD to that used for women can be taken as the cut-off point for the diagnosis of osteoporosis – namely, a BMD value that is 2.5 SD below the average for women.[15]

Since the introduction of working definitions of osteoporosis, much attention has focussed on their application in epidemiology, clinical trials and patient care. Several problems have emerged, however, largely due to the development of new measurement techniques applied at many different sites. It is now clear that the same T-score derived from different sites and techniques yields different information on fracture risk, even when adjustments are made for age. Thus, the T-score cannot be used interchangeably with different techniques and at different sites. For this reason, the reference standard adopted in terms of site and technology for diagnostic purposes is the hip (femoral neck) using dual energy X-ray absorptiometry.[15] Measurements at the hip have the highest predictive value for hip fracture.[16] Moreover, the hip is the site of greatest biological relevance since hip fracture is the dominant complication of osteoporosis in terms of morbidity and cost. Hence, in this study these standards for the definition of osteoporosis have been adopted.

Significance of osteoporosis

The clinical significance of osteoporosis lies in the fractures that arise. Common fractures include vertebral compression fractures, and fractures of

the distal radius and the proximal femur (hip fracture). In addition, when the skeleton is osteoporotic, fractures occur more commonly at many other sites, including the pelvis, proximal humerus, distal femur and ribs. Osteoporotic fractures occurring at the spine and the forearm are associated with significant morbidity but the most serious consequences arise in patients with hip fracture, which is associated with a significant increase in mortality (15–20%), particularly in the elderly.[17] Hip fractures account for more than 20% of orthopaedic bed occupancy in the UK, in Scandinavia and in several other countries.[13,18] After the age of 45 years, hip fractures account for as high a proportion of hospital bed occupancy as many other common disorders in women, including breast cancer and diabetes.[19] The acute hospital costs in the UK for hip, forearm and vertebral fractures in women have been estimated at £264 million, and the social care and acute costs for all osteoporotic fractures combined at £727 million.[20]

The likelihood that any individual will suffer an osteoporotic fracture is considerable. In many Western countries, the remaining lifetime probability of a hip fracture in women at the menopause lies between 15% and 28%[21–23] but varies from country to country. In this study, hip fracture rates in Edinburgh have been used (see chapter 4) and, based on these figures, the remaining lifetime risk at 50 years of age is 14.2% in women and 5.2% in men (*Table 1*). Even within Europe there is a marked variation in hip fracture probability (see *Table 1*). For example, men in Sweden have a risk that is comparable to that for women in the UK and significantly higher than that for women from Portugal or Turkey. The risk of other common types of osteoporotic fractures is nearly as high,[24–27] so that the combined fracture risk is 30–40%. Thus, more than one-third of adult women will sustain one or more osteoporotic fractures in their lifetime. This estimate is conservative since it does not include fractures at other sites and only takes into account those vertebral fractures that come to clinical attention; hence, the true risk of fracture is higher.

These indices of fracture risk compare with the lifetime risk in women aged 50 years of 9–12% for breast cancer and 30–40% for cardiovascular disease.[13] This indicates the widespread prevalence of osteoporosis in society. In comparison, the risks for men are about one-third of those in women and are even lower for forearm fractures; however, they still represent a considerable burden.

The frequency of many osteoporotic fractures, including hip fracture appears to be increasing. The reason for this is two-fold. First, there appears to have been an increase in age- and gender-specific rates in many countries,[28] although there is some evidence that, in England and Wales, the increases in these rates are now stable.[29] Second, life expectancy of individuals over the age of 50 years has increased and will continue to do so well into the 22nd century.[30] This means that, even in the UK, progressively more and more of the population will be elderly and at risk of fracture.[31] An approximately four-fold increase in hip fracture rates between 1990 and 2050 on a worldwide basis has been predicted in two surveys, assuming no increase in the secular trend.[32,33] The increase in fracture frequency is occurring in both men and women, owing to improvements in life expectancy. By the year 2025, it has been estimated that there will be as many fractures in men as there are in women today. Thus, the burden of osteoporosis is set to increase well into the future.

TABLE 1 *Lifetime and 10-year probabilities of hip fracture (%) by age and sex in four different areas of Europe*

Probability interval (years)	Age (years)	Malmö (Sweden)[a]		Edinburgh (UK)[b]		Porto (Portugal)[c]		Istanbul (Turkey)[c]	
		Men	Women	Men	Women	Men	Women	Men	Women
10	50	0.5	0.6	0.4	0.4	0.4	0.4	0.1	0.1
10	60	1.9	2.7	0.7	1.1	0.9	1.3	0.2	0.3
10	70	5.5	10.2	2.2	4.9	1.6	3.2	0.6	0.5
10	80	12.8	24.6	5.7	13.0	2.3	6.0	1.0	1.0
Lifetime	50	13.1	28.5	5.2	14.2	3.2	8.2	1.2	1.2

Hip fracture incidence from different regions taken from:
[a] *Kanis*, et al., *2000*[24]
[b] *Singer*, et al., *1998*[25]
[c] *Elffors*, et al., *1994*[26]

Intervention strategies

Against this background, the development of intervention strategies in osteoporosis has aroused much interest. Two distinct but not mutually exclusive strategies can be envisaged. The first is to identify patients at particular risk and to offer an intervention. Examples include the identification of: women with low BMD, patients who are likely to fall, and those with certain diseases or prior fragility fractures. A second strategy is a population-based or global strategy in which the aim is to modify a risk factor within the general community. For example, if BMD were to be increased by 10% in women, this might decrease the risk of fragility fractures by as much as 50%.[24] Such approaches might be directed at any or all stages of life. Lifestyle factors that have been advocated in a global strategy include stopping smoking, taking up physical activity and improving nutrition in terms of calcium and/or vitamin D. There is evidence from randomised controlled studies that intervention using a combination of calcium and vitamin D in the elderly living in sheltered accommodation decreases the risk of hip fractures by approximately 28%.[35] It is unclear whether or not this is due to the calcium, the vitamin D or the combination. Another successful, potentially global strategy is the use of hip protectors, again in high-risk populations such as nursing home communities. In a recent randomised study in community healthcare centres, hip protectors significantly decreased the risk of hip fracture by 60%.[36]

General global strategies

More general global strategies such as advice on diet, smoking and exercise are problematic. An example is provided in the case of calcium nutrition. Numerous case–control studies have suggested that individuals with high intakes of calcium have a significantly decreased risk of hip fracture.[9,37] On this basis, there is an impetus, particularly in the USA, to increase the recommended dietary allowances for calcium;[18] however, the basis of these recommendations is uncertain. So too is their potential impact, which can be illustrated from a large case–control study of hip fractures undertaken in Southern Europe.[38] In this study of 3 million individuals, 3000 hip fractures occurred in men and women over the age of 50 years. High intake of calcium in the form of dairy products was associated with a significant decrease in fracture risk in women (relative risk (RR) = 0.71; 95% confidence interval (CI), 0.58 to 0.87) and a borderline effect in men (RR = 0.81; 95% CI, 0.62 to 1.06). The proportion of the population in whom low calcium intakes were observed and who were therefore at increased risk (attributable risk) was low, so that of these 3000 hip fractures, approximately 110 were associated with a low calcium intake. After taking into account whether relationships are causal and reversible, and the likely impact of a public health campaign, the numbers needed to treat (NNT) to prevent one hip fracture will be large (see *Table 2*) and, in this example, an NNT value of 2 million was obtained.

These considerations have led to the view that population-based strategies are not feasible at present.[18,39,40] The reversible determinants of peak bone mass are conjectural, and no controlled studies have been undertaken to modify bone mass in a way that has proved favourable for skeletal health. The global approach of treating all postmenopausal women with oestrogens is unethical and unfeasible at our current state of knowledge.

High-risk strategies

Prevention of osteoporotic fracture is, therefore, more appropriately envisaged today as targeting interventions at those segments of the community

TABLE 2 *An estimate of the effect of a global strategy to increase milk consumption in a population of 3 million men and women aged 50 years and over[37] (Reproduced with permission from Elsevier Science)*

	Number	NNT[a]
Population, aged 50 years and over	3,000,000	
Number of hip fractures	3,000	3,000
Hip fractures associated with low calcium intake	110	27,000
– causally associated (80%)	88	34,000
– reversible with calcium (70%)	62	48,000
Impact of public health campaign (2.4%)	1.5	2,000,000

[a] *To prevent one hip fracture*

considered to be at high risk. As in the case of a population strategy, this might be directed at appropriate individuals at any age. Since bone mass, at least up to the age of 75 years or so, is largely a function of peak bone mass, it could be argued that high-risk strategies should be directed towards the optimisation of peak bone mass. Unfortunately, the major contributions to peak bone mass (race and heritability) are immutable, and the impact of other potential factors is of uncertain value. For this reason, effective high-risk strategies are most appropriately directed in later life, particularly in women at the menopause, when accelerated bone loss occurs. Interventions used at this age are largely pharmacological. Of these, the greatest attention has been directed at the use of gonadal steroids in women at high risk of fracture.

Population screening

There are a number of problems that indicate that a widespread approach to the management of osteoporosis at the menopause with HRT or other interventions is problematic. The first is that the tests that might be used in population screening for the identification of patients at risk (e.g. BMD) at age 50 years or so lack sensitivity.[18] At the hip, the fracture risk increases approximately twofold for each SD decrease in BMD. At this gradient of risk, the sensitivity of the test to predict fractures over 10 years in women aged 50 years is low. Even if 25% of postmenopausal women were targeted, the sensitivity would remain below 50% (*Table 3*).[41] Sensitivity does not increase for the prediction of all fractures in women aged 65 years. Moreover, the test estimates the short-term fracture risk and, beyond 10 years, risk prediction becomes less secure owing to variable rates of bone loss within the population.[42]

A second problem is the uncertainty relating to the ultimate impact of intervention for a finite period with HRT (current recommendations are 5–10 years) on hip fracture risk much later in life.[43] Most epidemiological information indicates that, whereas the risk of hip fracture is markedly reduced in women taking HRT, the effects appear to fall off once treatment is stopped. This offset time appears to occur over a period of 15–20 years.[44] Thus, interventions directed at the menopause for 5 years are likely to have little or no effect at age 70 or 75 years, when the risk of hip fracture in the community begins to increase most markedly. For these and other reasons, no sound case can be made at present for screening at the menopause, whereas there may be a case to be made in later life, when the prevalence of risk factors in addition to BMD is much higher; however, such an approach has not yet been validated. Until such times, osteoporosis must be tackled using a case-finding strategy.

Case finding

The principles of case finding are to identify individuals at risk on the basis of common clinical risk factors and, thereafter, to undertake assessment of BMD. Whereas the assessment of BMD forms a cornerstone for the diagnosis of osteoporosis, other risk factors have been identified that contribute to risk independently of BMD. Examples include age, rapid rates of bone loss, prior fragility fractures and a family history of fracture. For example, individuals with a prior fragility fracture have a two-fold increase in risk of further fracture, even when this risk is adjusted for BMD. The combination of a dichotomous variable (e.g. fracture, present or absent) and a continuous variable (e.g. BMD) yields a continuous variable, which in this case has a gradient of risk greater than that afforded by BMD alone. As can be seen from *Table 3*, an increase in the gradient of risk improves sensitivity without trading-off specificity. Thus, stratification of risk is made more optimal than the use of either of these risk indicators alone. This approach has been adopted in many practice guidelines.[42,45–47]

The identification of patients with fragility fractures and subsequent measurement of BMD forms an intuitive strategy, provided that intervention can decrease the burden of fracture.

Health economics in osteoporosis is in its infancy. The vast majority of studies in this area have concentrated on the use of HRT, and only limited data are available on the use of non-HRT interventions. These non-HRT interventions, however, form the bulk of treatments available for established osteoporosis. The efficacies of interventions in osteoporosis and established osteoporosis have now been examined in many published studies. Several bisphosphonates, calcitonin, calcitriol, gonadal steroids and analogues, and calcium have been licensed for use in osteoporosis. Indices of efficacy studied include their effects on BMD and, in some cases, their effects on fracture (reviewed in chapter 2). The logical elements of a case-finding strategy are therefore complete but it requires a justification to compete with other clinical priorities. The most straightforward scenario is to marshal the arguments in a health economics setting for the treatment of patients with established osteoporosis. Such

TABLE 3 *Estimates of positive predictive value (PPV), sensitivity and specificity of measurements to predict any osteoporotic fracture over 10 years or to death in women aged 50 or 65 years, according to different population cut-offs to define a high-risk category*[41] *(Reproduced with permission from Elsevier Science)*

Gradient of risk (RR/SD)	High risk category (% of population)														
	0.5			5			10			15			25		
	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)
Women aged 50 years															
1.5	17.3	1.5	99.6	12.7	10.7	95.4	10.7	18.0	90.5	10.3	26.1	85.7	8.9	37.6	75.8
2.0	31.3	2.6	99.6	19.2	16.2	95.7	15.1	25.5	91.0	13.8	35.1	86.3	11.3	47.5	76.4
2.5	45.0	3.8	99.7	24.8	21.0	96.0	18.7	31.6	91.4	16.5	41.9	86.7	12.9	54.5	76.9
3.0	56.7	4.8	99.8	29.4	24.9	96.3	21.5	36.3	91.7	18.5	47.0	87.0	14.0	59.2	77.1
4.0	73.0	6.2	99.9	35.8	30.3	96.6	25.1	42.3	92.0	20.9	52.9	87.4	15.1	63.8	77.4
5.0	82.3	7.0	99.9	39.5	33.4	96.8	26.8	45.3	92.2	21.8	55.2	87.5	15.3	64.7	77.5
6.0	87.8	7.4	99.9	41.5	35.0	96.9	27.5	46.5	92.3	21.9	55.6	87.6	15.1	63.7	77.4
Women aged over 65 years															
1.5	37.8	1.3	99.6	28.8	10.2	95.9	24.4	17.3	91.2	23.7	25.3	86.7	20.7	36.7	76.9
2.0	60.2	2.1	99.8	40.8	14.5	96.6	32.9	23.4	92.2	30.7	32.7	87.9	25.3	45.0	78.3
2.5	76.3	2.7	99.9	49.8	17.7	97.1	39.0	27.7	92.9	35.4	37.7	88.7	28.2	50.1	79.1
3.0	86.1	3.1	99.9	56.2	19.9	97.4	43.1	30.6	93.4	38.3	40.8	89.2	29.8	52.9	79.6
4.0	95.3	3.4	100.0	63.5	22.6	97.9	47.5	33.8	93.9	41.2	43.8	89.7	30.9	54.8	79.9
5.0	98.7	3.5	100.0	67.0	23.8	98.1	49.2	34.9	94.1	41.7	44.4	89.8	30.4	54.0	79.8
6.0	100.2	3.6	100.0	68.5	24.3	98.2	49.4	35.1	94.1	41.2	43.8	89.7	29.4	52.1	79.4

arguments have not yet been fully formalised in the UK, in part because of the lack of availability until recently of treatments of proven efficacy.

The increasing awareness of osteoporosis combined with the current availability and development of specific treatments is likely to increase the demand for management of patients with osteoporosis. In the past, management has been largely confined to specialists but the increasing availability of diagnostic tools and well-proven treatments, and the increasing numbers of patients identified, indicate that the burden of management will fall increasingly on the primary care physician. The aim of this study is to provide a framework for the cost-effective management of established osteoporosis. The terms of reference do not cover the treatment of patients with osteoporosis but without fragility fractures. However, the ultimate goal of effective treatment strategies is to prevent the first fracture, and the approach used was designed so that these strategies could be considered at a later date.

The evidence for efficacy of interventions in osteoporosis is considered first using an evidence-based approach. In subsequent chapters, the additional assumptions on risks, costs and quality of life are described. These data are finally incorporated into a health economics model to address the major aims of this study.

Chapter 2

Therapeutic intervention in osteoporosis

In approaching a systematic review of trials of efficacy for application to health economics models, there are two strategies. The first is to review the randomised controlled trials (RCTs) that examine fracture outcomes. This has the advantage of incorporating outcomes of clinical significance. The major disadvantage is the relative paucity of trials in which fracture is examined as the primary outcome compared with studies on BMD. This is partly because regulatory authorities worldwide accept studies of BMD as the criteria for efficacy for prevention of osteoporosis.[48–50] The second option is to review studies of prevention of bone loss and to infer antifracture efficacy from the known relationship between BMD and fracture. This approach was used in early pharmacoeconomic evaluations.[8,51] 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.[47,50,52] Indeed, recent RCT data indicated that treatment-induced changes in BMD may underestimate antifracture efficacy – that is, the decrease in fracture rate is greater than can be explained on the basis of the measurement of BMD alone.[53]

The approach used was the more direct approach – namely to examine and model fracture outcomes based on RCT evidence from a systematic review of the literature. In view of the paucity of trials that reported fracture as a primary outcome, studies in which fracture was reported as a secondary outcome measure were also included. The advantage of reviewing only RCTs is that they provide the highest level of evidence. A disadvantage is that evidence from epidemiological studies is not considered. This was appropriate in the context of this study but the censoring of epidemiological evidence is problematic in the field of osteoporosis. Hip fracture is the most serious consequence of osteoporosis but very few RCTs on hip fracture outcomes are available. This is because regulatory authorities and, hence, the pharmaceutical industry recognise the efficacy of treatments for osteoporosis on the basis of effects on vertebral fracture.[48,49] Vertebral fractures are more common in middle age when hip fractures are rare; hence, trials in vertebral fracture are more economic to set up in terms of the numbers of patients required to demonstrate efficacy. The argument runs that, since osteoporosis is a sys-temic disease and treatments induce systemic effects, an agent that decreases vertebral fracture risk will also do so at other sites vulnerable to osteoporosis.

The epidemiological information is, in general, in keeping with this view. Examples include the use of hormone replacement, calcium, calcitonin and etidronate, for which RCT data indicate a vertebral fracture efficacy that is supported by similar findings in case–control studies on hip fracture.[54,55] There are, however, dangers in making assumptions. The magnitude of hidden biases cannot be assessed. Moreover, the magnitude of effect on hip fracture risk cannot be assumed to be similar to the effect on vertebral fracture. Indeed, as reviewed later, recent studies with raloxifene have shown a clinically significant (50%) effect of treatment on vertebral fracture risk but an insignificant magnitude of effect on fractures of the appendicular skeleton. For these reasons, the systemic review and primary analyses were confined to an RCT information base but other evidence is pointed out and used when appropriate.

Methodology

A systematic review was undertaken to compare the effectiveness of pharmacological and non-pharmacological interventions in preventing osteoporotic fractures in patients with osteopaenia, osteoporosis or established osteoporosis.

Inclusion criteria

- ***Types of participants***: only those studies were included in which the participants had been diagnosed as having established osteoporosis, osteoporosis or osteopaenia, whether primary or secondary.
- ***Types of intervention***: studies were included in which any of the following types of intervention were used:
  – bisphosphonates
  – vitamin D

  - 1-alpha 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
  - selective [o]estrogen receptor modulators (SERMs)
  - non-pharmacological interventions.
- ***Outcome measures***: all studies were included in which vertebral or non-vertebral fracture was reported.
- ***Study design***: only RCTs were included. Trials were accepted as RCTs if the allocation of patients to treatment groups was described as randomised.

Exclusion criteria

It had originally been intended to include all relevant trials, whatever the language of publication. However, it was only possible to include those published in English, French, German, Italian or Spanish. This led to the exclusion of two studies that were published only in Japanese: one was an open-label randomised trial of vitamin K_2,[56] and the other a crossover study comparing alfacalcidol with calcium – the first year of which was, in effect, an RCT.[57] A third study, published only in Japanese, provided a relatively lengthy abstract in English,[58] and the information which this offered was used. The report of a further trial was published in both Danish[59] and English,[60] and thus was included.

Only published studies were included, with a cut-off date of March 2000.

Literature search

Literature searches of the electronic databases listed in *Table 4* were undertaken. Each database was searched as far back as possible, with no language restrictions. Update searches were carried out on MEDLINE, EMBASE and the Cochrane Library in March 2000.

Search strategies of relevant clinical keywords were developed through reference to published strategies and consultation with experts, and by iterative searching, whereby keywords identified in references retrieved by initial scoping searches were used to extend the search strategy and so increase the sensitivity of retrieval. The strategy developed by the Cochrane Collaboration to identify RCTs was used to retrieve studies relating to the treatment of osteoporosis.

TABLE 4 *Sources searched*

Biological Abstracts
Cochrane Controlled Trials Register/Central
Cochrane Database of Systematic Reviews
Current Research in Britain (CRIB)
Current Research Worldwide (CRIW)
EMBASE
HealthSTAR
Index to Theses
Index to Scientific and Technical Proceedings (Institute for Scientific Information)
Science Citation Index (Institute for Scientific Information)
MEDLINE
NHS Database of Abstracts of Reviews of Effectiveness (DARE)
NHS HTA
NHS Economic Evaluation Database (NHS EED)
National Research Register (NRR)
Pascal
PubMed
Quality of Life in Medicine bibliography

Sensitivity of the keyword strategies was tested by comparing the results of searches with reference lists from existing reviews.

The search strategy for MEDLINE is presented in appendix 1. The search strategies used for 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 *Science Citation Index*. Reference lists of published reviews were also checked. Attempts to identify further studies were made by consulting experts, health technology assessment and guideline producing agencies, and research and trials registers via the Internet. Relevant pharmaceutical companies were also invited to provide up-to-date literature relating to their products. In addition, the five journals identified by the electronic searches that yielded the greatest numbers of relevant articles were handsearched from January 1990 onwards (see appendix 2).

Titles and, when available, abstracts of all studies identified in the searches were assessed by a single researcher for relevance to the review. In cases of doubt, the full article was obtained. To ensure the reliability of the selection process, two subject

experts each checked a sample of 20 abstracts against the inclusion criteria. As a result of this exercise, it was decided to include only those studies in which it was specified that patients suffered from osteoporosis or osteopaenia. It was not sufficient that, on the balance of probability, most or all patients would be likely to have osteoporosis or osteopaenia because of their age or medical status.

Search results

Electronic searching yielded a total of 12,378 citations, 118 of which were related to studies that appeared to fulfil the inclusion criteria for this review. A total of 88 RCTs were identified by this means. A further eight relevant trials were identified from the reference lists of identified trials and relevant review articles,[61–68] and an additional four by hand-searching only.[69–72] No trials were identified by pharmaceutical companies that had not been identified by other means.

Full copies of all apparently eligible studies were then obtained. A total of 83 individual RCTs met the review inclusion criteria and are listed after the main reference list (page 125), followed by a list of studies that were excluded, and reasons for this (page 132).

Details of eight trials were only available as conference abstracts or publications of comparable length.[70,72–78] Although the methodology of another trial[79] was mentioned in a longer publication,[80] its results were only available from conference abstracts.[79,81] In addition, as mentioned earlier, it was only possible to use the English-language abstract of a full Japanese publication.[58]

Data extraction

Data from the included studies were extracted by a single reviewer, using a predefined data extraction form.

Publication bias

In an attempt to assess the magnitude of publication bias, separate funnel plots were drawn, plotting effect size (in terms of the vertebral fracture RR) against sample size, for all interventions for which five or more trials reported vertebral fracture incidence in terms of the numbers of patients suffering fractures.[82]

Meta-analysis of combined data

Studies that met the entry criteria were eligible for inclusion in the meta-analyses, provided that fracture incidence was reported as the number of patients sustaining fractures. This enabled the calculation from published data of the RR of patients in the intervention group developing a new fracture or fractures compared with those in the control group. Studies in which only numbers of fractures or fracture rates (that is, numbers of fractures per hundred or thousand patient years) were reported were excluded from the meta-analyses. Their inclusion would have violated the basic statistical assumption that the occurrence of one event does not increase the likelihood of a subsequent event[83] since, once an individual has suffered an osteoporotic fracture, the risk of a subsequent fracture increases.[84,85] In practice, the bias may be small since the number of individuals sustaining multiple vertebral fractures is small.

Ideally, the meta-analyses should have included only those studies in which fracture was a primary endpoint. Sensitivity analyses were therefore undertaken to assess the effect of excluding trials in which fracture was not a primary endpoint.

The studies that contributed data to the meta-analyses were also heterogeneous in terms of patient characteristics (age, gender, severity of disease, etc.), the nature of the interventions used (varieties of drug, doses and methods of administration), the degree of blinding and standards of reporting. Since the endpoint of interest was fracture, it was considered appropriate (*pace* Meunier, 1999)[86] to include open-label studies; however, in relation to vertebral fracture, sensitivity analyses were carried out to assess the effect of excluding those studies in which it was not specified that the outcome assessors were blinded to treatment status.

The meta-analyses were carried out using the computer software package, EasyMA 97b,[87] using a fixed-effects model.

Quality assessment

A quality assessment was undertaken to inform the sensitivity analyses.[88] The methodological quality of all trials that met the inclusion criteria was assessed using a tool developed by Gillespie and colleagues.[89] This 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. It included the following items:

- adequacy of randomisation and masking of randomisation

- blinded assessment of outcomes – whether outcome assessors were blind to patients' treatment allocation
- withdrawals – whether the outcomes of those 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[90] were incorporated in the tool (see appendix 3).

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

Blinding of the quality assessors to author, institution or journal was considered unnecessary.[91,92]

One researcher undertook quality assessment. To ensure the reliability of the assessment process, two experts also assessed a sample of five studies each using the same tool. This exercise resulted in clarification of scoring in relation to the method used to identify vertebral fracture.

Evidence from clinical trials

Each of the eligible studies is summarised in appendix 4. A summary of the studies together with an evaluation of their quality is given in appendix 5, listed by therapeutic class. The therapeutic classes included the bisphosphonates, vitamin D and its derivatives, calcitonins, calcium, oestrogens and related compounds, all of which are licensed for use in osteoporosis in the UK. In addition, fluoride salts, thiazide diuretics, ipriflavone and the anabolic steroids that are used by specialist centres were included. Protein supplements were also included, since these have been shown to decrease morbidity in hip fracture patients, together with vitamin K_2, which is used in Japan. Finally, physical exercise was reviewed as it is commonly recommended as a lifestyle intervention in osteoporosis.

Studies in which an active intervention was compared with placebo or no treatment are discussed first, by intervention, followed by a discussion of those studies in which two or more active interventions were compared. However, evidence relating to side-effects and continuance from studies in which active interventions were compared, has been incorporated into the relevant sections of those studies that used a placebo or an untreated control group.

Bisphosphonates

In all, 18 RCTs were identified that met the inclusion criteria and in which the effects of bisphosphonates were compared with those of placebo or no treatment in patients with osteoporosis or osteopaenia.[77,93–110] In these studies, patients in both the intervention and control groups received calcium and/or vitamin D in comparable doses. Studies in which a bisphosphonate was compared with another active intervention are discussed later (page 36).

The studies identified were relatively homogeneous in that all recruited women with primary osteoporosis or osteopaenia (details of each study are summarised in appendix 4). However, the studies varied in terms of the mean ages of patients, their durations, and the drugs and doses used (see appendix 5).

One study was designed as a 2-year, double-blind, randomised, placebo-controlled trial.[109] However, after the initial 2 years, patients were allowed to choose whether to continue the original blinded treatment or to take calcium alone. Those who completed the full 3 years, whether on blinded therapy or on calcium, were then eligible for inclusion in a 2-year, open-label, follow-up study in which all patients took intermittent cyclical etidronate,[100] and were subsequently re-randomised to receive intermittent cyclical therapy with either etidronate or placebo.[111] Only the results of the original 2-year, double-blind, RCT were used here.

In two studies of risedronate, the arm that was treated with 2.5 mg daily, was discontinued after 1 year by an amendment to the trial protocol.[100,106]

Three trials were open-label in design.[103,104,110] For further details of methodological quality, see appendix 5.

Vertebral fracture was a primary outcome measure in five trials,[98,100,106,108,109] whereas in another trial symptomatic vertebral fracture was a primary outcome measure and

morphometric vertebral fracture a secondary measure.[99] In a further eight studies, vertebral fracture was only included as secondary outcome measure,[94,96,97,101,103,104,107,110] while in a study that included vertebral fracture as an outcome measure, no differentiation between primary and secondary outcome measures was apparent.[95]

In two trials, non-vertebral fracture was a primary outcome measure.[99,100] Such fractures were a secondary outcome measure in 11 trials.[77,94,96–98,101,105,106,108–110]

In two studies, symptomatic fractures (vertebral and non-vertebral) were noted only as part of the safety monitoring[93,102] and, in one of these, only aggregated figures for vertebral and non-vertebral fracture were reported.[93]

Vertebral fractures reported in terms of the number of patients in each arm suffering such fractures were reported in 11 trials.[94,96–103,106,108,109] In one of these, only symptomatic fractures were reported[102] and, in another three, the numbers of patients for whom fracture data were available were not specified.[94,96,97] In a fourth trial, data were broken down into three periods and cumulative figures for the whole study period were not provided.[108]

In 12 studies, non-vertebral fractures were reported in terms of the numbers of patients in each arm sustaining such fractures,[93,94,97–102,105,106,108–110] and, in one, data were provided on the numbers of patients in each arm suffering hip and wrist fractures.[102]

The results in terms of vertebral fracture may not have been directly comparable in all cases: in four studies, it was specified that only fractures in previously unfractured vertebrae were included[106,108–110] and, in another, criteria were used that allowed the inclusion of both these fractures and worsening fractures in previously fractured vertebrae – but only fractures in previously normal vertebrae were reported;[100] in two studies, it was stated explicitly that further fractures in previously fractured vertebrae were included,[98,99,107] and this was implicit in a further study.[101] In six studies, it was not clear whether the criteria used would allow the inclusion of further fractures in already affected vertebrae[94–97,103,104] and, in two studies, only symptomatic vertebral fractures were reported.[93,102]

The definition of vertebral fracture also varied between studies. In two, a minimum reduction of 15% in vertebral height was required for a vertebral deformity to be termed a fracture[100,106] and, in a third study, a minimum reduction was required of either 15% in posterior height or 20% in anterior or middle height.[104] In eight studies, a minimum reduction of 20% was required[94,98,99,101,103,107–110] and, in another, the results from two trials were combined, one of which had used a definition of at least 15% and the other 25%.[97] In two studies, the definition being used was not specified.[95,96]

Results

Information was available for alendronate, etidronate, pamidronate and risedronate. At the time of censoring data collection, no publications were available for clodronate. The effects of each agent for which suitable data were provided are shown in *Table 5*. The three bisphosphonates had significant effects on vertebral fracture risk, ranging from 37% (risedronate) to 57% (etidronate). There was no significant difference in effect between treatments.

TABLE 5 *Efficacy of bisphosphonates on the RR of fracture compared with a control group*

Agent	RR (95% CI)	*p*-value
Vertebral fracture		
Alendronate	0.536 (0.439 to 0.656)	< 0.001
Etidronate	0.434 (0.236 to 0.800)	0.013
Risedronate	0.628 (0.506 to 0.779)	< 0.001
Pooled	0.569 (0.493 to 0.656)	< 0.001
Non-vertebral fracture		
Alendronate	0.825 (0.736 to 0.926)	< 0.001
Etidronate	1.011 (0.681 to 1.501)	0.96
Risedronate	0.737 (0.559 to 0.972)	0.031
Pooled	0.824 (0.745 to 0.931)	< 0.001

The effects of bisphosphonates on non-vertebral fractures were less marked than in the case of vertebral fractures (see *Table 5*). A significant risk reduction was observed with alendronate and risedronate but the magnitudes of the risk reductions were 17% and 26%, respectively. Etidronate had no apparent effect on non-vertebral fractures. In the case of alendronate, the effect on non-vertebral fracture was significantly less than on vertebral fracture. No evidence was found of a significant difference in response between bisphosphonates.

The most extensive data were available for alendronate (*Table 6*). Treatment was associated

TABLE 6 *Efficacy of alendronate on the RR of fracture compared with a control group*

Site of fracture	RR (95% CI)
All patients	
Vertebral[a]	0.544 (0.448 to 0.659)
Hip	0.611 (0.392 to 0.951)
Wrist	0.866 (0.672 to 1.115)
Other	0.862 (0.740 to 1.003)
All non-vertebral	0.825 (0.736 to 0.926)
Patients with prior fracture	
Vertebral	0.529 (0.408 to 0.687)
Hip	0.497 (0.244 to 1.013)
Wrist	0.528 (0.317 to 0.879)
Other	0.993 (0.763 to 1.293)
All non-vertebral	0.811 (0.648 to 1.013)
Patients without prior fracture	
Vertebral	0.558 (0.387 to 0.805)
Hip	0.795 (0.438 to 1.443)
Wrist	1.188 (0.869 to 1.624)
Other	0.803 (0.662 to 0.967)
All non-vertebral	0.889 (0.761 to 1.039)

[a] *All studies included in the meta-analysis used a 20% criterion for vertebral fracture*

with a significant effect on both vertebral and hip fractures. The effects on forearm and other fractures were not statistically significant. Efficacy on appendicular fractures appeared to be greater in patients with prior vertebral fracture. In the non-fracture arm of the Fracture Intervention Trial (FIT), patients were categorised according to BMD.[89] The effects on clinical fractures (including clinical vertebral fractures) and vertebral fractures assessed morphometrically were greater in patients with osteoporosis (*Table 7*) than in those with a T-score > 2.5 SD. There was, however, no significant difference. The RRs in patients with osteoporosis were comparable to our meta-analysis and, hence, these data were not used in any sensitivity analyses.

TABLE 7 *Effects of alendronate on the RR of fracture according to T-score*

T-score	RR (95% CI)
Vertebral fracture (morphometrically assessed)	
< –2.5	0.50 (0.31 to 0.82)
–2.5 to –2.0	0.54 (0.28 to 1.04)
–2.0 to 1.6	0.82 (0.33 to 2.07)
Clinical fracture (includes clinical vertebral fractures)	
< –2.5	0.64 (0.50 to 0.82)
–2.5 to –2.0	1.03 (0.77 to 1.39)
–2.0 to 1.6	0.82 (0.33 to 1.60)

In order to characterise effects more thoroughly, the available data for alendronate, etidronate and risedronate were pooled (*Table 8* and *Figures 1–5*). The pooled data suggested that bisphosphonates decreased the risk of vertebral fracture by 43%. The results are all fairly homogeneous (*Figure 1*). In one study, in which intermittent cyclical etidronate was used both alone and in combination with phosphorus,[109] the combination appeared more effective than etidronate alone. The pooled data also suggested that bisphosphonates decreased the risk of non-vertebral osteoporotic fractures by 18% (*Table 8* and *Figure 2*). The effect on vertebral fracture was significantly greater than on non-vertebral fracture.

TABLE 8 *Efficacy of bisphosphonates (pooled data) on the RR of fracture*

Site of fracture	RR (95% CI)	*p*-value
Non-vertebral fracture by site		
Hip	0.672 (0.459 to 0.983)	0.041
Forearm	0.833 (0.659 to 1.054)	0.13
Other	0.862 (0.741 to 1.003)	0.055
All non-vertebral	0.824 (0.745 to 0.913)	< 0.001
Definition of vertebral fracture		
15% deformity	0.628 (0.506 to 0.779)	< 0.001
20% deformity	0.526 (0.435 to 0.637)	< 0.001
Combined	0.571 (0.495 to 0.659)	< 0.01

Non-vertebral fractures were disaggregated whenever possible according to fracture site. Bisphosphonates had a significant effect on hip fracture risk – which was reduced by 33% (*Table 8*). In contrast, the effects on forearm and other non-vertebral sites was smaller, and the 95% CIs exceeded unity (*Figures 3–5*).

As already mentioned, the criteria for the diagnosis of incident vertebral fractures varied between studies. There were no differences in apparent efficacy according to the criteria used, although the mid-point estimate with the more stringent criteria was associated with somewhat greater efficacy (*Table 8*). This is not surprising since less stringent criteria capture more false-positives, which decrease the apparent efficacy.[112]

Very little difference was observed when results were pooled from studies with higher quality scores (*Table 9*). Results were pooled from only

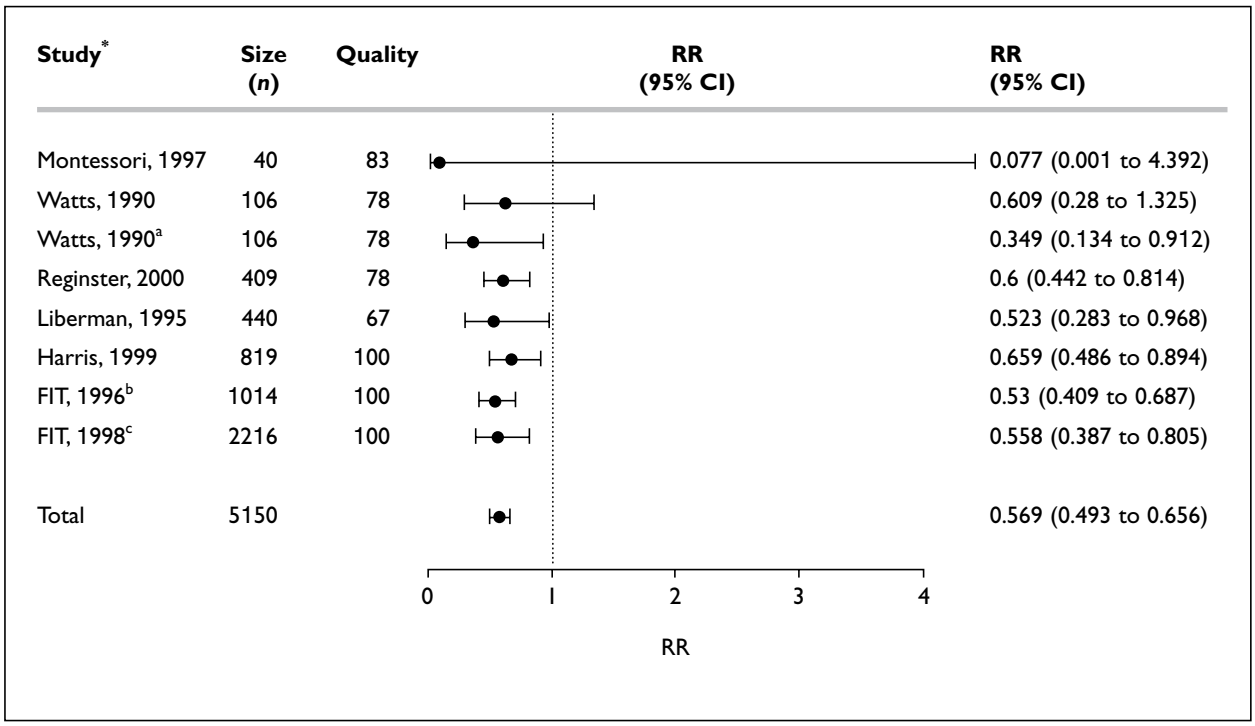

FIGURE 1 *Vertebral fracture in 5150 patients treated with bisphosphonates compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note linear scale)*

* *As listed on page 125*
[a] *Phosphate group;* [b] *fracture arm;* [c] *non-fracture arm*

those studies that scored at or above the mean quality score for all studies of bisphosphonates, that had the appropriate fracture as a primary endpoint, or whose outcome assessors were stated to be blinded to treatment allocation. When only the results from the higher-quality studies were considered, the effects of bisphosphonates in reducing the risk of hip fracture were no longer significant (see *Table 9*), an effect caused by the smaller sample size rather than by any change in point estimate.

The presence of vertebral fractures at study recruitment appeared to have an important effect. Vertebral fracture efficacy was similar in patients with or without prior vertebral fractures (*Table 10*). In contrast, the bisphosphonates decreased the risk of forearm fractures significantly – by 43% in patients with prevalent fractures – but did not reduce the risk in patients without prior vertebral fractures. The point estimate of the effect on hip fracture was also more marked in patients with prevalent vertebral fractures than in those without (38% vs 27%), although the difference was not significant.

Of those studies which presented results relating to vertebral fracture incidence in a form that could not be used in the pooled estimates, one found the RR in the aggregated treatment groups to be 0.55 compared with a control group.[95] In six, no statistically significant differences were found between treatment and control groups,[94,97,104,107,108,110] although in three of these it was suggested that there was a trend towards a lower incidence in the treatment groups[97,107,110] and, in another, there was a statement that although the difference between groups was not significant over the whole length of the 150-week trial, it became significant in weeks 60–150.[108]

In several studies, the results of non-vertebral fracture risk were presented in a form that could not be used in the pooled estimates. These results indicated that the incidence of non-vertebral fracture did not differ between treatment and control groups.[77,93,96,102]

Side-effects

The principal side-effects of oral bisphosphonates are gastrointestinal upsets. In the case of amino-bisphosphonates, these are upper gastrointestinal effects. For the non-aminobisphosphonates (clodronate and etidronate), the side-effects are confined to the lower gastrointestinal tract.

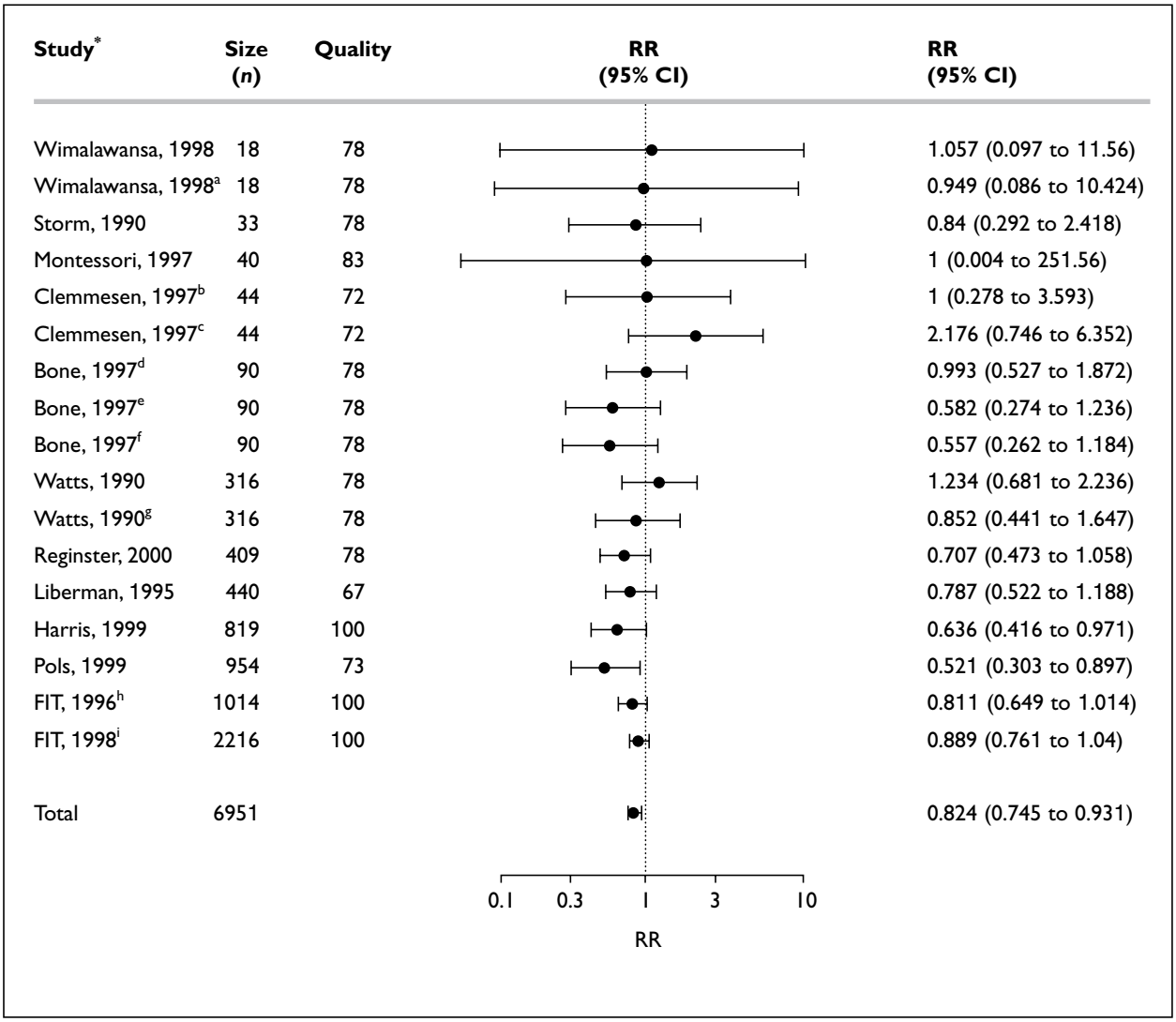

FIGURE 2 *Non-vertebral fracture in 6971 patients treated with bisphosphonates compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*

[a] *HRT group;* [b] *continuous treatment;* [c] *intermittent treatment;* [d] *1 mg dose;* [e] *2.5 mg dose;* [f] *5 mg dose;* [g] *phosphate group;* [h] *fracture arm;* [i] *non-fracture arm*

In the studies included in this review, alendronate was associated with adverse upper gastrointestinal events, which in some instances may have been associated with failure to take the drug with adequate quantities of water, or to remain upright afterwards, or both.[113] However, although a high frequency of adverse upper gastrointestinal events was noted in the RCTs of alendronate included here, it was not significantly higher in patients treated with alendronate than in those treated with placebo. It may be relevant that these studies excluded patients with gastrointestinal disease, which may account for the difference between RCT evidence and clinical practice.

In one of the etidronate trials reviewed here, no statistically significant differences in adverse effects were found between the treatment and control groups that might have been associated with etidronate (abdominal pain, diarrhoea and nausea),[109,114] although the use of phosphate as an activating agent was associated with a substantially higher reported rate of diarrhoea than in patients receiving placebo.[109] Another study found that 35% of women treated with etidronate without HRT complained of nausea but neither those treated with etidronate with HRT nor those on HRT alone complained of this.[110]

In a double-blind, placebo-controlled study of pamidronate, gastrointestinal adverse effects were found to be equally common in the pamidronate and placebo groups.[107] An open-label study, in

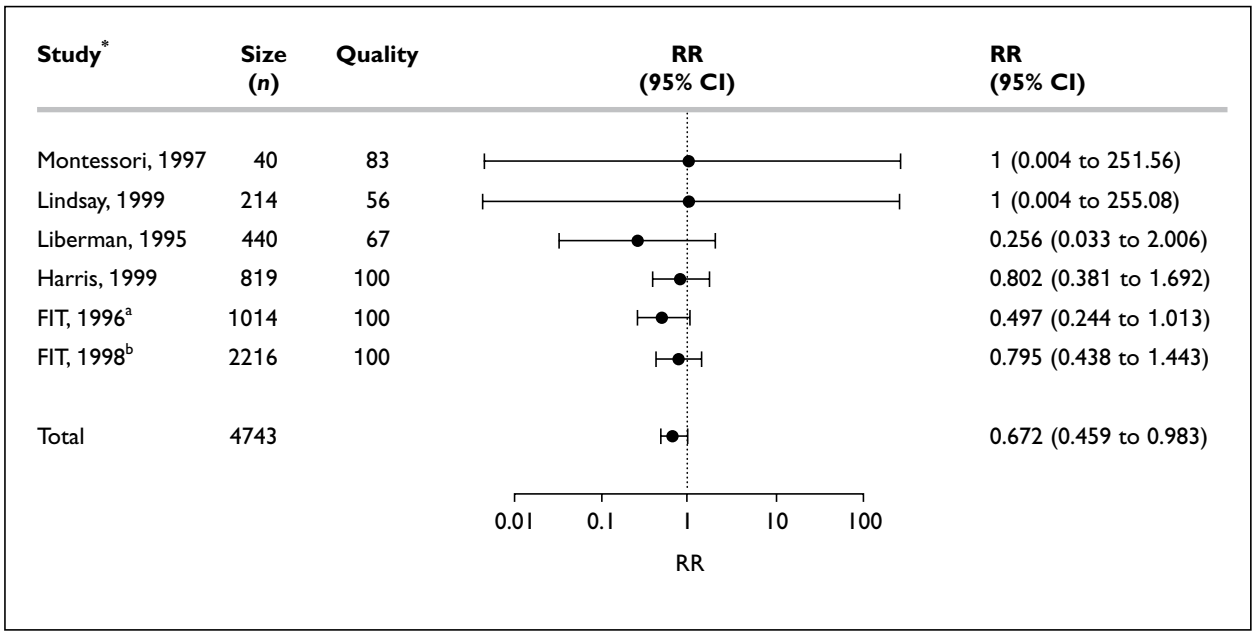

FIGURE 3 *Hip fracture in 4743 patients treated with bisphosphonates compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *Fracture arm;* [b] *non-fracture arm*

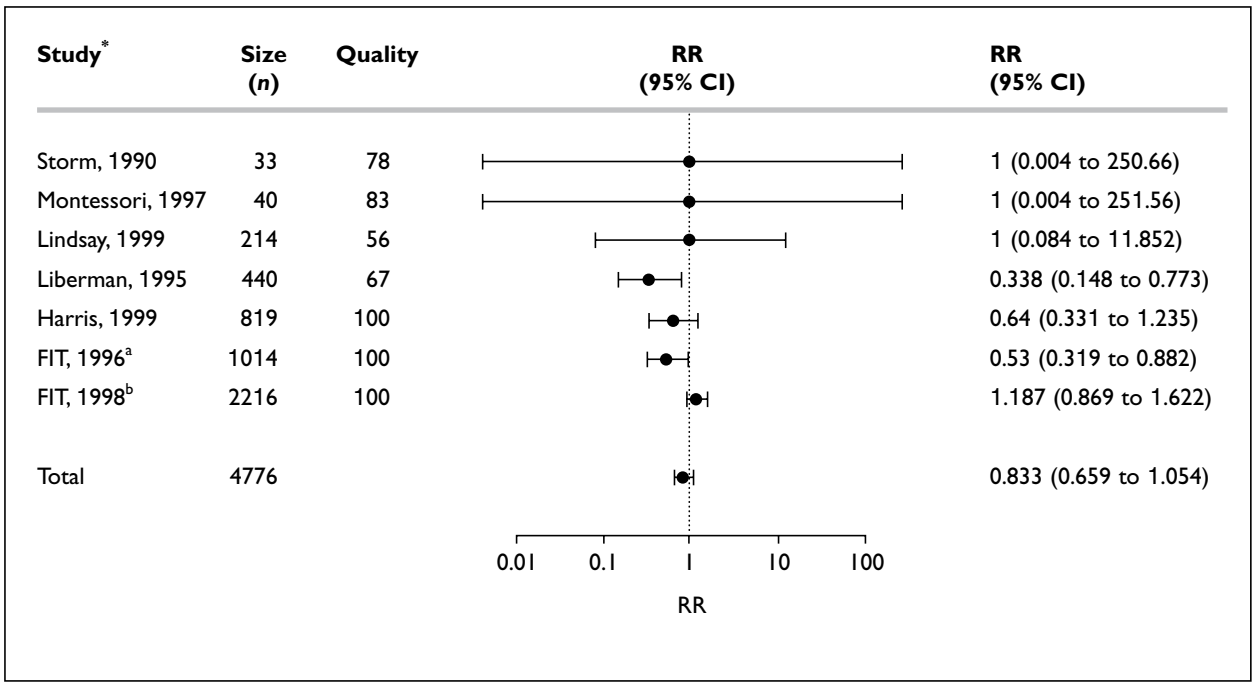

FIGURE 4 *Wrist fracture in 4776 patients treated with bisphosphonates compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *Fracture arm;* [b] *non-fracture arm*

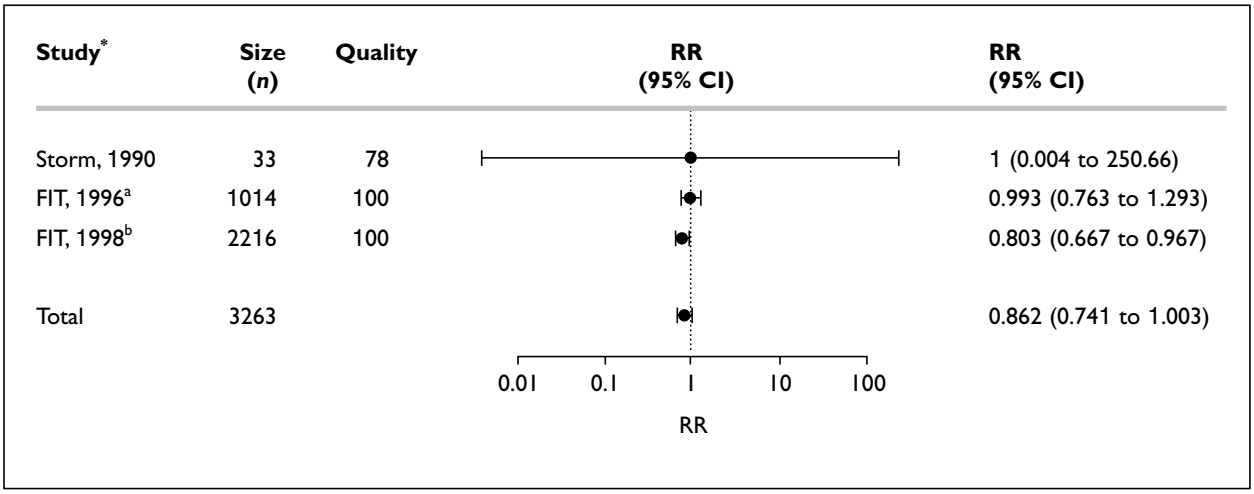

FIGURE 5 *Other non-vertebral fractures in 3262 patients treated with bisphosphonates compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *Fracture arm;* [b] *non-fracture arm*

TABLE 9 *Efficacy of bisphosphonates (pooled data) on the RR of fracture according to quality of study*

Site of fracture	RR (95% CI)	*p*-value
High-quality studies[a]		
Vertebra	0.574 (0.496 to –0.665)	< 0.01
Hip	0.694 (0.470 to 1.023)	0.065
Forearm	0.901 (0.704 to 1.152)	0.41
Other non-vertebral	0.862 (0.741 to 1.003)	0.055
All non-vertebral	0.833 (0.747 to 0.928)	< 0.001
Fracture as the primary end-point		
Vertebra	0.575 (0.490 to 0.675)	< 0.001
Non-vertebral	0.854 (0.738 to 0.989)	0.035
Assessors blinded to treatment		
Vertebra	0.561 (0.477 to 0.659)	< 0.001

[a] *Studies with a quality score at the mean or higher for bisphosphonates*

TABLE 10 *Efficacy of bisphosphonates (pooled data) on the RR of fracture according to the presence or absence of prior vertebral fracture*

Site of fracture	RR (95% CI)
Prior fracture	
Vertebra	0.575 (0.490 to 0.675)
Hip	0.620 (0.368 to 1.042)
Forearm	0.566 (0.377 to 0.848)
Other non-vertebral	No data
All non-vertebral	0.813 (0.693 to 0.954)
No prior fracture	
Vertebra	0.558 (0.387 to 0.805)
Hip	0.795 (0.438 to 1.443)
Forearm	1.187 (0.869 to 1.622)
Other non-vertebral	No data
All non-vertebral	0.889 (0.761 to 1.039

which intravenous pamidronate was compared with fluoride (see page 36), found that about 30% of patients treated with pamidronate suffered a transient fever. Fever did not affect patients treated with fluoride but, in this study, gastric intolerance was limited to those treated with fluoride.[115]

In three of the four studies of risedronate, the distribution of adverse upper gastrointestinal events was comparable in the intervention and placebo groups;[97,100,106] in the fourth study, no information on adverse events was given.[77]

Continuance

In the studies reviewed here, the percentage of patients receiving bisphosphonates who completed the protocol ranged from 58% to 95%.[94,102] In only four studies was compliance specifically discussed in terms of both the number of patients who continued to take the medication and the proportion of medication that they had taken. In the intervention arms of the FIT study, 89% of surviving patients in the fracture trial and 81% in the non-fracture trial were still taking the study medication at the final visit; in both instances, 96% of those who continued to take

the medication had taken at least 75% of their pills since their last clinic visit.[91,99] In another study,[102] over 90% of patients in the intervention arm were at least 90% compliant with the study medication. In a third study, 86% of patients overall took at least 80% of their medication. However, in this trial, only 62% of those in the intervention arm completed the protocol.[106] Compliance (as assessed by tablet count) in the intervention group of a fourth study was reported as 82%.[107] In an additional study (see page 37), in which monthly intravenous injections of pamidronate were compared with oral fluoride, 100% compliance was achieved in the pamidronate arm.[115]

A survey of compliance in 813 women treated with alendronate found that while 28.7% stated that they had discontinued treatment, prescription renewal records suggested that 30.2% had actually discontinued treatment. Gastrointestinal problems were the most common reason given for discontinuation – cited by 51.9% of women who had stopped taking the drug.[116]

Vitamin D

No RCTs were identified that both met the inclusion criteria and compared the effects of vitamin D with those of placebo or no treatment in patients with osteoporosis or osteopaenia. Trials comparing vitamin D with another active intervention are discussed later (page 36).

Vitamin D derivatives

Vitamin D derivatives are the 1-alpha hydroxylated forms of vitamin D (calcitriol, alfacalcidol and dihydrotachysterol). Calcitriol is licensed for use in the UK for the treatment of osteoporosis, whereas in some other countries the other derivatives are used. Apart from effective dose, there is no evidence that their mechanism of action differs; hence, they are considered together here.

The literature searches identified nine RCTs that met the inclusion criteria and compared the effects of vitamin D derivatives (calcitriol and alfacalcidol) with those of placebo or no treatment in patients with osteoporosis or osteopaenia.[63,64,117–123] These trials included those in which patients in both the intervention and control groups received calcium and/or vitamin D in comparable doses. Those studies in which vitamin D derivatives were compared with another active intervention are discussed later (page 36). Details of each study are summarised in appendix 4.

The trials varied in terms of their duration, the populations studied, and the drugs and doses used. Although most of the populations studied comprised women with primary osteoporosis, one study population was rheumatic disease patients with steroid-induced osteoporosis.[63]

In one paper, the data from two similar double-blind, placebo-controlled trials were combined.[118] At the end of the first year, all patients in the placebo arm crossed over to treatment. Hence, only the results of the first, placebo-controlled year are reported here. Two other studies were open-label.[64,120] For further details of methodological quality, see appendix 5.

Four trials had vertebral fracture as a primary outcome measure.[64,118,120,123] In three studies, vertebral fracture was a secondary outcome measure[63,119,133] and in two, in which vertebral fracture was included as an outcome measure, there was no apparent differentiation between primary and secondary outcome measures.[117,121]

Non-vertebral fractures were a secondary outcome measure in three studies,[63,122,123] and were mentioned in a further study that did not appear to differentiate between primary and secondary outcome measures.[121]

In only five studies were effects on vertebral fractures reported as the numbers of patients in each arm sustaining fractures.[117,119,121–123] In three trials, non-vertebral fractures were reported in terms of the numbers of patients in each arm sustaining such fractures.[117,122,123] In a further study, only the aggregated figures for vertebral and non-vertebral fractures were reported.[63]

Women with primary osteoporosis were enrolled in all the trials. The studies differed in terms of their definition of vertebral fracture. In three, a minimum reduction of 15% in vertebral height was required for a vertebral deformity to be termed a fracture,[118,119,122] whereas in four a minimum reduction of 20% was required.[64,120,121,123] In two studies the definition used was not specified.[63,117]

Results

The available data were pooled and the RRs of fracture in patients treated with vitamin D derivatives were compared with a control group. There was no evidence that vitamin D derivatives decreased the risk of either vertebral or non-vertebral fracture (*Table 11* and *Figures 6* and *7*).

TABLE 11 *Effects of vitamin D derivatives on the RR of fracture compared with a control group according to trial quality and prior vertebral fracture*

Site of fracture	RR (95% CI)	*p*-value <:
All patients		
Vertebra	0.982 (0.615 to 1.569)	0.94
Hip	0.346 (0.020 to 5.893	0.46
Wrist	2.718 (0.160 to 46.154	0.49
Other non-vertebral	No data	
All non-vertebral	1.353 (0.348 to 5.257)	0.66
Prior vertebral fracture		
Vertebra	1.003 (0.617 to 1.630)	0.99
Hip	0.980 (0.020 to 48.798)	0.99
Wrist	3.901 (0.144 to 100.00)	0.42
Other non-vertebral	No data	
All non-vertebral	1.948 (0.461 to 8.224)	0.36
High-quality studies[a]		
Vertebra	1.030 (0.620 to 1.710)	0.91
Hip	0.346 (0.020 to 5.893)	0.46
Wrist	2.718 (0.160 to 46.154)	0.49
Other non-vertebral	No data	
All non-vertebral	1.353 (0.348 to 5.257)	0.66
Fracture stated as primary end-point		
Vertebra	0.757 (0.134 to 4.286)	
Assessors blinded to treatment		
Vertebra	0.576 (0.253 to 1.314)	0.19

[a] *Studies that scored at or above the mean for quality for vitamin D derivatives*

There was no statistically significant difference between calcitriol and alfacalcidol in terms of efficacy (*Table 12*), although the central RR estimate for alfacalcidol was lower than for calcitriol, for both vertebral and non-vertebral fractures.

Those studies in which a 20% decrease in vertebral height was used to define vertebral fracture appeared to favour treatment more than those in which a 15% definition was used; however, the effect on vertebral fracture risk was not statistically significant using the 20% criterion (*Table 13*).

Little difference was seen when the analysis was confined to the higher-quality studies (see *Table 11*).

Again, little difference in efficacy was seen in those trials in which only patients with previous fractures were included (see *Table 11*). No trials were identified that included only those patients without prior fractures.

Of those studies in which results relating to vertebral fracture incidence were presented in a form that could not be used in the pooled estimates, it was reported in one that calcitriol significantly reduced vertebral fracture rates in the treatment group,[118] and in another that alfacalcidol alone lowered fracture incidence compared with untreated patients, although its efficacy seemed to be increased by the simultaneous administration of calcitonin.[64] In a third study, the occurrence of new vertebral

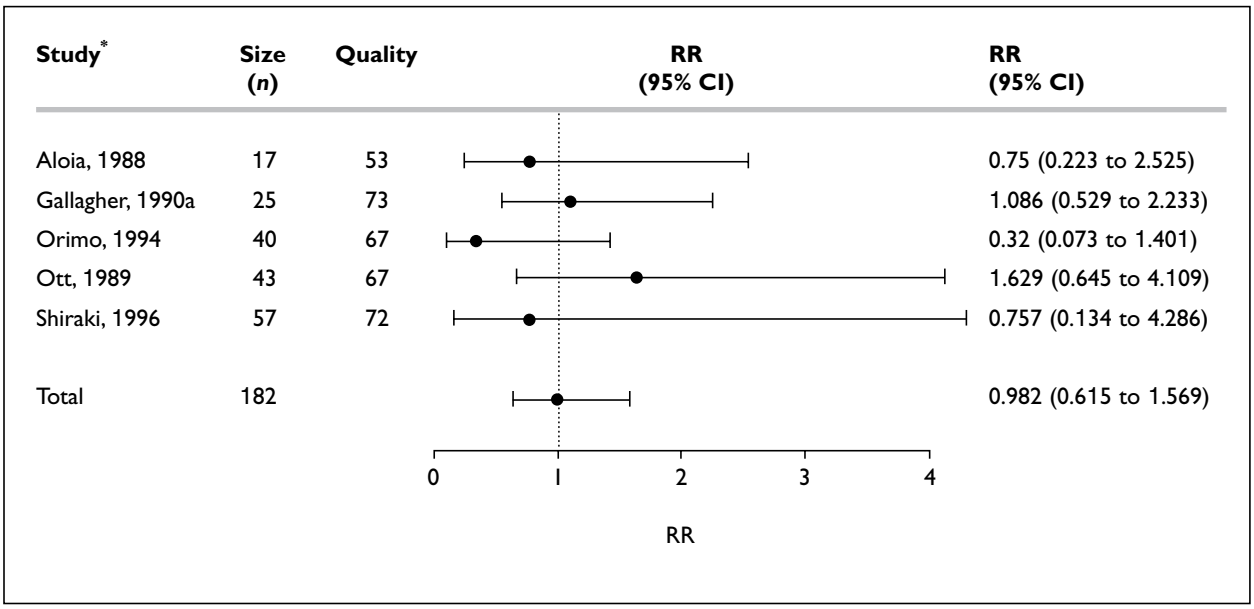

FIGURE 6 *Other non-vertebral fractures in 182 patients treated with vitamin D derivatives compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note linear scale)*

* *As listed on page 125*

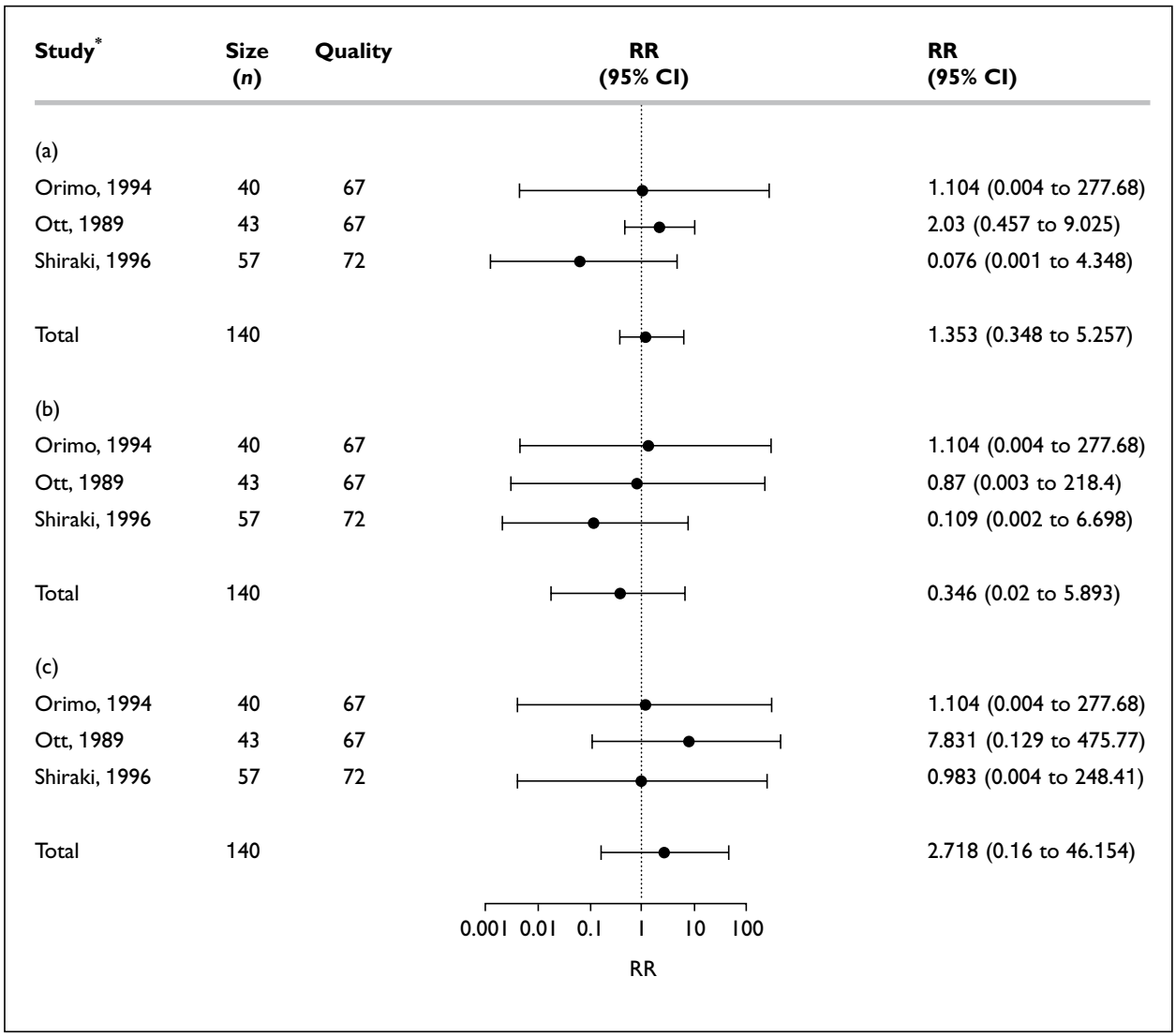

FIGURE 7 *RRs with 95% CIs of (a) non-vertebral fracture, (b) hip fracture and (c) forearm fracture in 140 patients treated with vitamin D derivatives compared with controls by mean size of treatment arm(s) (note logarithmic scale)*

* *As listed on page 125*

fractures was significantly reduced in patients treated with alfacalcidol and calcium relative to placebo.[120] Alfacalcidol alone was less effective than alfacalcidol plus calcium. Although calcium alone did not appear to be effective, this may be misleading, as the calcium group of patients was more severely osteoporotic at baseline than the other groups.

A study by Tilyard and colleagues is commonly cited as a pivotal study of efficacy for calcitriol in vertebral osteoporosis.[124] In this trial, calcium alone was compared with calcitriol alone; this is therefore considered as a comparator study (see page 36). Fracture rates were expressed as events per person-year and thus not included in this meta-analysis.

There were no data relating to non-vertebral fracture, other than those which contributed to the pooled estimates. However, in one study of calcitriol in rheumatic disease patients with steroid-induced osteoporosis, the data for vertebral and non-vertebral fractures were pooled.[19] There was no significant difference between the treatment and control groups.

As the duration of the studies was relatively short, the long-term effects of vitamin D derivatives on fracture frequency are unknown.

Side-effects

In several studies, calcitriol was found to be associated with hypercalciuria or hypercalcaemia in all or most of the patients in the intervention group.[63,117,7119,122] In most of these studies, this was not sufficiently serious to lead to withdrawal from the study but, in another study reviewed

TABLE 12 *Effects of vitamin D derivatives on the RR of fracture compared with a control group according to agent*

Site of fracture	RR (95% CI)	*p*-value
Vertebral fracture		
Calcitriol	1.152 (0.688 to 1.928)	0.59
Alfacalcidol	0.459 (0.149 to 1.414)	0.18
Hip		
Calcitriol	0.870 (0.003 to 218.40)	
Alfacalcidol	0.249 (0.009 to 6.768)	
Forearm		
Calcitriol	7.831 (0.129 to 475.77)	
Alfacalcidol	1.042 (0.021 to 51.993)	
All non-vertebral fractures		
Calcitriol	2.030 (0.457 to 9.025)	
Alfacalcidol	0.193 (0.007 to 5.068)	0.32

TABLE 13 *Effects of vitamin D derivatives on the RR of vertebral fracture compared with a control group according to the criteria used to diagnose incident vertebral fracture*

Fracture definition	RR (95% CI)	*p*-value
15%	1.266 (0.717 to 2.235)	0.42
20%	0.459 (0.149 to 1.414)	0.18
Not specified	0.750 (0.223 to 2.525)	

later (page 36), two withdrawals from the calcitriol group resulted from persistently elevated serum calcium.[124] In one study, it was considered that hypercalciuria could have been avoided by parenteral administration of the drug.[117] No adverse effects of hypercalcaemia on renal function were reported.[122] In the study reviewed later, 4% of women withdrew from the calcitriol arm of the study because of gastrointestinal symptoms.[124]

Continuance

In the studies reviewed here, the percentage of patients receiving vitamin D derivatives who completed the protocol ranged from 65% to 91%.[122,123] In only one study was compliance specifically discussed in terms of the proportion of medication taken by study completers – specified to be 97% in both intervention and control groups.[121]

Calcitonin

Calcitonin is a naturally-occurring, 32-amino acid peptide that has been used for many years in the management of osteoporosis. The agent most widely used conforms to the structure of salmon calcitonin, which has a higher potency than calcitonin from several other species, including man. Because of its polypeptide nature, calcitonin has, for many years, been given as a parenteral injection and is licensed for use on this basis in the UK. In many regions of the world, however, an intranasal formulation is also available, which post-dates the original formulations by many years. For this reason, there are no large RCTs in which antifracture frequency using the parenteral formulation has been examined by today's standards. In the development of intranasal calcitonin, the major thrust has been to demonstrate equivalence with parenteral calcitonin in terms of effects on BMD.

A major use of calcitonin has been in the management of acute crush fracture syndrome. Following acute vertebral crush fracture, patients may be immobilised and suffer pain, and the risk of refracture is high. Calcitonin, given for 1–3 months following acute vertebral crush fracture, has been shown in several RCTs to decrease morbidity, improve remobilisation and prevent immobilisation bone loss.[125–127] The mechanism for the decrease in bone pain induced by calcitonin is not known for certain but may involve the release of endogenous endorphins. The use of calcitonin in this manner is beyond the scope of this review, which focuses upon its long-term use, but a small effect on bone pain is included in the quality-adjusted life-year (QALY) estimate (see chapter 3).

A total of 15 RCTs were identified that met the inclusion criteria and in which the effects of injected or intranasal calcitonin were compared with those of placebo or no treatment in patients with osteoporosis or osteopaenia.[60,61,64,65,93,128–137] These trials include those in which patients in both the intervention and the control groups received comparable doses of calcium and/or vitamin D, and one in which the effect of adding sequential calcitonin to cyclical parathyroid hormone was studied.[131] In a further trial, intramuscular and intranasal calcitonin were compared.[132] This was a very small, 6-month trial comparing the effects of the same dose of calcitonin (100 U on alternate days) administered intramuscularly and intranasally to postmenopausal women with osteoporosis. None of the patients from either arm sustained vertebral or non-vertebral fractures.

Studies in which calcitonin was compared with other active interventions are discussed later (see page 36). Details of all the studies are summarised in appendix 4.

The reported trials varied in terms of their duration, the populations studied and the doses

used. Although in the majority, women with primary osteoporosis or osteopaenia were enrolled, in one men with established osteoporosis were enrolled, in another men and women with primary osteoporosis and, in a further study, men and women were recruited with steroid-induced osteoporosis (see appendix 5).

Nine of the 14 trials (all but one of which used injected calcitonin) were open-label,[61,64,65,128,130,135–137] although in four the outcome assessors were stated to be blinded to treatment allocation.[61,64,134,135] Only interim results were available for the Prevention of Osteoporotic Fractures (PROOF) study.[48,133,138] For further details of methodological quality, see appendix 5.

In seven trials, vertebral fracture was a primary outcome measure.[60,64,128,130,133–135] In three, vertebral fracture was a secondary outcome measure[129,131,136] and, in another, symptomatic fractures were noted only as part of the study's safety monitoring, and vertebral and non-vertebral fractures were not reported separately.[93] In three studies that included vertebral fracture as an outcome measure, there appeared to be no differentiation between primary and secondary outcome measures.[61,65,137]

The results in terms of vertebral fracture were not directly comparable in all cases. In one study it was stated that only fractures in previously unfractured vertebrae were included,[135] whereas in another three, criteria were used that explicitly allowed the inclusion as fractures of instances of further collapse in already affected vertebrae.[61,129,131]

The criterion used to define incident vertebral fracture also varied. In five studies, a minimum reduction of 20% in a vertebral height was required,[60,64,131,134,135] and was probably required in a further study.[129] In another study, a minimum reduction of 25% was required.[130] Only symptomatic fractures were recorded in one trial[93] and may have been recorded in another.[137] The definitions used in the remaining trials were not clear.[61,65,128,133,136]

In only one trial was non-vertebral fracture a primary outcome measure;[60] such fractures were a secondary outcome measure in a further five studies,[131,133–136] and were mentioned in two further studies in which there appeared to be no differentiation between primary and secondary outcome measures.[61,137] Non-vertebral fractures were not mentioned at all in five studies.[64,65,128–130]

Vertebral fracture incidence, in terms of the number of patients in each arm suffering such fractures, was reported in only three studies.[60,133,136]

Non-vertebral fracture incidence, in terms of the number of patients in each arm suffering such fractures, was reported in six studies.[60,78,131,134–136]

Results

The effects on vertebral and non-vertebral fracture risk are shown in *Table 14*. For both the intranasal and the parenteral formulation, the RR decreased substantially but with wide CIs. A significant decrease in fracture risk was confined to vertebral fracture in patients given the intranasal formulation.

TABLE 14 *Effects of calcitonin on fracture risk according to formulation used*

Mode of delivery	RR (95% CI)	*p*-value
Vertebral fracture		
Intranasal	0.611 (0.419 to 0.891)	0.011
Injected	0.077 (0.001 to 4.247)	
Non-vertebral fracture		
Intranasal	0.511 (0.139 to 1.876)	0.31
Injected	0.589 (0.200 to 1.734)	0.34

Apart from the effective dose, which varies because of differing bioavailability, there is no known difference in ultimate effect of the two formulations. For this reason the data were pooled. The combined data (*Table 15*) indicated that calcitonin reduces vertebral fracture by 40%. The magnitude of the risk reduction was similar for all non-vertebral fractures combined but the effect was not significant (*Figures 8–11*). There was no decrease in forearm fractures, with a central estimate close to unity. Thus, although no single study was large enough to demonstrate significant results, the pooled data suggested that calcitonin decreased the risk of vertebral fracture. With the exception of forearm fractures, calcitonin may also decrease appendicular fractures to a similar degree, but this has not been demonstrated to conventional levels of statistical significance.

These conclusions do not change when the pooled data are taken only from those studies that scored above the mean quality score for all studies on calcitonin, that had the relevant fracture as a primary endpoint, or that stated that the outcome assessors were blinded to study outcome (see *Table 15*).

TABLE 15 *Effects of calcitonin on fracture risk compared with a control group according to trial quality*

Type of fracture	RR (95% CI)	*p*-value <:
All data		
Vertebral	0.600 (0.412 to 0.874)	0.0077
Hip	0.681 (0.145 to 3.198)	0.61
Wrist	0.947 (0.197 to 4.565)	0.95
Other non-vertebral	0.380 (0.074 to 1.941)	
All non-vertebral	0.530 (0.224 to 1.254)	0.17
High-quality studies[a]		
Vertebral	0.611 (0.419 to 0.891)	0.011
Hip	0.634 (0.118 to 3.418)	0.60
Wrist	0.714 (0.123 to 4.146)	0.71
Other non-vertebral	0.200 (0.003 to 14.310)	
All non-vertebral	0.556 (0.225 to 1.375)	0.20
Fracture stated as primary outcome		
Vertebral	0.611 (0.419 to 0.891)	0.011
Hip	0.969 (0.040 to 23.562)	0.98
Wrist	0.969 (0.040 to 23.562)	0.98
Other non-vertebral	No data	
All non-vertebral	0.443 (0.107 to 1.836)	0.26
Assessors blinded to treatment		
Vertebral	0.611 (0.419 to 0.891)	0.011

[a] *Analysis confined to studies in which the quality score was at or above the mean for all studies with calcitonin*

No trials were identified in which patients with prior fracture were excluded. Little difference in efficacy was seen in trials in which only patients with prior fracture were included compared with all trials combined (*Table 16*).

The study in which a 20% definition of vertebral fracture was used appeared to favour treatment more than those studies in which no definition was provided; however, the result for the latter group was not statistically significant (see *Table 16*).

As the durations of the studies were relatively short, the long-term effect of calcitonin on fracture frequency is not known.

Of the studies in which the results relating to vertebral fracture incidence were presented in a form that could not be used in the pooled estimates, in three a significant reduction in the numbers of new fractures in the treatment group was found compared with a control group.[61,134,135] In a further four studies, a trend towards a lower incidence of fractures was found in patients treated with calcitonin compared with control groups, but the numbers were too small to be of any statistical significance.[65,128,130,137] In one study,[64] low-dose intermittent calcitonin failed to lower the rate of vertebral fracture compared with no treatment, although it appeared to augment the effect of alfacalcidol, and, in another study,[111] in which cyclical parathyroid hormone was compared with and without the addition of sequential calcitonin, more fractures were found in the calcitonin group than in the control group; however, this was not statistically significant. In one study,[129] fracture data were not given on the grounds that very few fractures were found in either group.

In three studies, results for non-vertebral fracture incidence were presented in a form that could not be used in the pooled estimates.[61,93,137] In all, fewer fractures were found in patients treated with calcitonin than in controls, but this was not statistically significant in any of the studies.

Side-effects

In the trials reviewed here, adverse effects were reported from both injected and intranasal calcitonin; these included hot flushes[128,131,136,139] and gastrointestinal complaints such as nausea.[61,128,131,136,139] In some cases, intranasal calcitonin also irritated the nasal mucosa,[60] and was associated with rhinitis and minor local nasal or respiratory disorders.[129]

However, in one trial it was indicated that, in women with established postmenopausal osteoporosis, intranasal calcitonin was associated with significant reductions in intensity of pain, limitation of action by pain, and analgesic use.[139] This is consistent with the findings of another study, in which calcitonin, 50–100 IU, injected either intramuscularly or subcutaneously daily or on alternate days for an average of 91.6 ± 47 days, resulted in over 90% of patients with osteoporosis (including

TABLE 16 *Effects of calcitonin on fracture risk according to the presence or absence of prior vertebral fracture and the criteria for diagnosis of incident vertebral fracture*

Type of fracture	RR (95% CI)	*p*-value
Prior vertebral fracture		
Vertebral	0.685 (0.450 to 1.029)	
Hip	0.587 (0.089 to 3.737)	
Wrist	0.943 (0.183 to 4.864)	0.66
Other non-vertebral	0.211 (0.016 to 2.854)	
All non-vertebral	0.610 (0.170 to 2.124)	0.40
Diagnostic criterion		
20%	0.308 (0.113 to 0.838)	0.021
Not specified	0.670 (0.447 to 1.004)	0.052

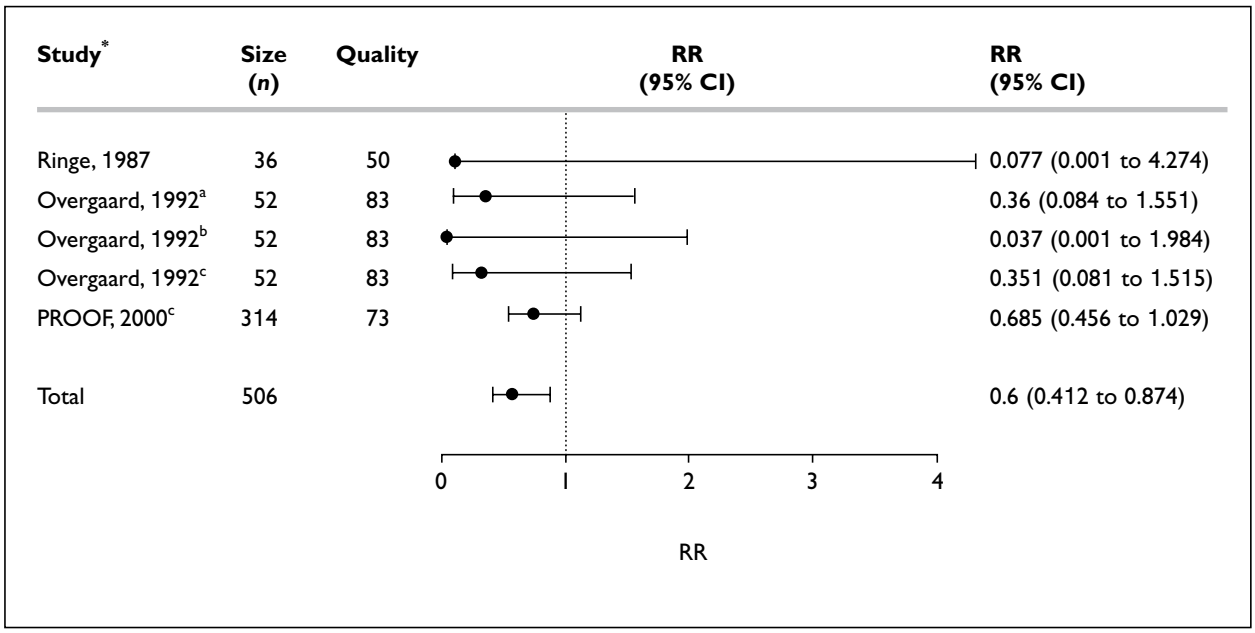

FIGURE 8 *Vertebral fracture in 506 patients treated with calcitonin compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note linear scale)*

* *As listed on page 125*
[a] *50 IU;* [b] *100 IU;* [c] *200 IU*

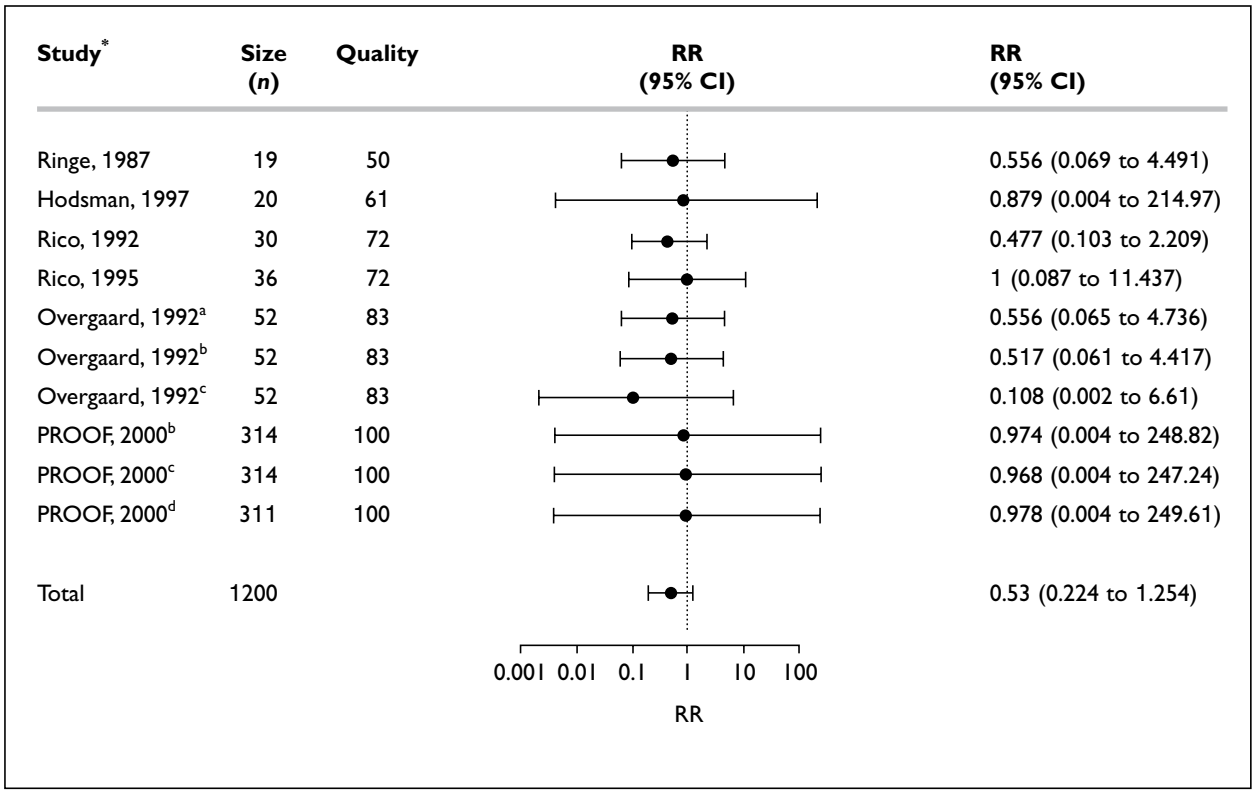

FIGURE 9 *Non-vertebral fracture in 1200 patients treated with calcitonin compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *50 IU;* [b] *100 IU;* [c] *200 IU;* [d] *400 IU*

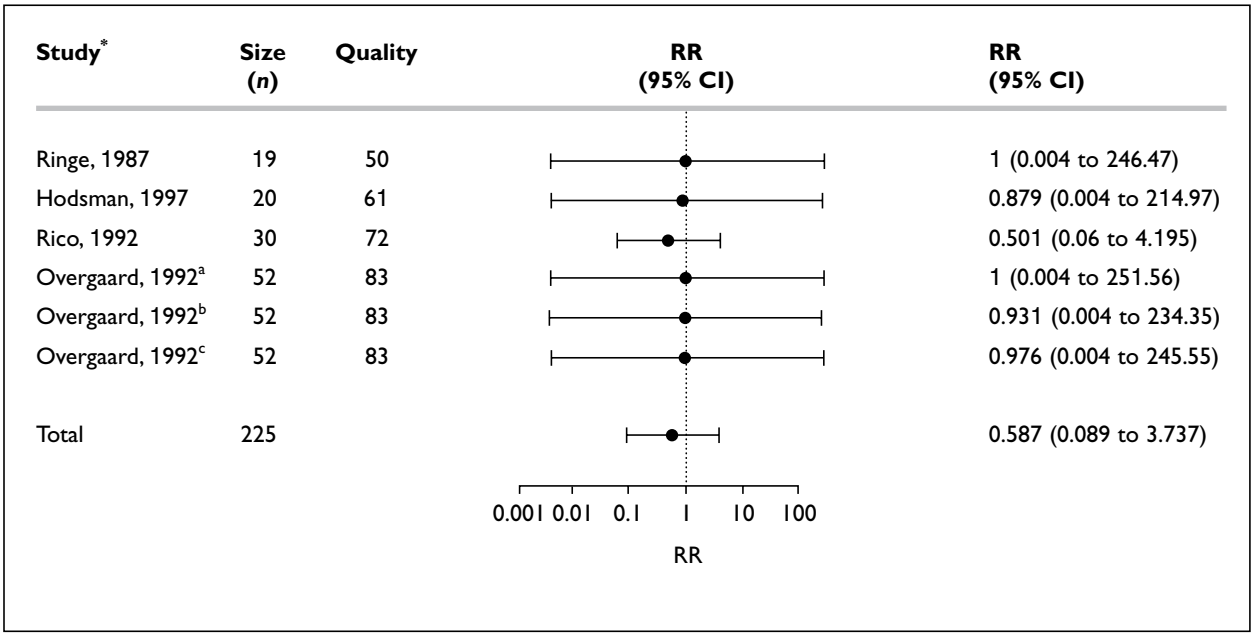

FIGURE 10 *Hip fracture in 225 patients treated with calcitonin compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *50 IU;* [b] *100 IU;* [c] *200 IU*

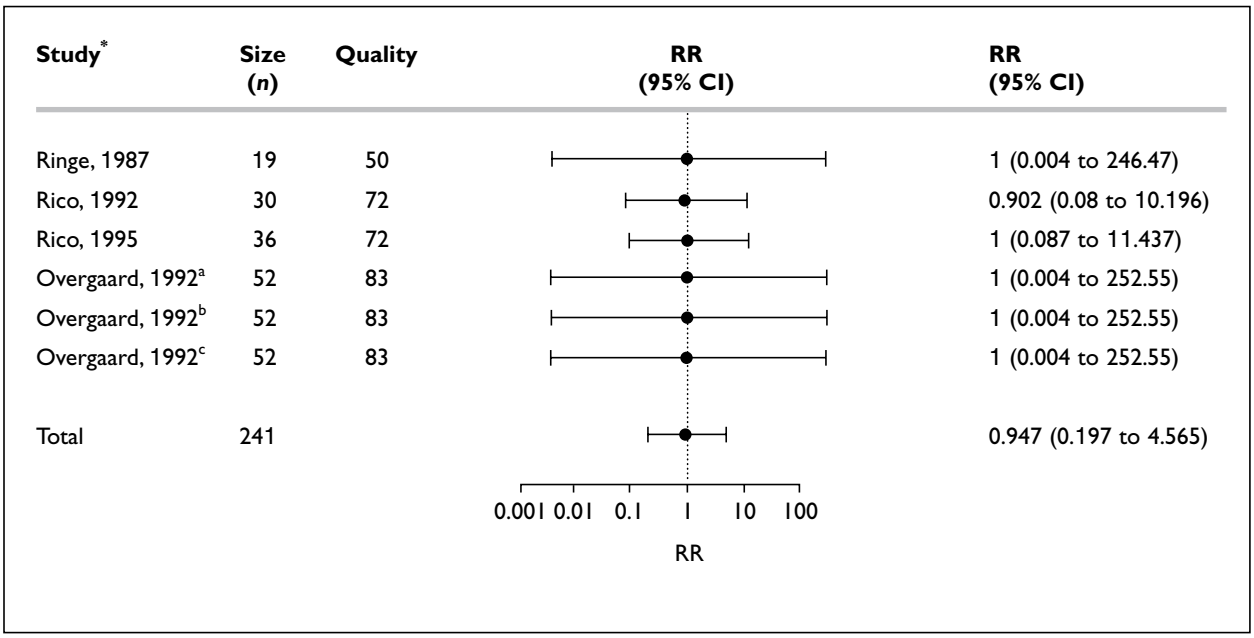

FIGURE 11 *Wrist fracture in 241 patients treated with calcitonin compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *50 IU;* [b] *100 IU;* [c] *200 IU*

post-traumatic osteoporosis) reporting significantly less pain both at rest and on moving.[140]

Continuance

In the studies reviewed here, the percentage of patients receiving injected calcitonin who completed the protocol ranged from 50% to 100%.[64,132] For intranasal calcitonin, the range was 57–84%.[130,132] Compliance was specifically discussed in only one study – 15% of patients were reported to be excluded from analysis of the results because of poor compliance.[65]

Calcium

Calcium is the most widely used agent in osteoporosis alone or in combination with other treatment modalities. Although many RCTs have examined the effects of calcium on BMD and bone fracture,[37,141] very few satisfied the entry criteria set for the purposes of this study.

Two RCTs were identified that met the inclusion criteria and in which the effects of calcium, with or without vitamin D, were compared with the effects of placebo or no treatment in patients with osteoporosis or osteopaenia. Those studies that compared calcium with another active intervention are discussed later (see page 36).

In one trial, the spine antifracture and bone-sparing efficacy of calcium was investigated in elderly women with low self-chosen calcium intakes, with and without pre-existing vertebral fractures.[142] Although participants were not selected on the basis of low BMD, the study was designed to evaluate vertebral fracture in two groups – women with and without prevalent vertebral fractures on entry. For logistical reasons, it was necessary to randomise patients to treatment without reference to their prevalent fracture status but, when separated into fracture and non-fracture groups for analysis, these subgroups were found to be similar in age and customary calcium intake. Only the data on those women with pre-existing vertebral fractures are examined here.

The second trial was a very small open-label pilot trial comparing calcium and vitamin D_2 with no treatment in postmenopausal women with established osteoporosis.[80]

For details of the durations of the studies, and the doses used, see appendix 5. Details of methodological quality are also given in appendix 5; the studies are summarised in appendix 4.

Vertebral fracture was a primary outcome measure in the first study.[142] It was also an outcome measure in the second study, in which there appeared to be no differentiation between primary and secondary outcome measures.[80]

The results in terms of vertebral fracture may not have been directly comparable between the two studies. In one,[142] it was implied that the criteria used allowed the inclusion of fractures in previously fractured vertebrae, while in the second,[80] this was not clear. Similarly, in one study the definition of vertebral fracture used required a reduction in minimum height of 20%,[142] in the other the definition used was not specified.[80]

In neither study was non-vertebral fracture an outcome measure.

Results

In only one study was vertebral fracture reported in terms of the number of patients suffering such fractures.[142] Fewer patients suffered fracture in the intervention group than in the control group (RR 0.55, 95% CI, 0.33 to 0.93), suggesting that calcium is effective in reducing the risk of vertebral fracture in elderly women with low calcium intakes and prior vertebral fractures. Although in the second study a higher fracture rate was found in the calcium group than in the untreated group, this was not statistically significant.[80]

Side-effects

No side-effects were reported by either of the trials reviewed here. However, in a trial reported later (page 36), 4% of women withdrew from the calcium arm because of gastrointestinal symptoms.[124]

Continuance

In the only study that provided this information, 71% of patients receiving calcium completed the protocol.[124] Another specifically stated that median compliance in women with low self-reported calcium intake was 64%; this was an overall figure that included groups with and without pre-existing vertebral fractures.[142]

Oestrogens

The major use of oestrogens is in the prevention of postmenopausal symptoms. Oestrogens are, however, widely recommended for the prevention of osteoporosis. Numerous RCTs have shown that oestrogens prevent bone loss[141] and, on this basis, oestrogens are approved for the prevention of osteoporosis. With the exception of women with hysterectomy, HRT is prescribed with opposed

progestogens, usually on an intermittent basis. This results in withdrawal bleeding and, for this reason, few studies exist in which fracture outcomes are examined in women well past the menopause.

Four RCTs were identified that met the inclusion criteria and in which the effects of oestrogens were compared with those of placebo or no treatment in patients with osteoporosis or osteopaenia.[79,104,110,143,144] These included trials in which patients in both the intervention and control groups received calcium and/or vitamin D in comparable doses. Trials in which oestrogens were compared with other active interventions are discussed later (page 36).

The trials reported here varied in terms of their durations and the doses used. They were relatively homogeneous in terms of their populations (see appendix 5).

Two trials were open-label.[104,110] For further details of methodological quality, see appendix 5. Fuller details of each study are presented in appendix 4.

In only one trial was vertebral fracture a primary outcome measure.[144] In two, it was a secondary outcome measure[104,110] and, in one study that included vertebral fracture as an outcome measure, there was no apparent differentiation between primary and secondary outcome measures.[143] Non-vertebral fractures were a secondary outcome measure in one study.[110]

The results, in terms of vertebral fracture, were not directly comparable in all cases: whereas one study included only fractures in previously unfractured vertebrae,[110] another used criteria which explicitly allowed the inclusion of fractures in vertebrae that were already fractured at baseline.[143] In the remainder, it was not clear whether the criteria used would allow the inclusion of further fractures in already affected vertebrae.

The criterion used to define incident vertebral fracture varied also. In one study, a minimum reduction of 15% in anterior, middle or posterior height was required,[143] in a second a minimum reduction of either 15% in posterior height or 20% in anterior or middle height was needed,[104] while in a third a minimum reduction of 25% in anterior, middle or posterior height was required, together with a reduction of 15% or more in area.[110] The definition used was not reported in one study.[144]

Results

Vertebral fractures were reported as the number of patients sustaining such fractures in only one study,[143] and non-vertebral fractures were reported in the same way in another.[110] The results from these studies are shown in *Table 17*.

TABLE 17 *Effects of oestrogen and oestrogen-like molecules on fracture risk*

Type of fracture	RR (95% CI)	*p*-value
Oestrogen		
Vertebral	0.583 (0.262 to 1.301)	
All non-vertebral	1.000 (0.068 to 14.795)	
Ipriflavone		
Vertebral	0.490 (0.186 to 1.294)	0.15
All non-vertebral	0.192 (0.003 to 13.594)	

There was no evidence that oestrogens decreased the risk of non-vertebral osteoporotic fractures. However, the numbers of patients were too small to provide conclusive data. In relation to vertebral fractures,[143] there appeared to be a trend for oestrogens to decrease the risk of fracture (RR = 0.583, 95% CI, 0.262 to 1.301).

Of the studies that did not report fracture incidence in terms of the numbers of patients suffering such fractures, in one the number of new vertebral fractures was almost identical in both the intervention and control groups[104] whereas, in another, treatment was associated with a reduction in fractures of the vertebrae and neck of femur.[144] In yet another, a statistically non-significant trend towards a lower rate of new vertebral fracture was found in the treatment group.[110]

Side-effects

Oestrogens have a number of associated extraskeletal effects, both beneficial and adverse. Beneficial effects may include reduction of menopausal symptoms such as hot flushes,[145] protection against colorectal cancer[146] and also, possibly, improved mood and protection against Alzheimer's disease.[147,148] However, oestrogens may also increase the risk of breast cancer, venous thromboembolic events, gallbladder disease and, unless opposed by progestogen, endometrial cancer.[145,149–152] It is not clear whether they offer protection against coronary heart disease (CHD).[153] The assumptions that were used for modelling are reviewed later (page 47).

In the studies reviewed here, women treated with HRT were reported to suffer from pelvic congestion in one,[104] while in another, all withdrawals in women treated with HRT (either alone or in combination with etidronate) were attributed to oestrogen-related adverse events.[110]

Continuance

In the studies reviewed here, the percentage of patients receiving HRT who completed the protocols ranged from 83%[110] to 92%.[143] In none of the studies was compliance discussed specifically.

In other studies, compliance in patients prescribed HRT for osteoporosis has been found to vary, with reports of 36% and 49% compliance after 1 year, and 61% after 6 months–1 year.[154–156]

Oestrogen-like molecules

Oestrogen-like molecules include tibolone and ipriflavone. Several RCTs have shown that tibolone reduces the rate of bone loss. It also alleviates postmenopausal symptoms but no studies of fracture outcomes have been reported with tibolone. Ipriflavone is a flavinoid that appears to have oestrogen-like activity. It is not licensed for use in the UK, although it is available in some other countries. It has, however, been used by specialist centres in the UK. Three RCTs were identified that met the inclusion criteria; in these the effects of ipriflavone were compared with those of placebo or no treatment in patients with osteoporosis or osteopaenia.[157–159] In these trials, patients in both intervention and control groups received comparable doses of calcium.

These trials were homogeneous in terms of the populations studied. They varied in terms of duration of treatment and the dose of ipriflavone used (see appendix 5). Details of methodological quality are also given in appendix 5, and summaries of each study are presented in appendix 4.

Vertebral fracture was a secondary outcome measure in all three trials and non-vertebral fracture was also an outcome measure in one trial.[159]

The studies may not have been comparable in terms of the criterion used to define incident vertebral fracture. In two studies no definition was given, while in the third a 20% reduction in vertebral height was used.[157–159]

In only two studies was vertebral fracture incidence reported in terms of the number of patients in each arm sustaining such fractures.[158,159] Non-vertebral fracture incidence was reported in only one study.[159]

Results

The results from the two studies that provided usable data in relation to vertebral fracture were pooled and the RRs of fracture in individuals treated with ipriflavone compared with a control group are presented in *Table 17* and *Figure 12*. Both of these studies scored above the mean quality score for relevant studies, both had blinded outcome assessors, and in both only patients with prior fractures were included.

The combined analysis did not demonstrate that ipriflavone reduced the risk of either vertebral or non-vertebral fractures.

In the study that presented results relating to vertebral fracture incidence in a form which could not be used in the pooled estimates,

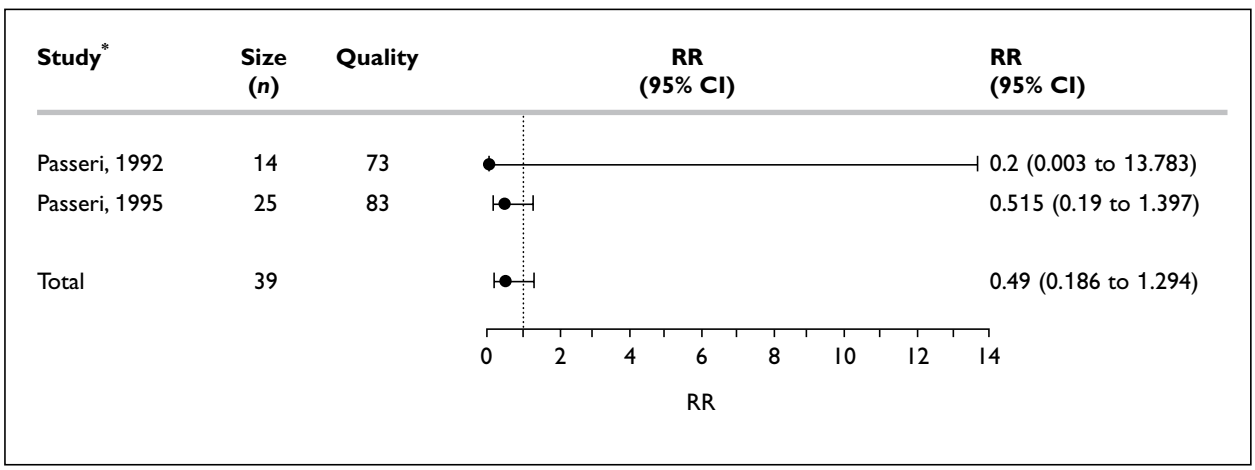

FIGURE 12 *Vertebral fracture in 39 patients treated with ipriflavone compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note linear scale)*

* *As listed on page 125*

new fractures occurred more frequently in the control group than in the treatment group.[157]

Side-effects

In a review of the safety data available from 60 studies of ipriflavone,[160] there was no statistical difference between the numbers of patients treated with ipriflavone and those in the placebo-treated control groups who suffered adverse reactions (14.5% versus 16.1%) or discontinued treatment because of adverse drug reactions (5.9% versus 5.0%). The majority (approximately 80%) of complaints in those treated with ipriflavone and placebo alike were gastrointestinal in nature (heartburn, vomiting, gastric or abdominal pain, constipation, diarrhoea). However, skin reactions (rash, itching, erythema) and, to a lesser extent, neurological (headache, depression, drowsiness), musculoskeletal (asthenia, fatigue) and cardiovascular (tachycardia) symptoms were also noted. Laboratory abnormalities included transient changes in liver and kidney function tests, and in haematological parameters, but no increase was noted in the occurrence of diseases related to such abnormalities.[160]

In two of the studies reviewed here, gastrointestinal complaints (mild gastralgia, diarrhoea) were found to be more common in patients treated with ipriflavone than in control groups,[157,158] although in the third study such symptoms were equally divided between the two groups.[159] In one study, treatment was associated with a considerable improvement in pain scores and a significant reduction in analgesic consumption.[157]

Continuance

In the study that provided the fullest information on withdrawals, 56% of patients receiving ipriflavone completed the protocol.[159] Whereas this figure is very low, it is comparable to that for the control group (54%). This was the only study in which compliance was specifically discussed in terms of the proportion of medication taken by patients who completed the study: of these, all used at least 75% of the dispensed medication during the first year of the study and 93% (93%, treatment group; 92%, control group) continued to use at least 75% of the medication for the whole 2-year period.[159]

Anabolic steroids

Many anabolic steroids have been used in the management of osteoporosis. Those still currently used include stanozolol, which can be given by mouth, and nandrolone, given by intermittent injection. Neither are currently licensed for use in the UK but are used in specialist centres.

Only one RCT was identified that met the inclusion criteria; the effects of anabolic steroids were compared with those of placebo in patients with osteoporosis or osteopaenia.[161] The agent used was stanozolol. Studies comparing anabolic steroids with other active interventions are discussed later (page 36).

Details of the duration of the trial, the population studied and the regimen used are presented in appendix 5, together with details of methodological quality. A summary of the study is presented in appendix 4.

Vertebral fracture was a secondary outcome measure in this study. However as the number of patients suffering such fractures was not reported, it was not possible to determine the RR of suffering vertebral fracture in the intervention group compared with the control group. There was no statistically significant difference between the two groups in terms of numbers of fractures.

Side-effects

The side-effects of stanozolol include derangement of liver function tests and fluid retention.[19] Androgenic side-effects are comparatively rare. Nevertheless, in the trial included here,[161] 22% of patients receiving stanozolol (and none in the control group) complained of hoarseness, while 30% complained of increased facial hair compared with 9% in the control group. Virilisation is the side-effect most commonly encountered in women treated with nandrolone decanoate, with reported mean incidences of vocal changes in up to 38% of patients and hirsutism in 24%.[162] However, in another study, no signs of virilisation were reported in patients receiving this treatment.[163] In a third study, voice lowering was reported in 86% of patients receiving nandrolone compared with 12% in the control group, but no instances of hirsutism were reported.[164] Although vocal changes are generally considered to be irreversible, a study of the effects of nandrolone on bone mineral content found that, in the majority of cases, these were reversible on prompt discontinuation of treatment.[165]

In one study, nandrolone improved pain and mobility significantly more than alfacalcidol.[166]

Continuance

In the only study of anabolic steroids that provided separate information on the number of completers

in the different study arms, 91% of patients receiving steroids completed the protocol.[161] No information was available relating to compliance in terms of both the number of patients who continued to take the medication and the proportion of medication that they had taken.

Fluoride

Various formulations of fluoride have been used in the management of osteoporosis since the 1930s. The interest has been in the very marked increases in cancellous bone mass and, with the exception of parathyroid hormone now under clinical development, fluoride is the sole truly anabolic agent available. Though widely used in some countries, it is not licensed for use in the UK. It is, however, used by specialist centres, and is generally reserved for those with severe vertebral disease without evidence of marked osteoporosis at appendicular sites.

In all, 11 RCTs were identified that met the inclusion criteria; in these the effects of fluorides were compared with those of placebo or no treatment in patients with osteoporosis or osteopaenia.[79,80,167–175] The trials included those in which patients from both the intervention and control arms received calcium and/or vitamin D in comparable doses; those studies in which fluoride was compared with another active intervention are discussed later (page 36). One trial, in which the comparison was of continuous versus pulsed dosing of fluoride,[73] is also discussed briefly below.

The trials reported here varied in terms of their durations, the populations studied and the doses used. Although in the majority, the studies were of postmenopausal women with osteoporosis, in one trial men and women with severe osteopaenia were studied[175] and, in another, men with early idiopathic osteoporosis.[173]

Four trials were open-label,[79,80,173,174] although in two of these the outcome assessors were stated to be blinded to treatment allocation.[173,174] For further details of methodological quality, see appendix 5. Details of the studies are presented in appendix 4.

Vertebral fracture was a primary outcome measure in six trials,[168–172,174] while in a further three trials, vertebral fracture was included only as secondary outcome measure.[167,173,175] In two trials that included vertebral fracture as an outcome measure, no differentiation between primary and secondary outcome measures was evident.[79,80] In six studies, vertebral fracture incidence was reported as the number of patients in each arm sustaining fractures.[79,168,170,171,173,174]

Non-vertebral fracture was a primary outcome measure in one trial[172] and a secondary outcome measure in five others.[168,169,171,173,174] Non-vertebral fracture incidence was reported in eight studies as the numbers of patients in each arm sustaining such fractures.[168–175]

The results in terms of vertebral fracture effects may not be directly comparable in all cases: in one study it was stated explicitly that incident fractures included fractures in already fractured vertebrae,[168] and this was implied in four further studies.[171–174] However, it was stated in one study, and implied in another, that recurrent fractures were not allowed.[169,175] In one study, separate figures were given for patients with new and recurrent fractures and, also, by specifying the numbers who were fracture-free, those who had either new or recurrent fractures.[170] In three studies, it was not clear whether the criteria used would allow the inclusion of further fractures in already affected vertebrae.[79,80,167]

The criterion used to define new vertebral fractures also varied in these studies. In two, a minimum reduction in vertebral height of 15% was required,[168,172] while in five a minimum reduction of 20% was required[169–171,173,174] and in another 25%.[175] In three studies the definition used was not specified.[79,80,167]

Results

The results from those studies providing usable data were pooled and the RR of fracture in patients treated with fluoride compared with a control group are presented in *Table 18* and *Figures 13–16*.

The pooled data indicated that fluoride reduced the risk of vertebral fracture. The results on vertebral fracture effects were relatively homogeneous but with one marked outlier[79] – a small study with poor reporting quality (*Figure 13*). In a second outlier, a new fracture was defined as a 15% reduction in vertebral height.[168] When the results were pooled from only those studies with a quality score above the mean quality score for all fluoride studies, the efficacy of fluoride in relation to vertebral fractures was enhanced (see *Table 18*). All these studies used a 20% decrease in vertebral height to define a new fracture.[170,171,173,174]

In contrast, there was no evidence that fluoride decreased the risk of non-vertebral fracture, even

TABLE 18 *Effects of fluoride on the risk of fracture compared with a control group according to trial quality*

Type of fracture	RR (95% CI)	*p*-value
All studies		
Vertebral	0.794 (0.647 to 0.973)	0.026
Hip	1.778 (0.758 to 4.170)	0.18
Wrist	0.766 (0.371 to 1.583)	0.82
Other non-vertebral	No data	
All non-vertebral	0.975 (0.782 to 1.217)	0.82
High-quality studies[a]		
Vertebral	0.350 (0.253 to 0.486)	< 0.001
Hip	1.799 (0.759 to 4.264)	0.18
Wrist	0.874 (0.271 to 2.818)	0.82
Other non-vertebral	No data	
All non-vertebral	0.940 (0.747 to 1.184)	0.60
Fracture stated as primary outcome		
Vertebral	0.347 (0.230 to 0.523)	< 0.001
All non-vertebral	1.584 (1.006 to 2.494)	
Assessment blind to treatment		
Vertebral	0.350 (0.253 to 0.487)	< 0.001

[a] *Analysis confined to studies in which the quality score was at or above the mean for all studies*

when incomplete/stress fractures that are a known side-effect were excluded from the analysis (see *Table 18* and *Figures 13–15*), and little difference was seen when results were pooled from only those studies which scored at or above the mean quality score for all studies involving fluoride.

When only the results from those studies that had vertebral fracture as a primary endpoint were used, the RR of vertebral fracture was lower than that obtained from the overall results, but higher than that obtained from the higher quality studies only (see *Table 18*). The lowest RR of all was obtained by pooling the results from those studies in which it was stated that the outcome assessors were blinded to treatment allocation. However, the RR of non-vertebral fracture was higher in the one study that had such fractures as a primary endpoint than for all studies.

Fluoride appeared to be more effective in preventing new vertebral fractures in patients without previous vertebral fractures than in those with such fractures (*Table 19*); however, the former was based on one study only, of men with early idiopathic osteoporosis.[173] There appeared to be a trend towards a greater efficacy in terms of non-vertebral fractures in patients without prior fracture but this was not statistically significant (see *Table 19*).

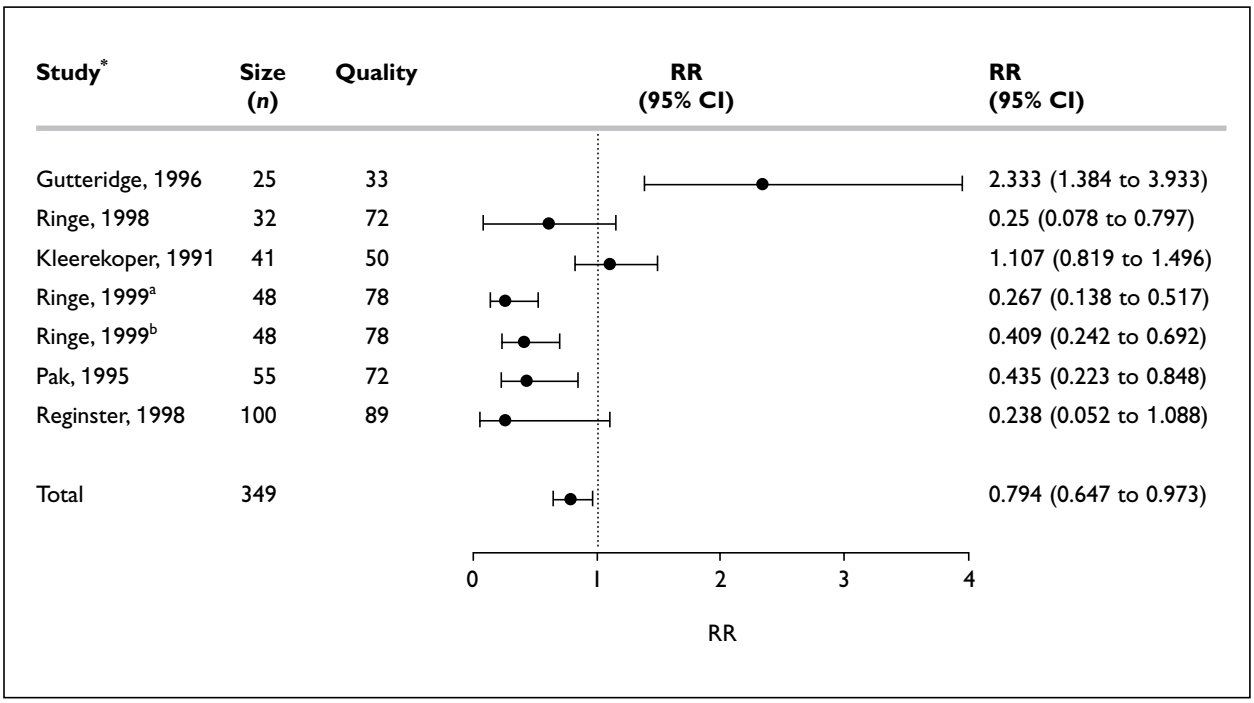

FIGURE 13 *Vertebral fracture in 349 patients treated with fluoride compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note linear scale)*

* *As listed on page 125*
[a] *Cyclic;* [b] *continuous*

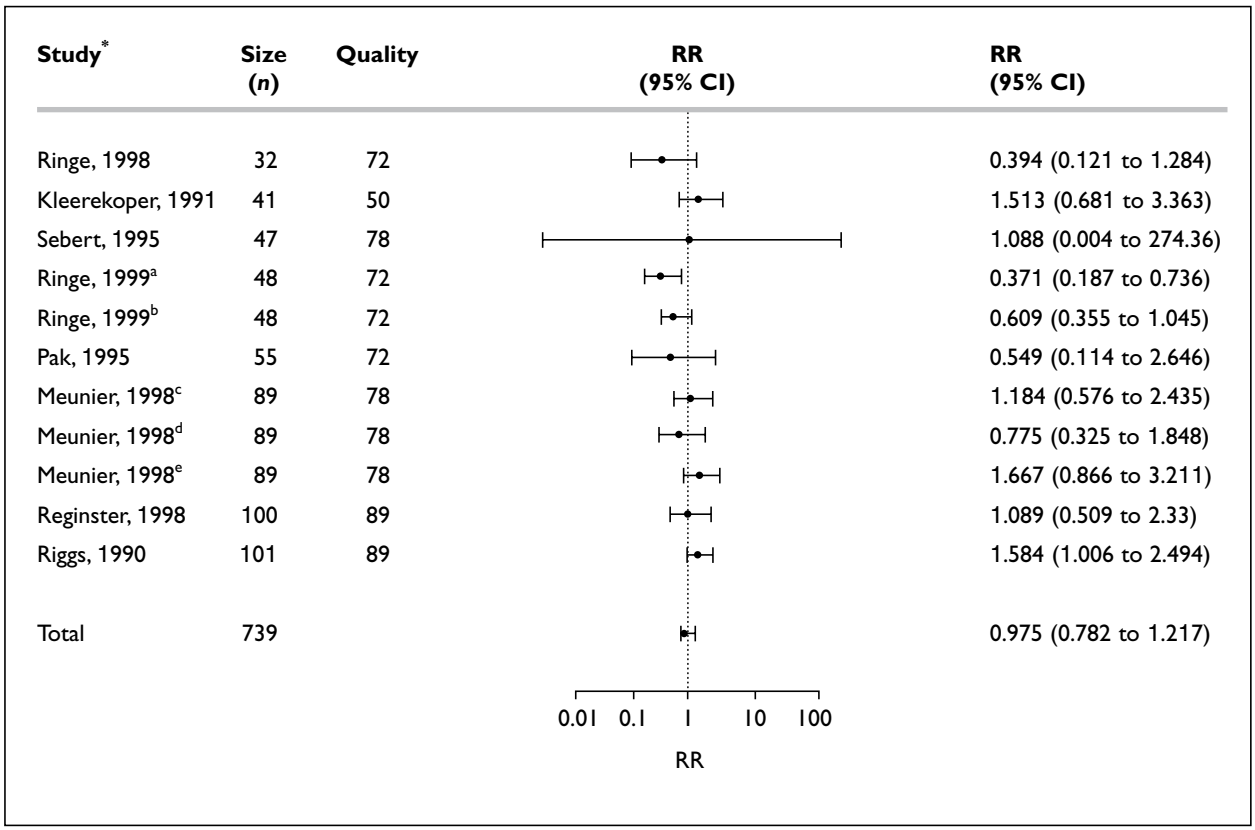

FIGURE 14 *Non-vertebral fracture in 739 patients treated with fluoride compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *Cyclic;* [b] *continuous;* [c] *50 mg;* [d] *150 mg;* [e] *200 mg*

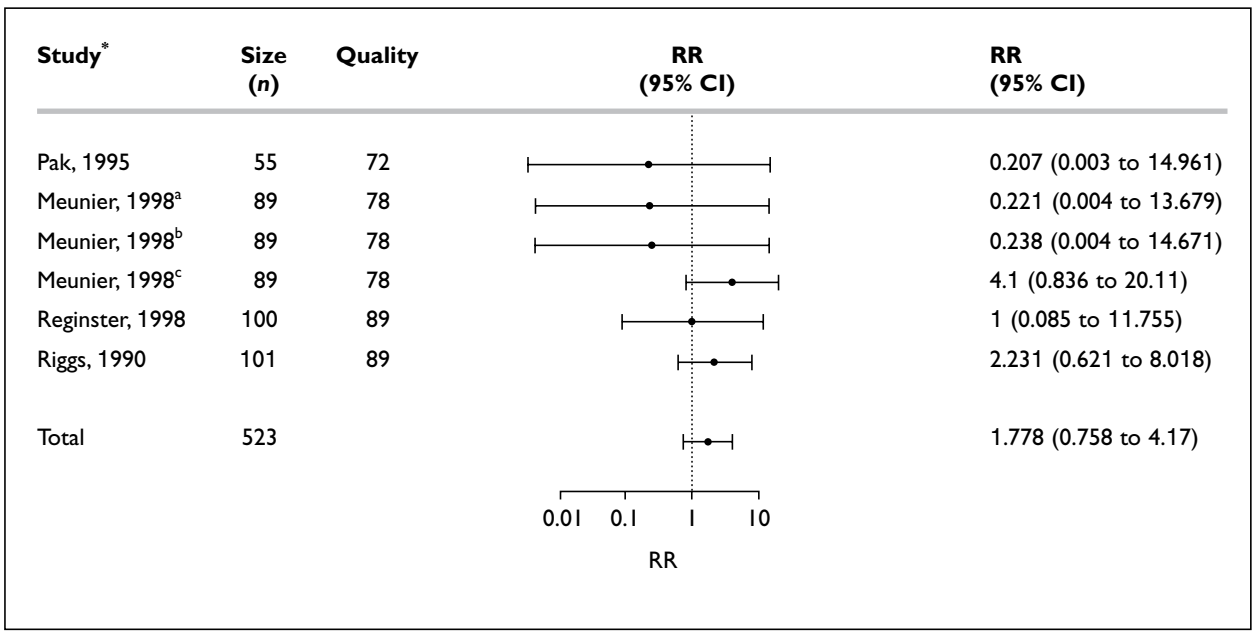

FIGURE 15 *Hip fracture in 523 patients treated with fluoride compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *50 mg;* [b] *150 mg;* [c] *200 mg*

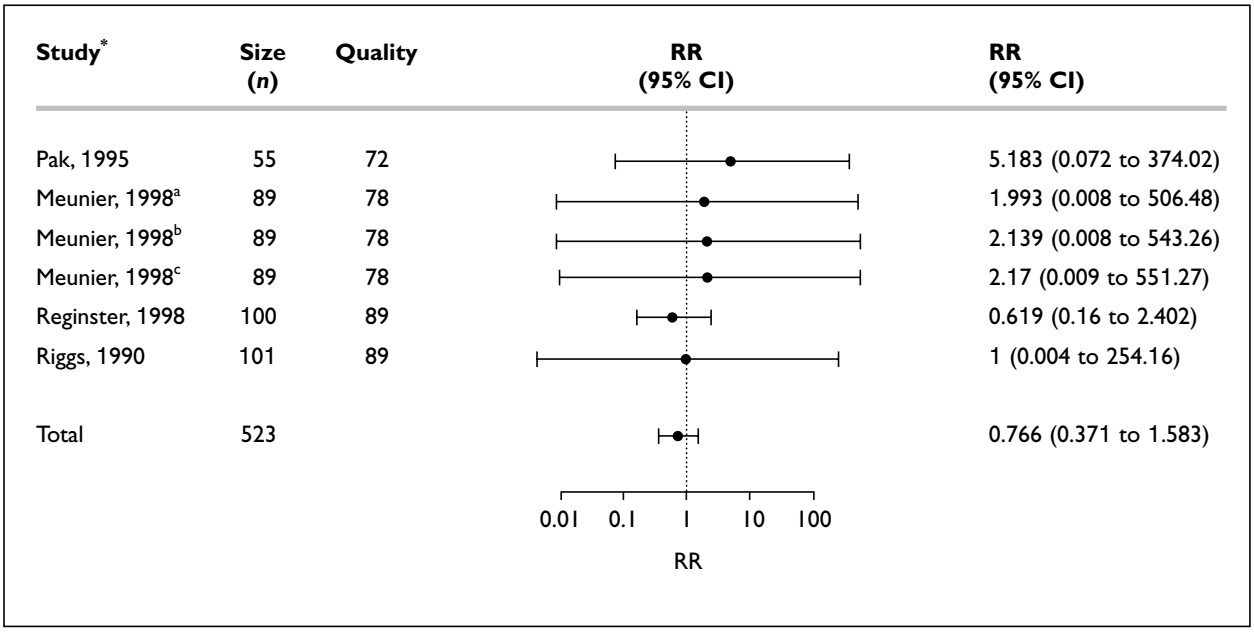

FIGURE 16 *Wrist fracture in 523 patients treated with fluoride compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *50 mg;* [b] *150 mg;* [c] *200 mg*

TABLE 19 *Effects of fluoride on fracture risk compared with a control group according to the presence or absence of prior vertebral fracture(s)*

Type of fracture	RR (95% CI)
Prior vertebral fracture	
Vertebral	0.686 (0.544 to 0.864)
Hip	1.953 (0.777 to 4.906)
Wrist	0.829 (0.347 to 1.978)
Other non-vertebral	No data
All non-vertebral	0.998 (0.788 to 1.268)
No prior fracture	
Vertebral[a]	0.250 (0.078 to 0.797)
Hip	No data
Wrist	No data
Other non-vertebral	No data
All non-vertebral	0.412 (0.130 to 1.308)

[a] *Based on only one study, in men*[173]

TABLE 20 *Effects of fluoride on vertebral fracture risk according to the criteria used to define incident vertebral fracture*

Fracture definition	RR (95% CI)	*p*-value
15%	1.107 (0.819 to 1.496)	
20%	0.350 (0.253 to 0.486)	< 0.001
Not specified	2.333 (1.384 to 3.993)	

In the studies in which a 20% decrease in vertebral height was used to define an incident vertebral fracture, greater apparent efficacy was seen than in those that used a 15% change or did not specify the criterion used (*Table 20*); however, the results for both the latter cases are not statistically significant.

In those studies in which results relating to vertebral fracture incidence were presented in a form that could not be used in the pooled estimates, no statistically significant difference in fracture incidence was seen between patients treated with fluoride and the control group.[80,167,169,172,175]

In only one study, other than those which contributed to the pooled estimate, was any information given on the incidence of non-vertebral fracture – it was indicated that approximately one-sixth of participants in the treatment group suffered stress fractures compared with none in the control group.[79]

In a 3-year, double-blind, randomised trial, the effects were compared of administering the same dose of sodium monofluorophosphate daily, either continuously or for 3 in every 6 months;[73] the mean number of new vertebral fractures increased equally in both groups.

Side-effects

Fluoride has been associated with painful lower extremity syndrome. In several of the studies

reviewed here, fluoride treatment was associated with a significantly increased incidence of lower extremity pain.[169,172–174,176] In one trial, this was associated with significantly increased incidences of osteomalacia and microfractures of the lower extremities[168] and, in another, with a statistically significant increase in incomplete fissure fractures compared with placebo (RR = 13.00; 95% CI, 3.17 to 53.33).[172] In two trials,[75,115] patients in the fluoride group withdrew from the study because of stress fractures and, in one of these, some patients also withdrew from the fluoride group because of gastrointestinal symptoms.[75]

Fluoride has also been associated with an increase in gastrointestinal complaints and several studies reported such complaints (pain, bloating, nausea or a change in bowel habit).[168,172,176] The incidence of such complaints decreased when enteric-coated tablets or capsules were used.[168]

In one study,[72] a significant reduction in back pain was found in women treated with fluoride with or without alfacalcidol but not in those treated with alfacalcidol alone.

Continuance

In the studies reviewed here, the percentage of patients receiving fluoride who completed the protocol ranged from 50% to 78%.[168,173] In only three studies was compliance specifically discussed in terms of both the numbers of patients who continued to take the medication and the proportions of medication that they had taken. In one study, of the patients who took the medication, only 50% of those in the fluoride group took more than 75% of that medication compared with 72% in the placebo group.[168] In a second study, evaluable patients in both the fluoride and the control groups took, on average, 87% of their tablets.[171] Finally, in a third study, compliance – as assessed by pill count – was 95% in the fluoride group.[170]

Thiazide diuretics

Thiazide diuretics are not licensed for use in the management of osteoporosis. Many studies have shown that thiazides reduce the rates of bone loss and, in case–control studies, their use is associated with a significant decrease in fracture risk. However, there were no RCTs that met the inclusion criteria.

SERMs

SERMs have oestrogen-like activity at skeletal sites but a spectrum of activity at extraskeletal sites that differs significantly from oestrogens. Tamoxifen is widely used in the management and prevention of breast cancer recurrence and, in postmenopausal women, has been shown to prevent bone loss and decrease fracture frequency.[141] Several other SERMs are being developed for osteoporosis and raloxifene is now available in the UK.

There were no studies with tamoxifen that were eligible for inclusion. Two RCTs were identified in which the effects of raloxifene were compared with those of placebo or no treatment in patients with osteoporosis or osteopaenia.[177,178] In these trials, both the intervention and control groups received comparable doses of calcium and vitamin D.

Both trials were relatively homogeneous in that both studied postmenopausal women with osteoporosis, although in one study all the women, and in the other only some women, had at least one vertebral fracture at entry.[177,178] The trials varied in terms of their duration and the doses of calcium and vitamin D used (see appendix 5).

Details of methodological quality are given in appendix 5, and summaries of each study are presented in appendix 4.

Vertebral fracture was a primary outcome measure in one study[177] and a secondary outcome measure in the other.[178] Non-vertebral fracture was a secondary outcome measure in both studies.

Vertebral fracture incidence was reported as the number of patients in each arm sustaining fractures in both studies but in only one study was non-vertebral fracture incidence reported as the number of patients in each arm sustaining such fractures.[177] In the other study, none of the patients had sustained a hip fracture.[178]

The results in terms of vertebral fracture effects were not directly comparable between the two studies. In one, only fractures in previously unfractured vertebrae were reported[177] whereas, in the other, the criteria used would allow the inclusion of fractures in vertebrae that were already fractured at baseline.[178] In addition, the definition of incident fracture used in one study required a minimum reduction of 20% in vertebral height,[177] while in the other a minimum reduction of 15% was required.[178]

Results

The results from both trials were pooled and the RRs of vertebral fracture in patients treated with raloxifene compared with controls are presented in *Table 21* and *Figure 17*.

TABLE 21 *Effects of raloxifene on fracture risk compared with a control group according to the presence of prior vertebral fracture at trial entry and dose used*

Type of fracture	RR (95% CI)	*p*-value
All studies		
Vertebral	0.661 (0.579 to 0.755)	< 0.001
Hip	1.141 (0.663 to 1.966)	0.63
Wrist	0.887 (0.684 to 1.151)	
Other non-vertebral	No data	
All non-vertebral	0.920 (0.792 to 1.068)	
Prior vertebral fracture		
Vertebral	0.674 (0.581 to 0.780)	< 0.001
Hip	2.784 (0.095 to 81.961)	0.55
Wrist	No data	
Other non-vertebral	No data	
All non-vertebral	No data	
No prior vertebral fracture		
Vertebral	0.575 (0.436 to 0.757)	< 0.001
All studies, 60 mg dose		
Vertebral	0.715 (0.595 to 0.868)	< 0.001
Hip	No data	
Wrist	No data	
All non-vertebral	No data	
All studies, 120 mg dose		
Vertebral	0.606 (0.449 to 0.735)	< 0.001
Other non-vertebral	No data	

Raloxifene significantly decreased the risk of vertebral fracture. The results of the study with the higher quality score were even more favourable (RR = 0.596; 95% CI, 0.516 to 0.688; $p < 0.001$);[177] however, not only did this study differ from the other in quality but it was also substantially larger, it used a 20% definition of vertebral fracture criteria and the patients enrolled were not as severely osteoporotic.

Raloxifene appeared to be as effective in preventing new vertebral fractures in women with previous vertebral fractures than in those without (see *Table 21*).

Raloxifene, 120 mg daily, appeared to be marginally but not significantly more effective than 60 mg daily in preventing vertebral fracture (see *Table 21*). No data were available to allow this comparison to be made for non-vertebral fractures.

In contrast, raloxifene has not been shown to reduce the risk of non-vertebral fracture (see *Table 21* and *Figure 18*).

In the study in which non-vertebral fracture data was not provided as the number of patients in each arm sustaining such fractures, there was no significant difference between the numbers of fractures in each group.[178]

Side-effects and compliance

Like oestrogen, raloxifene has a number of associated side-effects, some adverse and some

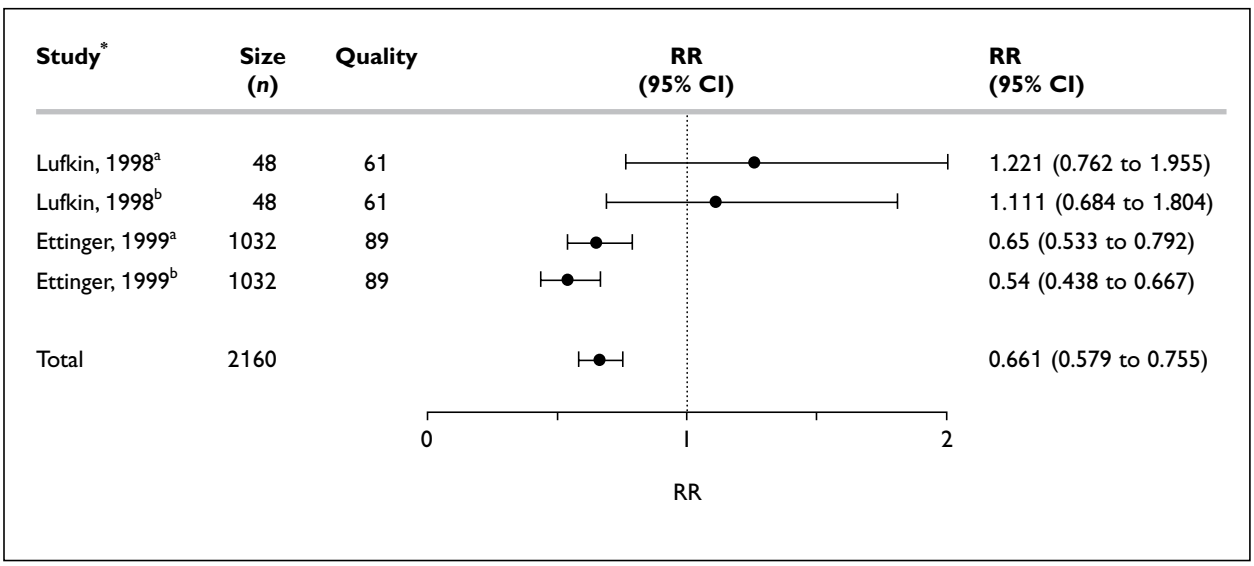

FIGURE 17 *Vertebral fracture in 2160 patients treated with raloxifene compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note linear scale)*

* *As listed on page 125*
[a] *60 mg;* [b] *120 mg*

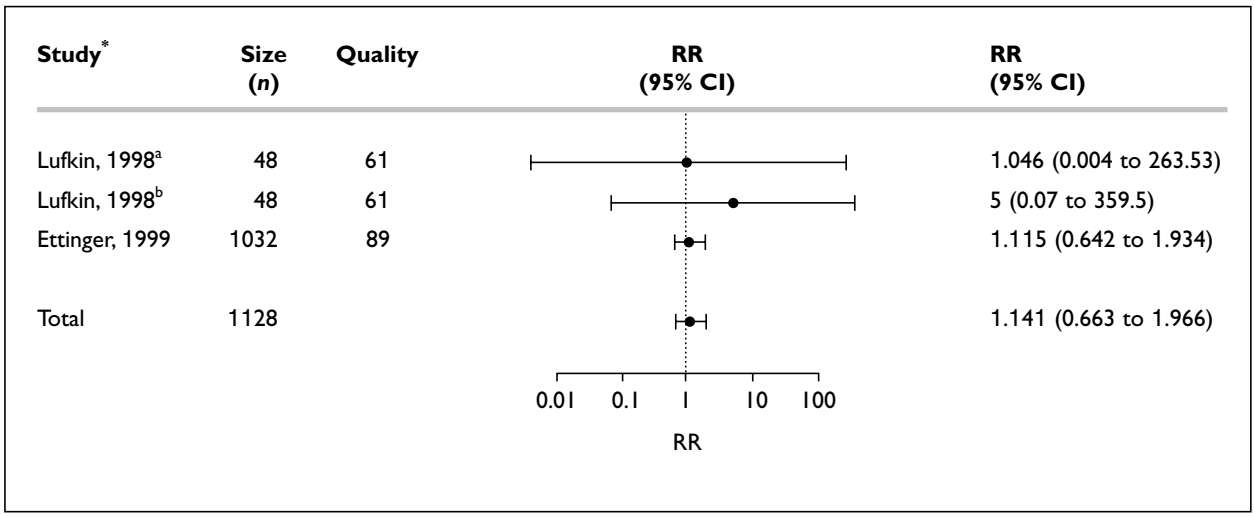

FIGURE 18 *Hip fracture in 1128 patients treated with raloxifene compared with controls by mean size of treatment arm(s): RRs with 95% CIs (note logarithmic scale)*

* *As listed on page 125*
[a] *60 mg;* [b] *120 mg*

potentially beneficial. Most seriously, it increases the risk of venous thromboembolism approximately three-fold.[177,179] In two studies, hot flushes were also found to increase in a dose-dependent manner.[177,180] In contrast, in two other studies, treatment with raloxifene was reported as not being associated with a higher incidence of hot flushes compared with placebo at doses of either 60 or 120 mg daily.[178,181]

Raloxifene also lowers fibrinogen levels, and lowers total and low-density lipoprotein cholesterol without reducing high-density lipoprotein cholesterol.[178,180–182] However, as yet there are no data available to suggest that it reduces the number of cardiovascular events.[183] In one of the trials reported here, it was suggested that raloxifene may also have a preventive role in relation to breast cancer.[177,182,184] In a multicentre study of women with osteoporosis,[182] the risk of invasive breast cancer was decreased by 76% over the 3-year study period (RR = 0.24; 95% CI, 0.13 to 0.44). For all breast cancers, RR = 0.35; 95% CI, 0.21 to 0.58. A combined analysis of the available data assessed the effect as RR = 0.42; 95% CI, 0.25 to 0.73.[184] The long-term effects are unknown and are presently being investigated in an independent trial.[182] In this study, the available data for patients with osteoporosis were used (RR = 0.35).

Unlike oestrogens, raloxifene does not cause endometrial hyperplasia;[178,181] hence, the risk of endometrial cancer is not increased.[182] It has no adverse effects on mood or cognitive function[185] or on breast tenderness.[177,180,181]

Continuance

In the studies reviewed here, the percentage of patients receiving raloxifene who completed the protocol ranged from 78% to over 90%.[48,177,178] In the only study in which there were comments on compliance, 92% of patients took more than 80% of the study medication and there were no differences in compliance between groups.[177]

Protein supplements

Only one RCT was identified that met the inclusion criteria, and in which the effects of an oral protein supplement were compared with placebo in vitamin-D-replete patients with a recent hip fracture.[186] For details of duration, population studied and regimens, see appendix 5. Details of the methodological quality are also presented in appendix 5 and details of the study are summarised in appendix 4.

Vertebral fracture was a secondary outcome measure in this study. It was reported only as the number of incident fractures and not as the number of patients suffering such fractures.

The definition of incident vertebral fracture used was a minimum reduction in vertebral height of 20%. It was implied that fractures in already fractured vertebrae would be included. Fewer fractures occurred in patients in the intervention group than in the control group but this was not statistically significant.

Associated effects

Patients who received protein supplements had significantly shorter stays in rehabilitation hospitals than those in the control group.[186]

Continuance

Of the patients in the treatment group, 73% completed the study compared with 81% in the control group.[186] No information relating to compliance was given.

Vitamin K_2

Vitamin K_2 is available for the management of osteoporosis in Japan but not in the UK. One RCT was identified that met the inclusion criteria, and in which the effects of vitamin K_2 were compared with placebo in ambulatory women with osteoporosis.[68] For details of duration, population studied and the regimen, see appendix 5. Details of methodological quality are also given in appendix 5, and a summary of the study is presented in appendix 4.

Vertebral fracture was a primary outcome measure in this study but was reported only in terms of the number of incident fractures, rather than the number of patients sustaining fractures.[68] The definition of incident vertebral fracture used in this study was a reduction in vertebral height of at least 20%. It was implied that fractures in already fractured vertebrae would be included. Non-vertebral fracture was a secondary outcome measure.

There were 13 vertebral and one non-vertebral fractures in 77 women in the intervention group, and 30 vertebral and five non-vertebral fractures in the 64 women in the control group. The combined incidence of vertebral and non-vertebral fractures was significantly lower ($p = 0.0273$) in the vitamin K_2 group than in the control group.

Side-effects and continuance

No information was given regarding either side-effects or continuance.

Exercise

In addition to the view that exercise is beneficial for peak skeletal development, exercise is commonly used in individuals with established osteoporosis either to decrease the rate of bone loss or to improve confidence and coordination, and thereby decrease the liability of falls.[19,141] This raises the question as to whether exercise might decrease the risk of fracture. One open-label RCT was identified that met the inclusion criteria.[187] In this the effect was investigated of brisk walking on BMD, the number of falls and the rate of spinal fractures in postmenopausal women who had sustained an upper limb fracture in the previous 2 years. For details of duration, population studied and regimen, see appendix 5. Details of methodological quality are also presented in appendix 5, and the trial is summarised in appendix 4.

Vertebral fracture was a secondary outcome measure of this study[187] and was reported as the group mean total number of fractures per year. The definition used was a 25% difference between anterior and posterior vertebral heights; only one fracture per vertebra was counted.

Clinical fractures formed a secondary outcome measure; these were reported only as the number of incident fractures and the rate per 100 person-years. No significant differences were reported between the intervention and control groups in relation to either radiographic or clinical fractures. During the course of the study, six fractures occurred in patients in the intervention group and four in the control group. It was not specified how many fractures were clinically diagnosed or radiographically diagnosed, although two women from each group were reported to have sustained fractures following a fall.

Associated effects

Brisk walking has been shown to be beneficial in increasing high-density lipoproteins and reducing obesity.[188,189] However, in the trial reviewed here, it was also found to be associated with a significantly increased risk of falling.[187]

Continuance

Compliance with this intervention was poor. The initial acceptability of the intervention was low: only 33% of the women who were contacted agreed to take part in the study, and only 19% of those initially contacted completed 2 years. Dropouts were said to be evenly distributed between individuals in the brisk walking group and those in the control group, who undertook upper limb exercises. Reasons for withdrawal after randomisation were given as unwillingness to continue (24%), illness (6%), death (1%), exercise-related trauma (1%) and other unspecified difficulties (9%). The study was of a relatively poor inner-city population and hence, the authors suggested, this level of compliance might not be typical of other areas.[187]

Comparisons with active treatments

A total of 25 RCTs were identified in which one active intervention was compared with another.[58,64,70,72,74–76,79,93,104.109,110,115,124,139,163,164,166,176,190–195] The trials varied in their duration, the populations studied and the regimens used (see appendix 5). Of these trials, 18 were

either stated to be open-label or there was no implication that they were blinded, for instance, by reference to the use of placebos,[64,72,74–76,79,93,104,109,110,115,124,139,164,176,190,191,193,194] although in six of them the outcome assessors had been blinded to treatment status.[64,124,164,190,191,193] For further details of their methodological quality, see appendix 5.

Vertebral fracture was a primary outcome measure in seven studies[70,75,109,124,139,166,176] and a secondary outcome measure in a further ten.[58,72,104,110,115,190,192–195] In six studies which included vertebral fracture as an outcome measure, there was no apparent differentiation between primary and secondary outcome measures.[74,76,79,163,164,191]

Non-vertebral fracture was a primary outcome measure in one study[193] and a secondary outcome measure in a further eight.[70,75,109,110,115,124,176,192] It was mentioned in two further studies that did not appear to differentiate between primary and secondary outcome measures.[74,191]

In one study, data were collected on symptomatic fractures only as part of adverse event reporting; vertebral and non-vertebral fractures were not reported separately.[93]

In 13 studies, vertebral fracture incidence was reported as the number of patients in each arm sustaining such fractures.[58,70,72,75,109,124,163,166,190–193,195] In nine studies, non-vertebral fracture incidence was reported as the number of patients in each arm sustaining fractures.[79,93,109,110,115,124,176,192,193]

In one study,[70] which was published only in abstract form, the results were presented without unmasking the two groups.

The results from those studies that provided information on the numbers of patients sustaining vertebral and non-vertebral fractures, are summarised in *Tables 22* and *23*. In the majority of studies, there was no statistically significant difference between the treatments being compared. However, cyclical etidronate, 400 mg

TABLE 22 *Comparisons with active treatments: RR of vertebral fracture from all studies providing adequate data*

Study[a]	Intervention	Comparison	RR (95% CI)
Arthur, 1990	Calcitriol + calcium	Vitamin D_2 + calcium	1.444 (0.006 to 323.97)
Ebeling, 1998	Group A[b]	Group B[b]	8.550 (1.194 to 61.229)
Falch, 1987	Calcitriol	Vitamin D_3	1.539 (0.649 to 3.650)
Fujita, 1993	Cyclical etidronate, 200 mg/day	Alfacalcidol	0.444 (0.192 to 1.027)
Fujita, 1993	Cyclical etidronate, 400 mg/day	Alfacalcidol	0.347 (0.142 to 0.847)
Geusens, 1986	Intramuscular nandrolone decanoate	Alfacalcidol	0.714 (0.325 to 1.569)
Geusens, 1986	Intramuscular nandrolone decanoate	Intravenous calcium infusions	0.682 (0.318 to 1.460)
Geusens, 1986	Alfacalcidol	Intravenous calcium infusions + placebo of alfacalcidol	0.955 (0.524 to 1.739)
Guañabens, 1996	Fluoride	Cyclical etidronate	0.816 (0.349 to 1.989)
Gutteridge, 1990b	HRT + sodium fluoride	HRT	0.508 (0.200 to 1.293)
Lems, 1997	Cyclical etidronate, sodium fluoride and calcium	Cyclical etidronate and calcium	1.826 (0.616 to 5.418)
Mamelle, 1988	Sodium fluoride, calcium and vitamin D_2	Other regimens prescribed by French physicians	39.2% versus 50.8%
Pak, 1989	Cyclical calcitriol, intermittent slow-release sodium fluoride and calcium	Intermittent slow-release sodium fluoride and calcium	2.739 (0.619 to 12.121)
Rozhinskaya, 1999	Pooled fluoride + calcium and fluoride, alfacalcidol + calcium groups	Alfacalcidol	0.909 (0.156 to 5.302)
Shiraki, 1999	Alendronate + calcium	Alfacalcidol + calcium	1.049 (0.152 to 7.219)
Watts, 1990	Etidronate and calcium	Sodium-potassium phosphate, placebo and calcium	0.938 (0.367 to 2.396)
Watts, 1990	Etidronate, phosphate and calcium	Sodium-potassium phosphate, placebo and calcium	0.592 (0.201 to 1.745)
Watts, 1990	Etidronate, phosphate and calcium	Etidronate and calcium	1.584 (0.537 to 4.669)

[a] *See list of trials meeting inclusion criteria (page 125)*
[b] *Calcitriol or calcium, allocation not specified*

TABLE 23 *Comparisons with active treatments: RR of non-vertebral fracture from all studies providing adequate data*

Study[a]	Intervention	Comparison	RR (95% CI)
Adami, 1995	Alendronate, 10 mg/day, + calcium	Intranasal calcitonin + calcium	1.102 (0.094 to 12.876)
Adami, 1995	Alendronate, 20 mg/day, + calcium	Intranasal calcitonin + calcium	1.041 (0.089 to 12.173)
Lems, 1997	Cyclical etidronate, sodium fluoride and calcium	Cyclical etidronate and calcium	1.638 (0.642 to 4.180)
Mamelle, 1988	Sodium fluoride, calcium and vitamin D_2	Other regimens prescribed by French physicians	1.019 (0.570 to 1.824)
Pak, 1989	Cyclical calcitriol, intermittent slow-release sodium fluoride and calcium	Intermittent slow-release sodium fluoride and calcium	0.508 (0.062 to 4.181)
Thiébaud, 1994	Intravenous pamidronate, calcium and vitamin D	Fluoride, 20–30 mg/day, calcium and vitamin D	0.200 (0.003 to 13.888)
Tilyard, 1992	Calcitriol	Calcium	0.496 (0.246 to 0.999)
Watts, 1990	Etidronate and calcium	Sodium-potassium phosphate, placebo and calcium	1.684 (0.873 to 3.248)
Watts, 1990	Etidronate, sodium-potassium phosphate and calcium	Sodium-potassium phosphate, placebo and calcium	1.163 (0.569 to 2.379)
Watts, 1990	Etidronate, sodium-potassium phosphate and calcium	Etidronate and calcium	0.691 (0.371 to 1.287)
Wimalawansa, 1998	Etidronate, calcium and vitamin D	HRT, calcium and vitamin D	1.057 (0.097 to 11.560)
Wimalawansa, 1998	Etidronate, HRT, calcium and vitamin D	HRT, calcium and vitamin D	0.949 (0.086 to 10.424)
Wimalawansa, 1998	Etidronate, HRT, calcium and vitamin D	Etidronate, calcium and vitamin D	0.897 (0.082 to 9.836)

[a] *See list of trials meeting inclusion criteria (page 125)*

daily, appeared to be more effective in preventing vertebral fracture than alfacalcidol, 1 µg daily,[58] and, more tantalisingly, one of the two treatments compared by Ebeling and colleagues[70] was significantly more effective than the other in preventing such fractures; however, as noted above, the two groups were not unblinded. In one study, a significant reduction in vertebral fracture incidence in the second and third years of treatment was found in the calcitriol group compared with the calcium group.[124]

In relation to vertebral fracture, of those studies that did not provide information on the number of patients sustaining vertebral fracture, no significant difference between treatment groups was found in six.[74,76,104,110,164,166] In one study, a significant reduction was found in the rate of vertebral fracture in patients treated with calcitonin compared with those treated with calcium.[139] In a second study, a statistically non-significant trend towards a lower incidence of vertebral fracture was found in patients treated with pamidronate compared with those treated with fluoride.[115] In a third study, calcitonin appeared to be more effective in preventing vertebral fracture than the other treatments used.[194] A lower incidence of vertebral deformity was found in a fourth study in patients treated with calcitonin and alfacalcidol compared with those treated with either calcitonin or alfacalcidol alone, and alfacalcidol alone appeared more effective than calcitonin alone; however, the numbers were too small to be conclusive.[64]

In one study, there was no information on the number of patients sustaining non-vertebral fracture and no significant difference between treatment groups.[191]

Chapter 3

Synthesis of data and discussion

In the previous chapter, the evidence for efficacy of a wide range of interventions was reviewed, based on the literature available from 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 hand-searching or from reference lists. It therefore seems likely that few published studies have been missed. Only two of the identified trials were excluded because of language restrictions.

The potential to examine publication bias within each therapeutic class was limited by the number of studies available. The asymmetry of the funnel plot relating to bisphosphonates suggests that a number of small studies with effect sizes distributed around the null value may remain unpublished. Because of the smaller numbers of relevant studies identified, the situation in relation to vitamin D derivatives and fluoride is less clear (see appendix 5).

The quality of evidence

As published, most of the trials had potential methodological weaknesses. A summary of the quality assessment is provided in *Table 24*.

The quality of trial reporting appears to have improved over the last 20 years, as shown when the studies are categorised by year of main publication (*Table 25*). This improvement becomes more marked when those studies are removed that are available only as abstracts, rather than as full publications.

There has also been a tendency over time for trials to become larger. In those studies whose primary publication predated 1990, the mean number of patients was 92 (range 34–466), compared with 118 (range 14–414) in those published between 1990 and 1994, and 531 (range 22–7705) in those published in or post-1995.

The efficacy of intervention

As noted above, there was some heterogeneity between studies in terms of study populations,

TABLE 24 *Summary of quality assessment according to quality criteria*

	Included RCTs *n* (%)
Was randomisation to the study groups blinded?	
1. States random but no description or quasi-randomised	66 (80)
2. Small but real chance of disclosure of assignment	10 (12)
3. Method does not allow disclosure of assignment	7 (8)
Were assessors of outcome blinded to treatment status?	
1. Not mentioned	44 (53)
2. Moderate chance of unblinding of assessors	0
3. Action taken to blind assessors, or outcomes such that bias is unlikely	39 (47)
Were the outcomes of patients who withdrew described and included in the analysis?	
1. Not mentioned or states number of withdrawals only	15 (18)
2. States numbers and reasons for withdrawal, but analysis unmodified	36 (43)
3. Primary analysis based on all cases as randomised	32 (39)
Comparability of treatment and control groups at entry	
1. Large potential for confounding or not discussed	28 (34)
2. Confounding small; mentioned but not adjusted for	12 (14)
3. Unconfounded; good comparability of groups or confounding adjusted for	43 (52)
For hip or other appendicular skeleton fracture	
0. Not applicable	34 (41)
3. X-ray confirmation of diagnosis	13 (16)
4. No confirmation of diagnosis	36 (43)
For vertebral fracture	
0. Not applicable	3 (4)
1. Inadequately described method	27 (33)
2. Radiological method: uses anterior/posterior height ratio	12 (14)
3. Radiological method: uses anterior, middle and posterior height in criteria OR reports radiologically confirmed clinical events only	41 (49)

TABLE 25 *Summary of quality assessment: mean scores*

Mean scores	Year of publication			
	1980–89	1990–94	1995–2000	All trials
All publications				
Fully blinded randomisation	1.13	1.25	1.36	1.29
Blinded assessment of outcome	1.93	1.92	1.95	1.94
Withdrawals	2.07	2.13	2.30	2.20
Comparability of groups at baseline	1.87	2.04	2.36	2.18
Confirmation of hip or other appendicular skeleton fracture	1.66	1.55	1.50	1.53
Appropriateness of method of diagnosis of vertebral fracture	2.00	1.96	2.37	2.18
Total [a]	**60%**	**61%**	**66%**	**64%**
Excluding abstracts				
Fully blinded randomisation	1.13	1.27	1.44	1.29
Blinded assessment of outcome	1.93	2.00	2.06	2.01
Withdrawals	2.07	2.23	2.42	2.29
Comparability of groups at baseline	1.87	2.09	2.61	2.30
Confirmation of hip or other appendicular skeleton fracture	1.66	1.60	1.57	1.59
Appropriateness of method of diagnosis of vertebral fracture	2.00	2.05	2.59	2.30
Total [a]	**60%**	**63%**	**71%**	**67%**

[a] *Expressed as a percentage of total possible score*

interventions, and capture of primary endpoints, including the definition of incident vertebral fracture. Where possible, sensitivity analyses were used to explore the implications of such heterogeneity.

Vertebral fracture

The data reviewed above suggested that bisphosphonates, calcitonin, fluoride, raloxifene, and possibly vitamin K_2, reduced the risk of vertebral fracture in patients with osteoporosis or osteopaenia. Calcium also appeared to be effective in patients with low calcium intakes. There was no evidence that vitamin D derivatives, oestrogen, oestrogen-like molecules, anabolic steroids, protein supplements or brisk walking reduced this risk.

The question arises whether efficacy differs in patients recruited into a study 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 in established osteoporosis. Information was available for bisphosphonate, fluoride and SERMs. For none of the treatments (*Table 26*) was there a significant difference when patients were stratified according to the presence

TABLE 26 *RRs (with 95% CIs) of vertebral fracture compared with placebo or no treatment in patients with and without prior vertebral fracture*

Intervention	RR (95% CI)		
	All patients	Prior fracture	No prior fracture
Vertebral fracture			
Bisphosphonates	0.569 (0.493 to 0.656)	0.575 (0.490 to 0.675)	0.558 (0.387 to 0.805)
Fluoride	0.794 (0.647 to 0.973)	0.686 (0.544 to 0.864)	0.250 (0.078 to 0.797)
SERMs	0.661 (0.579 to 0.755)	0.674 (0.581 to 0.780)	0.575 (0.436 to 0.757)
Non-vertebral fracture			
Bisphosphonates	0.824 (0.745 to 0.913)	0.813 (0.693 to 0.954)	0.889 (0.761 to 1.039)
Fluoride	0.975 (0.782 to 1.217)	0.998 (0.788 to 1.268)	0.412 (0.130 to 1.308)
SERMs	0.920 (0.792 to 1.068)	No data	No data

or absence of prevalent vertebral fractures. A trend was observed in the case of fluoride but this did not reach statistical significance. It would therefore appear appropriate to use information based on all patients eligible for study.

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.[112] For example, if in biological reality, ten fractures occurred in the placebo arm and five in the treatment arm, this would give a 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 power of a study by reducing the number of false-positives.[186] In this review, studies that used a 20% definition produced results more favourable to the intervention than those which used a 15% definition. The available data are summarised in *Table 27*. No comparative data were available for oestrogens (all 15% criteria) or calcium (all 20% criteria).

Non-vertebral fracture

Bisphosphonates were the only intervention that was demonstrated by the meta-analyses reported above to reduce the risk of non-vertebral fracture generally in patients with osteoporosis or osteopaenia. However, no intervention has been demonstrated to protect against non-vertebral fracture in subjects without prior fracture (see *Table 26*).

When only the hip fracture data were taken into account, bisphosphonates were again the only intervention that was demonstrated by the meta-analyses reported above to reduce the risk of such fracture generally in patients with osteoporosis or osteopaenia. However, if these results are subdivided according to an individual's fracture status, bisphosphonates were not shown to have a significant effect in reducing the risk of hip fracture even in those with prior fracture (see *Table 10*). This is probably due to the decrease in power of the analysis, since there was little difference in the control group estimate between the combined and disaggregated analysis.

Duration of study

There is growing awareness that the efficacy of interventions with time may be non-linear. If so, this has important implications for modelling when the modelling period exceeds the duration available from RCTs. The available information, shown in *Table 28,* suggested that transients could occur – in the sense that mid-point estimates of efficacy appear to be less favourable the longer the duration of study, for both vertebral and non-vertebral fractures. In most instances, it was not possible to consider year-by-year effects. Were this to show a waning of treatment effect with time, it would have important implications for health economics modelling, in that caution would be needed when modelling treatment duration for longer than the duration of the RCTs.

Comparison of treatments

The midpoint estimates for efficacy are summarised in *Table 29*. For the purposes of vertebral fracture frequency, diagnostic criteria were used that included a 20% decrease in vertebral height to define an incident fracture where available. For forearm fracture, estimates were used when available (e.g. bisphosphonates). In the absence of data, and for humeral fracture, it was assumed that efficacy would be equivalent to our estimates of efficacy for non-vertebral fractures. When the central estimate of efficacy was markedly affected by quality, high-quality studies were used in

TABLE 27 *Efficacy of interventions according to the criteria used to define incident vertebral fractures*

Intervention	RR (95% CI)	
	15% decrease in vertebral height	20% decrease in vertebral height
Bisphosphonates	0.628 (0.506 to 0.779)	0.526 (0.435 to 0.637)
Vitamin D derivatives	1.266 (0.717 to 2.235)	0.459 (0.149 to 1.414)
Calcitonin	0.670 (0.477 to 1.004)[a]	0.308 (0.133 to 0.838)
Fluoride	1.107 (0.819 to 1.496)	0.350 (0.253 to 0.486)
Raloxifene	1.166 (0.832 to 1.635)	0.596 (0.516 to 0.688)

[a] *Criteria not specified*

TABLE 28 *RR of vertebral and non-vertebral fracture in intervention compared with control arm, according to duration of study (or, when data available, by year within study)*

	RR (95% CI)		
Length of study	**1 year**	**2 years**	**Over 2 years**
Vertebral fracture			
Bisphosphonates	No data	0.481 (0.260 to 0.888)	0.571 (0.495 to 0.659)
Vitamin D derivatives	0.347 (0.086 to 1.403)	1.113 (0.680 to 1.824)	No data
Calcitonin	0.077 (0.001 to 4.274)[a]	0.308 (0.113 to 0.838)	0.685 (0.456 to 1.029)
Oestrogen-like molecules	0.200 (0.003 to 13.783)	0.515 (0.190 to 1.397)	No data
Fluoride	0.540 (0.273 to 1.070)	No data	0.653 (0.524 to 0.816)
SERMs	1.166 (0.832 to 1.635)	No data	0.596 (0.516 to0.688)
Non-vertebral fracture			
Bisphosphonates	0.518 (0.300 to 0.894)	0.915 (0.688 to 1.216)	0.827 (0.739 to 0.924)
Vitamin D derivatives	1.104 (0.004 to 277.68)	1.371 (0.338 to 5.559)	No data
Calcitonin	0.556 (0.069 to 4.491)[a]	0.525 (0.204 to 1.350)	1.062 (0.043 to 26.059
Oestrogen-like molecules	No data	No data	No data
Fluoride	No data	1.234 (0.809 to 1.883)	0.892 (0.686 to 1.161)
SERMs	No data	No data	0.920 (0.792 to 1.068)

[a] *Data derived from 6-month study in subjects with steroid-induced osteoporosis*

TABLE 29 *Comparative effects of different agents to reduce fracture risk*

Intervention	**Site of fracture**			
	Vertebra[a]	**Hip**	**Forearm**	**Humerus**[b]
Alendronate	0.544	0.611	0.866[c]	0.825
Bisphosphonates	0.526	0.672	0.833	0.824
Calcium[d]	0.55	–	–	–
Vitamin D derivatives[e]	0.459[c]	0.249[c]	1.042[c]	0.193[c]
Calcitonin	0.308	0.681[c]	0.947[c]	0.530[c]
Fluoride	0.350	1.778[c]	0.776[c]	0.975[c]
Oestrogen	0.583[cdf]	–	–	–
SERMs[d]	0.596	1.141[c]	0.887[c]	0.920[c]

[a] *Assessed as 20% decrease in vertebral height (see* Table 27*)*
[b] *Assumed to be equivalent to non-vertebral fracture (see* Table 25*)*
[c] *Confidence estimate crosses unity*
[d] *Single study*
[e] *For alfacalcidol alone*
[f] *Criterion for vertebral fracture = 15%*

sensitivity analyses (for forearm fractures, in the case of bisphosphonates). Estimates of forearm and humeral fractures are included since they are incorporated into the health economics model.

It was evident that bisphosphonates, calcitonin, calcium, fluoride and SERMs all significantly decreased vertebral fracture frequency. Although the risk estimate for vitamin D derivatives was quantitatively similar, the CIs cross unity. With respect to hip fracture, significant effects were seen only with the bisphosphonates, although the central point estimates for vitamin D derivatives and for calcitonin were similar but not significant. Neither fluoride nor SERMs appeared to confer protection against hip fracture. Bisphosphonates were the only agent that significantly decreased appendicular fractures.

Onset and offset of action

In this review, it was assumed that the endpoint estimate of efficacy derived from RCTs would apply

to the 5-year treatment interval to be used for health economics modelling. As mentioned earlier, a longer time frame would provide a less secure basis since, for some treatments, transients in efficacy are found. Our own analysis suggested that vertebral fracture efficacy is more marked in the early years of treatment compared with later effects in the relevant RCTs. A notable exception may occur in the case of oestrogens and hip fracture risk. In a population-based, case–control study of oestrogen use, each year of use was associated with a risk of decrease of 6% (95% CI, 3 to 9).[197]

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.[44] A great deal of uncertainty surrounds the offset of therapeutic effect once treatment has stopped. Relatively rapid offset of effects has been observed with calcium, calcitonins and vitamin D metabolites. In the case of calcium supplements and vitamin D derivatives, prospective studies of the offset time have shown that bone mass at 2–3 years after treatment is the same as that in untreated individuals.[123,198,199] Such data suggest that no further gains can be expected from treatments that had been stopped 3 years earlier.

In contrast, it is a widely held view that no catch-up loss of bone occurs when treatment with oestrogens is stopped. The results of one study suggested a catch-up loss over a period of 2–3 years[200] but the results of another prospective randomised study suggested otherwise.[201] In the latter study, patients were followed for a 12-year period. One group received no treatment, another received HRT continuously and a third group received HRT for 5 years, followed by 7 years of no treatment. In the latter group, the value of BMD lay between that of the other two groups, at a value consistent with no accelerated bone loss or an offset time equal to infinity.

Nevertheless, a number of epidemiological studies have suggested that a slow catch-up of bone loss occurs over 15–20 years after stopping treatment with oestrogens or oestrogen-like agents, so that by the age of 80 years, the effect of a treatment for 5 or 10 years at the age of 50 years has all but disappeared. The evidence is derived from epidemiological studies of BMD as well as hip fracture rates.[55,197,202–205] In a recent population case–control study, use of oestrogens within the last 12 months was associated with a 62% decrease in hip fracture risk (RR = 0.38; 95% CI, 0.26 to 0.56). In individuals who had taken HRT 13–60 months previously, the risk reduction was 48% (RR = 0.52; 95% CI, 0.26 to 1.04). Use of HRT more than 5 years previously was associated with a 25% risk reduction (RR = 0.75; 95% CI, 0.52 to 1.07).[197]

In the case of the bisphosphonates, the offset of effect has not been fully characterised. 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 over 3 years, after stopping treatment with alendronate for 3 years, were comparable to those in placebo-treated patients[206] but the time course of change was not reported. A sustained effect of bisphosphonates was observed following a short course of alendronate in the treatment of osteoporosis.[207,208] Recent studies of the use of pamidronate and alendronate have suggested, however, that bone loss may eventually resume at an accelerated rate.[209,210] Similar findings have been reported for risedronate.[211] The offset times for anabolic regimens have not been characterised but bone loss occurred shortly after stopping treatment with fluoride.[212] Bone mass appeared to be preserved in oestrogen-treated women after stopping treatment with parathyroid hormone but continuing their HRT (R Lindsay, Helen Hayes Hospital, New York; personal communication, 1998). In contrast, offset times appeared to be shorter after stopping treatment with calcium and with alfacalcidol.[44,198]

An important impact of offset on therapeutic effect had been previously noted on fractures prevented.[43,214,215] A recent study showed the profound impact of different assumptions concerning offset time on cost-effectiveness.[44]

Several health economics analyses have examined the effects of intervention once treatment is stopped; most related to the effects of oestrogens.[216] Weinstein assumed that oestrogens decreased fracture risk to 0.33 and, after stopping treatment, the RR increased to 0.5 for a duration that equalled the exposure time of the active treatment.[7] Similar assumptions have been made by other investigators.[2,217,218] Others assumed a slow offset of effect so that a 10-year treatment at the menopause had a slow offset of effect up to the age of 75 years or more.[219,220] The most optimistic scenario assumed an infinite offset time.[10]

In this study, an offset time of 5 years has conservatively been assumed, except for calcium

TABLE 30 *Adverse effects most commonly reported in the reviewed studies*

Intervention	Adverse effect
Bisphosphonates	Upper gastrointestinal events
Vitamin D derivatives	Hypercalciuria; hypercalcaemia
Calcitonin (injected)	Hot flushes; gastrointestinal complaints
Calcitonin (intranasal)	Hot flushes; gastrointestinal complaints; rhinitis and minor local nasal or respiratory disorders
Calcium	Gastrointestinal symptoms
Oestrogen	Pelvic congestion; unspecified oestrogen-related adverse events
Oestrogen-like molecules	Gastrointestinal complaints
Anabolic steroids	Hoarseness; voice lowering; increased facial hair
Fluoride	Lower extremity pain, bone lesions and incomplete fractures; osteomalacia; gastrointestinal complaints
SERMs	Venous thromboembolism; hot flushes
Protein supplements	None
Vitamin K_2	No information
Exercise	Falls

and calcitonin for which an offset time of 3 years was assumed. An increased offset time of 10 years was examined in a sensitivity analysis.

Side-effects

As noted above, the various interventions reviewed here varied in their associated effects, both adverse and, in some cases, beneficial. The adverse effects most commonly found in association with the different interventions are set out in *Table 30*. It is important to recognise that a systematic review of side-effects has not been undertaken and only studies eligible for the meta-analysis have been reviewed.

In addition, other studies have shown that oestrogen increases the risk of breast cancer, venous thromboembolic events, gall-bladder disease and, unless opposed by progestogen, endometrial cancer. In addition to gastrointestinal complaints, ipriflavone may be associated with skin reactions and, to a lesser extent, neurological, musculoskeletal and cardiovascular symptoms.

Some of the interventions studied also have associated effects that are beneficial. Thus, calcitonin, ipriflavone and nandrolone have been associated with reductions in the intensity of osteoporotic pain and with improved mobility. In one study,[72] fluoride also appeared to be associated with a significant reduction in back pain. Oestrogen can reduce menopausal symptoms such as hot flushes and may provide protection against colorectal cancer. Raloxifene may have a preventive role in relation to breast cancer. Brisk walking reduces both high-density lipoproteins and obesity.

Continuance

As noted above, for each intervention there was considerable variation between studies in terms of the percentage of patients treated with the active intervention and who completed the protocol. This information is summarised for each intervention in *Table 31*.

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 in few studies specifically. Hence, the information provided is too heterogeneous to summarise further.

TABLE 31 *Continuance (percentage of patients completing protocol) as reported by reviewed studies*

Intervention	Continuance (%)
Bisphosphonates	58–95
Vitamin D derivatives	65–91
Calcitonin (injected)	50–100
Calcitonin (intranasal)	57–84
Calcium	71
Oestrogen	83–92
Oestrogen-like molecules	56
Anabolic steroids	91
Fluoride	50–78
SERMs	78–over 90
Protein supplements	73
Vitamin K_2	No information
Exercise	19

It was to be expected that continuance and compliance with medication would be higher in the context of an RCT than in real life. For example, although in the studies reviewed here over 80% of women taking oestrogen completed the various trials, other studies have reported considerably lower compliance in patients prescribed HRT for osteoporosis, with reports of 36% and 49% compliance after 1 year and 61% after 6 months to 1 year.[154–156]

Discussion

Evidence of efficacy has been identified in this review for only some of the interventions studied: bisphosphonates for vertebral and non-vertebral fracture; calcitonin, calcium, fluoride and raloxifene for vertebral fracture only. However, failure to demonstrate the efficacy of the remaining interventions and of calcitonin, calcium, fluoride and raloxifene in relation to non-vertebral fracture, may reflect the small size and short duration, as well as the inappropriate reporting of fracture outcomes, of the studies that were suitable for meta-analysis.

In addition, it was decided to study only RCTs in which information was provided on the skeletal status of individuals in terms of BMD or prior fragility fracture. Thus studies directed to the general population or individuals characterised at high risk by other means have been ignored. This has resulted in some important omissions. Finally, epidemiological information that provided a lower level of evidence has been ignored. The extent to which the totality of these omissions tempers views concerning efficacy is reviewed briefly below.

Bisphosphonates

The bisphosphonates, as a class, have been shown by RCTs to reduce vertebral and non-vertebral fractures, including hip fracture. An exception for the individual bisphosphonates is the apparent lack of efficacy of etidronate on hip fracture risk. The studies reviewed were undertaken in women with vertebral fracture and were not powered to assess hip fractures. However, an RCT published after our cut-off date indicated that risedronate decreased the risk of hip fracture by 30%.[221] In women with osteoporosis, the effect was more marked (RR = 0.6; 95% CI, 0.4 to 0.9). Also, epidemiological investigation has shown that the use of etidronate is associated with a significant reduction in hip fracture risk.[54] It is notable that the efficacy estimate is greater for vertebral fracture than for appendicular fractures. Thus, if the association is causal, there appears to be little difference in efficacy between bisphosphonates.

Vitamin D and calcium

Calcium is widely available throughout the world and is the major non-HRT intervention used in osteoporosis.[55] It is commonly used in combination with vitamin D (vitamin D_2 or vitamin D_3). No information is provided in this review relating to these agents, with the exception of two studies with calcium, one of which reported a significant decrease in vertebral fracture frequency in established osteoporosis. One epidemiological study has found that the risk of hip fracture appears to be decreased in women taking pharmacological amounts of calcium;[55] the effects persisted even after adjusting for potential confounding factors. Calcium supplements were taken on average at age 70 years, whereas the average age of hip fracture was 75 years.

A controlled prospective study in the elderly has shown that the combined use of calcium and vitamin D significantly decreased the frequency of hip fracture.[35,222] Over an 18-month follow-up period, 204 non-vertebral fractures occurred in the calcium group compared with 355 fractures in the placebo group. The decrease in both femoral and other non-vertebral fractures was significant. It should be noted that patients were drawn from sheltered accommodation and the possibility exists that some had coexisting vitamin D deficiency. Nevertheless, the dose of vitamin D used was physiological and the findings lend credibility to the retrospective studies suggesting that calcium with or without physiological doses of vitamin D decreases the risk of hip fractures. BMD was not systematically assessed in this study; hence, it was not included in our primary analysis. However, low BMD was found in a sample of patients surveyed and, for this reason, an effect on non-vertebral fractures was included in a sensitivity analysis. The risk of hip fracture was significantly reduced (RR = 0.738; 95% CI, 0.600 to 0.908), as was the risk of all non-vertebral fractures (RR = 0.793; 95% CI, 0.687 to 0.917). The latter estimate has been used for forearm and humeral fractures in a sensitivity analysis.

A further study with vitamin D alone was partly based in the community and partly drawn from nursing home occupants.[223] In this study, an intramuscular injection of 150,000–300,000 units was given annually to individuals aged 75 years or more. Treatment resulted in a significant decrease in fracture frequency.

These findings contrasted with those reported for the use of a modest dose of vitamin D alone (400 IU daily) in 2600 elderly men and women from Holland.[224] After a follow-up period of 42 months, 58 hip fractures had occurred in the vitamin D-treated group and 48 in placebo-treated patients. Other peripheral fractures occurred with equal frequency. It is possible that the apparent lack of efficacy relates to the low dose of vitamin D used and the high nutritional status with respect to calcium in Holland. Studies of calcium and vitamin D alone and in combination are presently being conducted in the UK, and many help distinguish the effects of these agents.

Vitamin D derivatives

The present review suggests that the 1-alpha hydroxylated derivatives of vitamin D do not significantly decrease the risk of fractures. Mid-point estimates were decreased for vertebral and hip fracture but not significantly so (see *Table 29*). Epidemiological studies would also suggest that any effect on hip fracture risk is not significant.[55] Tilyard and colleagues have published the results of a large prospective study.[124] This prospective, randomised but open-label study was undertaken in New Zealand in more than 600 postmenopausal women with vertebral fracture (see page 37). The study was not included in our primary analysis because the trial was a comparison of calcium alone versus calcitriol alone. Vertebral fracture rate did not increase in the first year of treatment; thereafter, there was a significant difference in fracture rate between patients receiving calcitriol and those receiving calcium (RR estimate = 0.31).

Calcitonin

The present study indicates that calcitonin significantly decreases vertebral fracture risk. Evidence that other fractures are decreased is not provided. This relates to the small numbers of patients enrolled to examine this end point. Some support for an effect on hip fracture risk is provided by a case–control study undertaken in Southern Europe.[55] The RR of hip fracture associated with the use of calcitonin was 0.63 (95% CI, 0.44 to 0.90). The study also had positive and negative controls. Oestrogens were shown to be associated with a decrease in risk whereas fluoride was associated with a modest increase in risk.

Oestrogens

Although oestrogens are widely considered to be the treatment of choice for the prevention of osteoporosis, the RCT evidence that this is associated with a decrease in fracture risk is wanting. In case–control studies, HRT has been consistently associated with a decrease in appendicular fractures including hip fracture.[55,151,197]

Efficacy was supported by a small prospective randomised study,[225] in which HRT decreased the risk of non-vertebral fractures by 71% (RR = 0.29; 95% CI, 0.10 to 0.90). Intention-to-treat (ITT) analysis gave an RR of 0.44 (95% CI, 0.21 to 0.93). The study was not included in our meta-analysis because women were not selected on the basis of low BMD. Evidence of efficacy was also supported by prospective population cohort studies.[151,226,227] In this study, estimates for efficacy on hip and forearm fractures were taken from Cauley and colleagues,[227] since the population was older (65 years or more), the study was prospective and women with a history of osteoporosis were assessed separately. The RR for hip fracture was 0.86 (95% CI, 0.42 to 1.75) and for forearm fracture 0.32 (95% CI, 0.13 to 0.78) in current users of HRT with a history of osteoporosis. For humeral fractures, the RR for all non-spinal fractures was used (RR = 0.63; 95% CI, 0.45 to 0.89). The estimate for hip fracture efficacy is conservative. For example, results from a case–control study suggested an efficacy of 50% or more.[197]

New data have recently become available from a study undertaken in the USA (the Women's Health Initiative). This showed a decrease in fracture risk but an increased risk of adverse cardiovascular events.

In addition to osteoporosis, HRT has many multi-system effects that could be of considerable consequence in the health economics setting.

HRT is widely used to control menopausal symptoms. Most women experience symptoms but only a minority find them a problem. For example, in a UK survey, 57% of women experienced hot flushes but only 22% considered them to be a problem.[228] HRT is very effective in controlling menopausal symptoms, and more than 40 RCTs relating to its use have been undertaken, most of which show significant benefit.[229] Although the treatment of menopausal symptoms has been shown to be cost-effective,[2] these effects were not incorporated in this report, since the proportion of patients with established osteoporosis and menopausal symptoms is very small.

The greatest potential benefit of HRT is on cardiovascular disease. Observational studies showed a consistent decrease in risk. A recent

meta-analysis found a summary RR of 0.70 (95% CI, 0.67 to 0.75). For opposed oestrogen, the RR was 0.66 (95% CI, 0.53 to 0.84).[230] Since healthy women preferentially take HRT, these observational studies are likely to be biased in its favour[194] and the extent of this bias is uncertain. In a review of 22 short-term RCTs in which cardiovascular events were recorded, the risk of cardiovascular disease was higher (RR = 1.39) in women taking HRT than in a control group.[232] More recently, the effect of HRT in women at risk from coronary artery disease was examined in a large RCT.[153] Overall, no effect was found (RR = 0.99; 95% CI, 0.80 to 1.22), although some protection was afforded in the later phase of the study.

In our base case, no protective effect of HRT on cardiovascular disease has been assumed but the results of the meta-analysis by Barrett-Connor and Grady were used in the sensitivity analysis.[230] In concordance with the observational studies, risk protection was assumed to disappear as soon as treatment stopped.[233,234]

For HRT, the adverse effects of greatest concern are related to breast cancer risk. The clinical information available was largely derived from epidemiological studies, which suggested that HRT is associated with a small increase in risk. Moreover, the association is plausible. For this study, a recent meta-analysis of 51 epidemiological studies was used, comprising 52,700 women with and 108,400 women without breast cancer.[149] The risk appeared to increase by 2.3% for each year that HRT was used. This is equivalent to the excess risk associated with a late menopause. Thus, a 5-year exposure might be assumed to increase the RR by 11.5% (i.e. RR = 1.12). In this study and conservatively, the collaborative group's estimate of long-term use (RR = 1.35; 95% CI, 1.21 to 1.49) has been used, based on the use of HRT for at least 5 years. It was assumed that the effect disappeared as soon as treatment was stopped.[235]

HRT has been associated with a large number of other beneficial and adverse effects that were not included in this analysis. Beneficial effects included reductions in colonic cancer (RR = 0.76; 95% CI, 0.70 to 0.82), rectal cancer (RR = 0.81; 95% CI, 0.72 to 0.92)[146] and Alzheimer's disease (OR = 0.71; 95% CI, 0.53 to 0.96), and increased survival.[148,236] Adverse effects included an increased risk of endometrial cancer with unopposed use,[152] which was substantially reduced by cyclic progestogen.[145] An increased risk of venous thromboembolic disease has also been reported.[237–239] The RR increases were 3.5 (95% CI, 1.8 to 7.0)[238] and 3.6 (95% CI, 1.6 to 1.8),[239] respectively, but the absolute risk increase was small (16.5/100,000 in women aged 45–64 years). Other possible adverse effects include gall bladder disease, vaginal bleeding, bloating and breast tenderness.[151]

Oestrogen-like molecules

There was no supplementary information on fracture rates with these compounds.

Anabolic steroids

There have been no prospective randomised studies, in which fracture outcomes were the primary end-point, to determine whether anabolic steroids reduce fracture frequency. In a retrospective case–control study, the use of anabolic steroids in women was associated with a marked (RR = 0.6) but not significant decrease in the RR of hip fracture.[55] Analysis of these data for Italy – where anabolic steroids are widely used – showed a significant effect.[240]

Fluoride and thiazides

Our own analysis indicated that fluoride can reduce vertebral fracture frequency but has no significant effect on hip fracture risk. The lack of effect on non-vertebral fractures was consistent with epidemiological studies.[55] Our conclusions concerning vertebral fracture effects were at variance with those of a recent meta-analysis,[241] in which fluoride had no apparent effect on vertebral fracture risk (RR = 0.87; 95% CI, 0.51 to 1.46). The disparity arises from differences in the studies excluded or included. In this review, studies in normal individuals, non-randomised studies and those without fracture end-points were excluded. Also, in the meta-analysis,[241] several studies were not included for reasons that were not apparent;[73,79,80] studies in men were also excluded.[173]

In this review, no studies were identified that showed antifracture efficacy for thiazides. In several longitudinal studies, rates of bone loss were reported to have decreased in men taking thiazides for hypertension.[242] In case–control studies, the use of thiazides was associated with a significantly decreased risk of hip fracture.[243–245] A meta-analysis of these case–control studies suggests that current use of thiazides is associated with a decrease in fracture risk of borderline significance (RR = 0.82; 95% CI, 0.62 to 1.08).[246]

SERMs

The data reviewed here on osteoporotic fracture represent the totality of information available for

raloxifene. The results of a large prospective study undertaken in women with breast cancer suggested that tamoxifen decreased the risk of hip fracture.[204] This observation may be important since the studies in raloxifene were not powered to demonstrate effects on appendicular fractures.

Raloxifene has been shown to have some HRT-like effects on biochemical markers of cardio-vascular disease (see page 35). It decreased total cholesterol by 3–6% and low-density lipoprotein cholesterol by 4–10%. High-density lipoprotein cholesterol and triglyceride concentrations did not change significantly. A meta-analysis of total cholesterol lowering in the setting of primary and secondary cardiovascular disease suggested that cardiac events decreased by 2% for every 1% reduction in serum cholesterol.[210] On this basis, in the sensitivity analysis it has been assumed that raloxifene might decrease cardiovascular risk by 20%.

As in the case of HRT, other beneficial or adverse effects have not been considered, including an increase in incidence of venous thrombo-embolic events. The increase in risk (RR = 3.1; 95% CI, 1.5 to 6.2) is comparable to that derived from observational studies with HRT.

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 established osteoporosis
- the mortality associated with established osteoporosis
- 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.

Whenever possible the data used to populate the health economics model have been derived from a UK information base. The sources of data, their limitations and the assumptions that derive from them are reviewed here. The uncertainties that are inherent in the estimates provide a rationale for subsequent sensitivity analysis.

Osteoporotic fracture

Definition

The definition of an osteoporotic fracture is not straightforward. An approach that is widely adopted is to consider low-energy fractures as being caused by osteoporosis. This has the merit of recognising the multifactorial causation of fracture. However, with high-energy trauma, fractures are more likely in osteoporotic individuals than those without osteoporosis.[248] There is also a disparity between low-energy fractures and fractures associated with reductions in BMD.[249] The classification is therefore incomplete.

A further approach is to characterise a fracture as osteoporotic only in the presence of osteoporosis, as defined by the T-score and WHO criteria,[13] or to identify the types of fracture that increase in frequency as the BMD falls. The association of several different fracture types with BMD was investigated in a large North American survey – the Study of Osteoporotic Fractures (SOF)[249] – and is the approach that some researchers have used to exclude some fracture types as not being due to osteoporosis. An additional criterion is to examine the pattern of fractures with age. A rising incidence of fractures with age does not provide evidence that the fracture type is caused by osteoporosis, since a rising incidence of falls could also be a cause. In contrast, a lack of increase in incidence with age is reasonable presumptive evidence that a fracture type is unlikely to be osteoporosis-related. 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.[84,250,251]

Irrespective of the methods used, opinions differ about the inclusion or exclusion of different sites of fracture. Those that are included here comprise hip fractures, vertebral fracture coming to clinical attention; fractures of the distal forearm and proximal humerus. These comprise the most common sites of osteoporotic fracture but, nevertheless, exclude fractures at other sites, such as pelvis, distal femur, rib and tibia. The proportion of fractures accounted for by other osteoporotic fractures in Sweden is summarised in *Table 32*.[41]

The proportion of all fractures accounted for by the sites chosen represent the majority (65–74%), depending on age. They also represent the major cause of morbidity. The fraction, however, depends critically on age. Thus, between the ages of 50 and 55 years, fractures of the hip, forearm and spine account for 57% of the morbidity from all osteoporotic fractures but account for 84% over the age of 85 years. In health economics modelling, the exclusion of other fractures will underestimate the benefits from treatment, although it should be acknowledged that the evidence for efficacy of any treatment at these sites is wanting.

A further assumption is that all fractures at a particular site that is included are caused by osteoporosis. This is clearly an oversimplification. Since some important fracture sites (e.g. pelvis)

TABLE 32 *Proportion of osteoporotic fractures (%) at the sites shown and the proportioned utility loss by age in women from Sweden[41] (Reproduced with permission from Osteoporosis International)*

Fracture type	Age range (years)							
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Proportion of fractures								
Vertebra	15	13	19	16	20	17	13	11
Hip	4	7	11	15	21	26	37	36
Forearm	39	37	36	26	23	16	13	10
Shoulder	12	10	8	13	10	10	6	8
Other	30	33	26	30	26	31	31	35
Proportion of disutility								
Vertebra	20	14	17	14	14	10	6	5
Hip	21	33	42	52	61	68	78	77
Forearm	11	9	7	5	4	3	2	1
Shoulder	5	3	2	3	2	2	1	1
Other	43	41	32	26	19	17	13	16

have been excluded, this may be offset by the assumption that all fractures at an included site are due to osteoporosis. An alternative approach is to quantify, by expert opinion, the proportion of fractures at each site caused by osteoporosis. This approach is used in Switzerland[252] and the USA[253,254] to characterise the burden of disease; however, it too is arbitrary and based on as many assumptions.

Fracture risks

The fracture risks used in this report are derived as far as possible from UK sources. There have been several recent surveys reporting fracture rates in the UK.[17,25,255,256] (van Staa T, Procter and Gamble Pharmaceuticals, Staines, UK: personal communication, 2001; Cooper C, Medical Research Council, Southampton, UK: personal communication, 2000) The data from van Staa are from general practice research data. The annual incidence of osteoporotic fractures from recent surveys is given in *Table 33*. For hip, forearm and proximal humeral fracture rates, the data from Singer and colleagues,[25] based on a population in Edinburgh, were used. These data were preferred to those from Cardiff, reported by Johanssen and colleagues,[256] since more fractures were analysed (15,293 versus 6467). Hip fracture rates in the series from Singer and colleagues[25] were midway between the estimates of Johansen and colleagues

TABLE 33 *Annual fracture risk in women by age (%)*

Age range (years)	Annual fracture risk (%)								
	Hip			Wrist			Shoulder		
	Singer, 1998[a]	Johansen, 1997[a]	Van Staa[b]	Singer, 1998[a]	Johansen, 1997[a]	Van Staa[b]	Singer, 1998[a]	Johansen, 1997[a]	Van Staa[b]
50–54	0.041	0.05	0.02	0.255	0.343	0.24	0.058	0.035	0.06
55–59	0.05	0.125	0.05	0.374	0.531	0.40	0.085	0.077	0.11
60–64	0.083	0.125	0.08	0.467	0.531	0.48	0.136	0.077	0.12
65–69	0.157	0.36	0.15	0.573	0.667	0.57	0.126	0.09	0.17
70–74	0.485	0.36	0.28	0.699	0.667	0.62	0.246	0.09	0.22
75–79	0.707	1.34	0.55	0.697	0.917	0.71	0.306	0.299	0.28
80–84	1.437	1.34	1.03	0.749	0.917	0.80	0.372	0.299	0.35
85–89	2.761	4.14	1.71	1.001	1.37	0.84	0.362	0.628	0.45
90+	3.851	4.14	2.33[c]	0.919	1.37	0.89[c]	0.391	0.628	0.47[c]

[a] *See list of trials meeting inclusion criteria (page 125)*
[b] *Van Staa, Procter and Gamble Pharmaceuticals, Staines, UK: personal communication, 2001*
[c] *90–94 years*

and van Staa, but were broadly comparable. Similarly, for forearm and shoulder fractures, fracture rates in Singer and colleagues lay midway between those of Johansen and colleagues and van Staa. Overall, the differences in risk were less than the ranges found within other countries. For example, estimates of hip fracture risk between series vary two-fold within Norway and Turkey.[26,257] There are few data relating to vertebral fracture incidence in the UK, and none are ideal. The problem is due in part to incomplete information and in part to the criteria used to define a vertebral fracture. Vertebral fractures that come to clinical attention are less common than fractures diagnosed from change in vertebral shape obtained by morphometric techniques. With respect to symptomatic fractures, data were available from the Trent region but comprised only those patients who required hospital admission,[258] thus underestimating the incidence considerably. Vertebral fracture rates were also available from general practice research data but their validity was uncertain. Age-stratified estimates of prevalence and incidence of vertebral deformities were available from the Chingford study but the sample size and age ranges were small.[259] (van Staa, Procter and Gamble Pharmaceuticals, Staines, UK: personal communication, 2001) More substantial data from several UK centres are available, although not yet published, from the EPOS (European Prospective Osteoporosis Study) database. These too are morphometrically-diagnosed deformities and provide incidence rates that will be substantially greater than the incidence of clinically diagnosed fractures (*Table 34*). In this study, it was considered preferable to estimate the incidence of clinically diagnosed fracture, since it is these patients who are most likely to be identified for treatment. Moreover, the QALY estimate ascribed to vertebral fractures pertains to clinically diagnosed fractures.

For these reasons, vertebral fracture rates were imputed from data available from Malmö, Sweden, on the incidences of hip and vertebral fractures that come to clinical attention.[24] 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 35*. Though data are limited, there appears to be a consistency in the pattern of different osteoporotic fractures in the Western world.[41] Thus, the assumptions that were made concerning proportionality appear reasonable. The rates shown (see *Table 35*) are substantially lower than those derived from radiographic surveys but higher than those reported from the General Practice Framework. For example, in women aged 70–74 years, the annual rate used was 0.68% compared with 0.12% from the General Practice Framework and 1.2% using morphometric criteria. The rate used thus lies between the two UK direct estimates.

TABLE 34 *Incidence of vertebral fracture (rate/1000/year) in Europe and the UK using morphometric criteria*

Age range (years)	Europe		UK	
	Men	Women	Men	Women
50–54	1.75	4.2	0	5.4
55–59	6.7	5.8	2.9	6.4
60–64	6.5	11.0	3.0	11.8
65–69	8.7	14.5	6.9	5.1
70–74	9.4	18.5	4.2	11.7
75–79	14.8	33.0	0	34.6

It is important to note that the QALY estimate for vertebral fracture is conservative (see page 65), and that morphometrically diagnosed fractures give rise to current morbidity and are associated with a high risk of future fractures. For this reason, cost-effectiveness was examined also, using the morphometrically-derived incidence rates in a sensitivity analysis and assuming from our calculations that 24% of morphometric deformities come to clinical attention.

There are several other uncertainties relating to the risks that were used. Regional estimates may not be representative of the UK and the use of these estimates in modelling future events gave rise to even greater concerns, for several reasons.

1. It was assumed that over 10 years (the time frame used in the base case), the risk of fracture will not change in the population. The secular trend in hip fracture risk appears to have flattened in the UK[29] 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 gender-specific incidence appears to be increasing in some countries.[260]
2. It was also assumed that the mortality hazard does not change over 10 years. However, mortality has continued to decrease and this is likely to continue in the future.[22] 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

TABLE 35 *Fracture risk (%) by age at the sites shown*

Age range (years)	Fracture risk (%)			
	Hip	Vertebral	Wrist	Proximal humerus
50–54	0.041	0.108	0.255	0.058
55–59	0.050	0.144	0.374	0.085
60–65	0.083	0.127	0.467	0.136
65–69	0.157	0.111	0.573	0.126
70–74	0.485	0.683	0.699	0.246
75–79	0.707	0.600	0.697	0.306
80–84	1.437	0.755	0.749	0.372
85–89	2.761	1.223	1.001	0.362
90+	3.851	1.155	0.919	0.391

(1 year). The fracture rates given will include those individuals with a first fracture and a minority who have previously sustained a fracture at that site. Thus, the risk of first fracture is overestimated. The overestimate is greater in the elderly than in the young.[24]

Thus there are factors that variously overestimate and underestimate fracture risk. In this study, these are not considered further since the cancelling out of the sources of error is 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 examined the risk of fracture as a function of BMD. In general, the lower the BMD value, the greater the risk of fracture. The increase in fracture risk is approximately doubled for each SD decrease in BMD. Thus, for an individual with a BMD value one SD lower than the average BMD for a given age, the fracture risk is about twice that for an individual with the average BMD for that age. The gradient of risk, however, varies according to the site of assessment and the technique used. The most extensive meta-analysis was undertaken by Marshall and colleagues.[16] For absorptiometric techniques, the gradient of risk depended on the site of measurement as well as the technique. For example, BMD measurements by dual-energy X-ray absorptiometry to predict hip fracture are better when the measurements are made at the hip rather than at the spine or forearm (*Table 36*). Thus, 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 zero SD. In contrast, the same T-score at the spine would yield a much lower risk estimate – approximately a four-fold increase (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 as well as measurements at other sites. For this reason, the proximal femur is the preferred and recommended site for diagnostic use,[15] and it is assumed here that this is the site that would be used for diagnostic purposes. For humeral fractures, no data are available and the gradient of risk with which all fractures were predicted (1.6/SD) was assumed. There is little difference in predictive power between measurements made at the femoral neck or in the region of total hip. In this study, the femoral neck was chosen since a UK reference range was available.

The gradients of risk that have been assumed are very similar to those found in the SOF study – the largest prospective study of fracture risk in women.[9] In this study, the risk of hip fracture increased 2.6-fold for each SD decrease in hip BMD – a value that is identical to the midpoint estimate of the meta-analysis by Marshall and colleagues[16] (see *Table 36*). At this site, the gradient of risk for forearm fractures was 1.6, and for vertebral fracture 1.9, compared with 1.7 and 1.7 in Marshall and colleagues' meta-analysis.

Fracture risk in osteoporosis

The computation of fracture risk from BMD in individuals demands a knowledge of the change of BMD in the ageing population, so that the average T-score can be computed according to age.

TABLE 36 *RRs (with 95% CIs) of fracture in women for a 1 SD decrease in BMD (absorptiometry) below the age-adjusted mean*[16] *(Reproduced with permission from the BMJ Publishing Group)*

Site of measurement	RR (95% CI) of fracture			
	Forearm	Hip	Vertebral	All
Distal radius	1.7 (1.4–2.0)	1.8 (1.4–2.2)	1.7 (1.4–2.1)	1.4 (1.3–1.6)
Femoral neck	1.4 (1.4–1.6)	2.6 (2.0–3.5)	1.8 (1.1–2.7)	1.6 (1.4–1.8)
Lumbar spine	1.5 (1.3–1.8)	1.6 (1.2–2.2)	2.3 (1.9–2.8)	1.5 (1.4–1.7)

In the approach used here, the relationship between Z-score and T-score at different ages was examined, using conversion factors calculated from a published survey of normal women in London.[261] This study measured BMD at the femoral neck. The same approach was used by the US National Osteoporosis Foundation (NOF) but, in their report,[9] the young normal reference range was not defined and the data were derived from measurements at the total hip site rather than the femoral neck.

The relationship between T-score and Z-score is given in *Table 37*. For example, for the average 90-year-old individual, Z-score = 0. This would be equivalent to a T-score of –2.72 SD. Similarly, a 70-year-old individual with an average BMD (Z-score = 0) would have a T-score of –1.65 SD, and someone with a Z-score of –1.0 would have a T-score of –2.65 SD (that is, –1 minus –1.65).

From these data, the annual risks of fracture can be computed for individuals with a T-score of –2.5 SD, that is, at the diagnostic threshold for osteoporosis (*Table 38*).

Consider, for example, a 70-year-old woman with an average BMD for her age (Z-score = 0 SD).

TABLE 37 *Converting Z-scores to T-scores*

Age (years)	NOF[9] [a]	Frost *et al.*, 2001[261]
	T-score = Z-score minus:	T-score = Z-score minus:
50	0.37	0.60
55	0.69	0.86
60	1.01	1.12
65	1.29	1.39
70	1.56	1.65
75	1.84	1.91
80	2.11	2.18
85	2.31	2.44
90	2.52	2.70

[a] *Conversions at ages 55, 65, 75 and 85 years have been estimated using linear interpolation*

The T-score is –1.65 SD, which in turn is 0.85 SD above the threshold for osteoporosis. The annual risk of hip fracture for a 70-year-old woman with osteoporosis, therefore:

= average risk for a 70-year-old individual × $(2.6)^{0.85}$
= average risk × 2.253
= 1.093%

The risk of a vertebral fracture:
= average risk × $(1.8)^{0.85}$
= average risk × 1.648
= 1.1256%

The risk of a forearm or humeral fracture:
= average risk × $(1.6)^{0.85}$
= average risk × 1.491
= 1.042% and 0.367%, respectively.

The annual risk of fracture for women at the threshold for osteoporosis is presented by age in *Table 38*. Note that for a risk at a given age (e.g. 70 years), the T-score conversion is used for that age and multiplied by the risk of the age interval (e.g. 70–75 years). Thus, the risk is overestimated at the start but, as the patient ages in the model, the risk is underestimated.

The approach used is an oversimplification. It is assumed that the increase in risk due to osteoporosis is a multiple of the RR and the population risk. The oversimplification arises because BMD is normally distributed in a population at a given age, whereas there is an exponential relationship between BMD and fracture risk. Thus, individuals with an average BMD have a lower-than-average risk of fracture.[262] Conversely, the average fracture risk is found in individuals with a lower-than-average BMD. For this reason, the calculations of fracture risk at the threshold for osteoporosis are overestimated. An indication of the overestimate in the case of hip fracture is presented in *Table 39*.

The risk of fracture in women at the threshold for osteoporosis differs from that of a population of osteoporotic patients, since few will have a

TABLE 38 *The estimated annual risk of fracture (%) at the sites shown in the female population and in women with a T-score of –2.5 SD*

Age range (years)	Fracture risk (%)							
	Hip		Vertebra		Wrist		Shoulder	
	Population	Osteoporosis	Population	Osteoporosis	Population	Osteoporosis	Population	Osteoporosis
50–54	0.041	0.252	0.108	0.330	0.255	0.623	0.058	0.142
55–59	0.050	0.240	0.144	0.378	0.374	0.809	0.085	0.184
60–64	0.083	0.310	0.127	0.286	0.467	0.893	0.136	0.260
65–69	0.157	0.453	0.111	0.213	0.573	0.966	0.126	0.212
70–74	0.485	1.093	0.683	1.126	0.699	1.042	0.246	0.337
75–79	0.707	1.242	0.600	0.849	0.697	0.914	0.306	0.401
80–84	1.437	1.950	0.755	0.911	0.749	0.870	0.372	0.432
85–89	2.761	2.896	1.223	1.260	1.001	1.025	0.362	0.371
90+	3.851	3.181	1.155	1.026	0.919	0.836	0.391	0.356

TABLE 39 *Risk of hip fracture in Swedish women at the threshold for osteoporosis[262] (reproduced with permission from Elsevier Science)*

Age (years)	RR compared with:	
	Average BMD	Population
50	4.6	2.9
60	3.0	1.9
70	1.9	1.2
80	1.2	0.74

T-score at the threshold value. From the distribution of BMD and the change with age, the risks of fracture can be compared.[24] The differences in risk are shown in *Table 40*. Thus, the RR is underestimated in the average osteoporotic patient, and this underestimate increases with age – from 65% at age 50 years to 158% at 84 years. For this reason, sensitivity analyses have been undertaken by increasing the stringency of the T-score: for example, a T-score of –3.5 rather than –2.5 SD.

Fracture risk in established osteoporosis

Risk ratios

A large number of studies have examined the risk of fracture following a fragility fracture. Fracture risk is increased over and above that explicable on the basis of age or BMD. The interrelationship between prior and subsequent fractures has recently been assessed by meta-analysis using a random effects model to derive summary estimates of RR.[263] The risk estimates derived from peri- or post-menopausal women are shown in *Table 41* adjusted for age but not BMD. There have been no studies that examined the risk of a forearm fracture following a hip fracture and an RR of 1.4 was used, equivalent to the lowest RR between fractures. The relevant risk functions are summarised in *Table 42*.

The analysis computes that (for example) an individual with a prior spine fracture has a risk of a further spine fracture that is 4.4-times greater

TABLE 40 *RR of hip fracture in women at, and at and below, the threshold (T) for osteoporosis (reproduced with permission from Elsevier Science)*

Age (years)	RR of hip fracture		B/A	A/B
	(A) when T = –2.5 SD	(B) when T ≤ 2.5 SD		
50	2.9	4.8	1.65	0.61
55	2.4	4.1	1.71	0.58
60	1.9	3.4	1.79	0.56
65	1.5	2.9	1.93	0.52
70	1.2	2.5	2.08	0.48
75	0.95	2.1	2.21	0.45
80	0.74	1.8	2.43	0.41
84	0.62	1.6	2.58	0.39

than that of an individual of the same age but without fracture. It is assumed thereafter that an individual with a T-score of –2.5 SD with a prior vertebral fracture has a 4.4-fold greater risk than an individual without such a fracture but the same T-score.

This assumption is an oversimplification for several reasons. Firstly, the risk estimates are not adjusted for BMD, which is likely to overestimate the risk by up to 20%. For example, in the SOF study of 7238 women aged 65 years or more, those with a prevalent vertebral deformity had a 4.1-fold higher risk of a further vertebral fracture. When adjusted for BMD, the RR was 3.8. Similarly, in women with vertebral fracture, the age-adjusted risk of hip fracture was 1.9, which fell to 1.8 after adjustment.[85]

Secondly, some downward adjustment of RR is required since, apart from BMD, the risks are relative to those without prior fracture rather than to the general population. The adjusted RR approximates to:

$$RR/(p.RR + (1 - p))$$

where p is the prevalence of the risk factor (prior fracture) and RR the unadjusted value.[264] 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% (0.05), the population RR is:

$$4.4/(0.05 \times 4.4 + (1–0.05)) = 3.76$$

When the prevalence is 10% of the population, the RR falls to 3.28. These overestimates of fracture risk are offset 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.[265] Also, the increase in RR varies according to age and is markedly higher in the young than in the elderly (*Table 43*).[265] These short-term RRs more than offset the overestimates arising from other simplifications. Thus, the assumptions used were conservative, particularly in younger individuals.

The simplifications used are amenable to sensitivity analysis and have been accommodated here.

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

TABLE 41 *Risk of fracture at the sites shown according to the site of a prior fracture[263] (reproduced with permission from the American Society of Bone and Mineral Research)*

Site of prior fracture	RR (95% CI) of subsequent fracture				
	Distal forearm	**Spine**	**Proximal humerus[a]**	**Hip**	**Pooled**
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*

TABLE 42 *The increased risk of subsequent fracture following a prior fracture*

Prior fracture site	Increased risk of subsequent fracture			
	Hip	**Vertebra**	**Wrist**	**Shoulder**
Hip	2.3	2.5	1.4	1.9
Vertebral	2.3	4.4	1.4	1.8
Wrist	1.9	1.7	3.3	2.4
Shoulder	2.0	1.9	1.8	1.9

TABLE 43 *Incidence (rate/1000) of hip fracture admissions in the general female Swedish population and of patients at 6 months or at 4 years following hospitalisation for vertebral fracture[265] (Reproduced with permission from Osteoporosis International)*

Age range (years)	General population	Incidence at 6 months (95% CI)	RR	Incidence at 4 years (95% CI)	RR
50–54	0.36	6.0 (4.2–8.4)	16.7	3.8 (2.7–5.4)	10.6
55–59	0.83	10.7 (8.6–13.3)	12.9	6.8 (5.4–8.6)	8.2
60–64	1.46	19.0 (16.9–21.5)	13.0	12.2 (10.5–14.0)	8.4
65–69	2.53	29.9 (27.0–33.3)	11.8	19.1 (16.8–21.8	7.5
70–74	5.05	39.0 (35.9–42.2)	7.7	24.9 (22.3–27.8)	4.9
75–79	10.73	50.7 (47.7–53.9)	4.7	32.3 (29.4–35.5)	3.0
80–84	18.52	65.9 (62.4–69.5)	3.6	42.1 (38.4–46.1)	2.3
85–89	32.2	85.7 (80.5–91.2)	2.7	54.7 (49.7–60.2)	1.7

0.5%. With a T-score of –2.5 SD, the RR increases by 2.60.85 = 2.25, equivalent to a hip fracture risk of 1.13%. In a woman with the same T-score but a prior spine fracture, the risk of hip fracture is increased 2.3-fold (see *Table 42*), giving a hip fracture risk of 2.26%. Further examples are given in *Table 44*.

In the absence of specific information, it was assumed that bone loss occurs at the same rate in untreated patients as in the general population.

Consequences of fracture

Death due to a hip fracture

Excess mortality is well described after hip fracture. In the first year following hip fracture, the mortality risk in women varies from 2.0 to > 10 depending on age (*Table 45*).[22] It classically follows a biphasic pattern, with a sharp increase 6 months to 1 year after the event and thereafter decreasing, but remaining higher than in the general population.[266] Since hip fracture patients have high coexisting morbidity, poor pre-fracture health is likely to contribute to the excess mortality. Case–control studies adjusting for pre-fracture morbidity indicate that a substantial component can be attributed to comorbidity.[267,268] 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, the excess mortality risk was estimated to be 3.35 (95% CI, 1.50 to 7.47) compared with a subsequent risk of 1.30 (95% CI, 0.85 to 1.98).[267]

The data that were used for death following hip fracture were unpublished data from the second Anglian audit of hip fracture, in which deaths up to 90 days were recorded (*Table 46*).[269]

Parker and Anand[266] estimated that 33% of deaths 1 year after hip fracture were totally unrelated to the hip fracture, 42% possibly related and 25%

TABLE 44 *Risk of fracture (%) at the sites shown in established osteoporosis with a T-score of –2.5 SD at the ages shown*

Site of prior fracture	Risk of subsequent fracture at the sites shown			
	Forearm	Spine	Shoulder	Hip
Age 50–54 years				
Forearm	2.06	1.06	1.49	1.18
Spine	0.46	1.45	0.59	0.76
Shoulder	0.26	0.27	0.27	0.28
Hip	0.35	0.63	0.48	0.58
Age 70–74 years				
Forearm	3.44	1.77	2.50	1.98
Spine	1.58	4.95	2.03	2.59
Shoulder	0.62	0.64	0.64	0.67
Hip	1.53	2.73	2.08	2.51

TABLE 45 *Mortality by age in Sweden (1994) in the general female population and in the year following hip fracture[22] (Reproduced with permission from Osteoporosis International)*

Age (years)	Population (rate/1000)	Hip fracture (rate/1000)	Excess mortality (RR)
50	2.25	35.8	15.9
55	3.07	25.7	8.4
60	5.06	54.8	10.8
65	8.23	39.6	4.8
70	15.53	97.1	6.3
75	25.8	80.8	3.1
80	47.1	199.5	4.2
85	83.4	166.1	2.0

directly related. These figures were not, however, stratified by age or gender and have been assumed to be constant for all ages.

The raw data for deaths at 90 days were multiplied by 67% to subtract the number of deaths that were assumed to be unrelated to the hip fracture; possibly related deaths were attributed to the hip fracture, which may overestimate the death rate.

As deaths beyond 90 days following hip fracture were not recorded in the Anglian audit, an assumption was made that no further deaths caused by hip fracture occurred after 90 days. It is noted that this may underestimate the mortality rate due to hip fracture, as it appears from a graph in Parker and Anand's paper[266] that, in relation to deaths at 90 days, there would be approximately 40% of additional deaths in the period 91–365 days. However, some redress has been made by assuming that the 42% of deaths possibly related to hip fracture were directly due to the fracture. Overall, the assumptions attribute 48% of all deaths within the first year as related to hip fracture.

The 0% death rate in nursing homes at ages 60–69 years shown in *Table 46* is empirical but appears to be lower than expected. Indeed, the relative mortality hazard is higher in younger age groups than in the elderly. In the first year after fracture, the RR in women aged 50–74 years was 3.2 compared with 1.6 at the age of 85 or more years.[270] Even higher risks were found in Sweden (see *Table 45*). This is unlikely to have a significant impact as, in the model, an assumption was made that patients can only enter a nursing home following a prior hip fracture, and the absolute risk of fracture at the age of 60 years is low.

First entry to nursing home following a hip fracture

The model has been populated with unpublished data from the second Anglian audit of hip fracture

TABLE 46 *Estimated 1-year mortality rates due to hip fracture*

Place of residence	Age range (years)	Mortality rate at 1 year (%)
Community	60–69	4[a]
Community	70–79	6
Community	80–89	11
Community	90+	16
Nursing home	60–69	0
Nursing home	70–79	13
Nursing home	80–89	22
Nursing home	90+	23

[a] *6% in Anglian audit but adjusted downwards from Swedish national data (see* Table 45*)*

(Institute of Public Health, 1999) summarised elsewhere.[271] The percentage of hip fractures that resulted in a first admission to a nursing home were 4% for those aged 60–69 years and 70–79 years, 12% for those aged 80–89 years and 17% for those aged 90 years and over.

Death due to vertebral fracture

Several studies have shown an increase in mortality following vertebral fracture.[272–274] 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 hip fracture, there is no acute excess.[272,274] It is notable that low BMD is also associated with excess mortality[275,276] but the degree of increased mortality after vertebral fracture is greater than that expected from low BMD. In the model, an excess associated with low BMD has been assumed (see later) but no additional mortality from vertebral fracture.

These studies used morphometric definitions of vertebral fracture. In contrast, other studies that examined mortality after vertebral fracture using clinical criteria have shown more marked

increases in mortality.[273,277] (Johnell O, Department of Orthopaedics, Malmo, Sweden: personal communication, 2001; McCloskey EV, WHO Collaborating Centre for Metabolic Bone Disease, Sheffield, UK: personal communication, 2001) 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)[273] and, in another study, the risk was more than eight-fold higher.[277] In the present model, incidence rates of clinically diagnosed fractures were used, so mortality may be underestimated. It was also assumed, perhaps conservatively, that intervention had no effect on mortality.

Death due other fractures

It was assumed that there was no increase in mortality from forearm or humeral fractures consistent with published surveys.[273,274,277]

Breast cancer and cardiovascular disease

Contracted breast cancer

The incidence of breast cancer was taken from cancer registrations[278] and is summarised in *Table 47*, assuming a population as reported by the Office of National Statistics.[279]

TABLE 47 *The annual incidence of breast cancer by age*

Age group (years)	Annual incidence of breast cancer	Average population
Osteoporotic population		
50–54	0.245	0.133
55–59	0.277	0.164
60–64	0.319	0.208
65–69	0.257	0.181
70–74	0.269	0.205
75–79	0.284	0.235
80–84	0.320	0.286
85+	0.362	0.343

Two large cohort studies showed that osteoporosis or low BMD was associated with a lower incidence of breast cancer.[280,281] Conversely, approximately 70% of breast cancer cases occurred in women with a BMD in the two highest quartiles (*Table 48*). The study by Cauley and colleagues[280] indicated that the risk of breast cancer was increased by 1.34 per one SD increase in BMD (measured at the proximal radius). This equates approximately to a 0.75 RR per one SD below the population average BMD. For this reason, the breast cancer risk was adjusted downwards (see *Table 47*). Thus, for example, the RR of breast cancer for women aged 70–75 years has been calculated as:

$$0.268 \times 0.75^{0.94}$$

TABLE 48 *The relationship between breast cancer and BMD*

Source	Quantile of BMD			
	1	2	3	4
Cauley, *et al.*, 1996[280]	9	20	37	34
Zhang, *et al.*, 1997[281]	13	19	20	48

It was assumed that interventions that increased the BMD of a patient would not change the risk of breast cancer adjusted because of a low T-score.

Death due to breast cancer

As the model is an individual patient-based simulation, the data required are the probabilities of death due to breast cancer in each year following diagnosis. As such, standard summary data such as total death rates due to breast cancer per year are inappropriate.

The data that were used are the 5-year survival rates for the years 1986–90 in England and Wales.[279] The 5-year survival rate was 68%. Comparison of 1-, 5- and 10-year survival rates showed a steep decline in mortality, followed by a flattening of the death rate after 5 years. It was assumed that any patient who survived beyond 5 years would not die from breast cancer.

For the 32% who died within the 5-year period, it was assumed that the survival period was 2 years. The model will record the patient as dying in the year that breast cancer was diagnosed but the QALYs accrued are doubled and the annual costs incurred by the patient are doubled for that year.

Death due to CHD

The number of deaths from CHD (International Classification of Disease codes 410–414) was taken from mortality statistics from the Office of National Statistics.[278] The population figures were from the same source. The estimated annual risks are presented in *Table 49*.

Non-fatal CHD events

The data for CHD events were derived from the total of CHD deaths and ratios of deaths to events as presented by Volmink and colleagues.[282] The ratios of non-fatal definite myocardial infarction (MI) and non-fatal possible MI to fatal definite

TABLE 49 *The annual incidence of non-fatal events and deaths due to CHD*

Age range (years)	Annual incidence of CHD (%)	
	Non-fatal events	Deaths
50–54	0.072	0.026
55–59	0.144	0.064
60–65	0.240	0.135
65–69	0.364	0.280
70–74	0.442	0.541
75–79	0.317	0.941
80–84	0.000	1.637
85–89	0.000	2.449
90+	0.000	3.251

MI plus fatal possible MI and fatal unclassified coronary death were 2.26 in the 50–64 years' age group and 0.82 in the 65–79 years' group. For modelling purposes, it was assumed that these ratios were for 55–59 years and 70–74 years, respectively. Estimates of the ratios for other age bands were made assuming a linear change between 55–59 years and 70–74 years.

These data do not contradict the ratio of 2.6 of non-fatal MIs to fatal MIs reported by Stampfer and colleagues,[234] who analysed the data for women between the ages of 30 and 63 years.

It was assumed that the MI ratios were applicable to CHD ratios.

The estimated risk of a non-fatal CHD incident is given in *Table 49*.

Death from other causes

These data were taken from interim life tables (*Table 50*)[283] and adjusted for deaths due to CHD and breast cancer in the general population.

Several studies have shown an increased mortality associated with low BMD of similar magnitude derived from measurements at the radius or heel.[275,276] At the radius, the increase in RR was 1.22 per 1 SD decrease in BMD adjusted for age,[275] and this value was used in the model. These data are shown in *Table 50*. When a patient died from other causes, the costs and QALYs from the previous year were halved for the year in which the patient died.

It was assumed that those interventions that increased the BMD of a patient would not change the risk of death due to other causes adjusted due to a low T-score.

TABLE 50 *The annual death rate due to other causes*

Age range (years)	Risk of death (%)	Risk of death adjusted for low BMD (%)
50–54	0.243	0.371
55–59	0.402	0.576
60–65	0.680	0.915
65–69	1.206	1.536
70–74	2.015	2.429
75–79	3.271	3.733
80–84	5.497	5.940
85–89	9.250	9.62
90–94	14.896	14.896
95–99	22.796	22.796
100+	27.008	27.008

Health state utility values

It was necessary to identify the best available utility estimates for health states associated with the consequences of established osteoporosis and its treatment for use in the model. The health states used in the model included healthy osteoporosis, established osteoporosis, hip fracture, vertebral fracture, wrist fracture, proximal humerus fracture, breast cancer and CHD. Previous economic evaluations of the prevention and treatment of osteoporosis relied on the use of assumptions or judgements obtained from expert panels such as the recent review undertaken by the NOF,[9] rather than using empirical evidence to value these health states. This is recognised as one of the main weaknesses of work in this area.[216,284] 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 dimension (EQ-5D) or the Health Utility Index (HUI)-III) or direct preference elicitation techniques, such as time trade-off (TTO) or standard gamble (SG). It was therefore decided not to rely on assumptions for this model but to make use of empirically derived figures when available.

Identifying the key studies

This review drew on papers identified from a series of systematic searches. These included searches of papers reporting economic evaluation of the prevention and treatment of osteoporosis, and those reporting on quality of life associated with the main fracture states. Information was also sought on breast cancer and CHD, since several treatments for osteoporosis may affect these out-

comes. Studies were identified through searches of electronic databases, hand-searching, citation searching, reference list checking and contacting of individuals known to researchers involved in the study. Details of the methods are presented in appendix 6.

A total of 1132 papers were found. Their abstracts were examined in order to identify those likely to be relevant to this study, which reduced the number to 173. A further sifting was undertaken to identify those papers presenting health state values likely to be relevant to this model. Most of the 173 papers were concerned with measuring quality of life in general and did not present preference-based health state values. Six published papers were found on fracture states and seven on breast cancer and CHD. The former group of papers is complete, while those for CHD and breast cancer represent only a selection. These 13 papers contained 36 health state values, since a number of papers reported on more than one state, values by different groups of respondents and/or used more than one valuation technique. These published papers were supplemented by two unpublished studies,[285,286] of which the first has now been published.

Results

The health state values were found to differ considerably from the assumptions used in previously published economic evaluations in this area (*Table 51*). The value for vertebral fractures used by the NOF of 0.97, for example, compares with values ranging from 0.31 to 0.80. These empirical estimates used a recognised preference elicitation procedure but there was a considerable range of values for each health state. This range reflects a number of differences in the derivation of the estimates including: the source of values, what is being valued, the valuation technique and the anchor states used in the valuation task. The selection of estimates for the model involved both technical and value judgements that are discussed below.

Methodological issues in selecting health state values

The source of values

The studies differed in terms of the samples being asked to undertake the valuations. Some estimates were obtained by asking patients to value their own health states, others by asking samples of patients to value hypothetical descriptions of the states. In other studies, values were elicited from samples of professionals (e.g. Hutton and colleagues, 1996)[287] or representative samples of the general population.[288] Having patients value their own health states has the advantage of avoiding the need to describe health states and may ensure that they have a better understanding of the impact of the state on their lives. However, it has the disadvantage that it limits the source of values to current patients. It has been argued that, for the purposes of informing resource allocation, the values of society at large are required and, hence, studies that used a representative sample of the general population would be more appropriate.[289]

What is being valued?

Respondents were asked to value specially constructed vignettes to describe each health state[290] or to use generic preference-based measures such as the EQ-5D.[292] The generic preference-based measures come with a set of values already obtained from a general population sample. The state-specific approach has the potential advantage of being more relevant and sensitive to the condition than generic measures.[292] The disadvantage is that the descriptions may only represent a proportion of the health states found in a sample of patients, and it is not clear how representative they would be of patients with the condition.

Generic preference-based measures have the advantage of being administered to a sample of patients and thus represent the variation in health states found in the population. To use these estimates, however, it is necessary to establish that the study sample accurately reflects the population used in the model, in terms of variables such as age, severity and other background variables that are likely to affect a patient's state of health. This can be difficult to achieve in practice, since most data in this area have been collected from patients recruited into trials with strict criteria for inclusion, which may not result in the mix of patients used in the model (and typically seen in the NHS) and in different countries.

Adjusting for the age composition of the samples

The health state values did not cover the full range of age groups used in the model. Some studies were limited to one age group (e.g. Brazier and colleagues, 2000);[286] others were based on such small numbers that it was not possible to estimate reliable age-specific values. One approach to extrapolating the findings

TABLE 51 *Empirical estimates of utility values for osteoporosis-related health states*

Source	Utility values	Methods		
		Health state description	**Valuation technique**	**Source of values**
'Healthy' osteoporotic				
NoF review[9]	1.0		Judgement	Panel of experts
Kind, *et al.*, 1998[296]	Age range (years) 45–49 0.840 50–54 0.850 55–59 0.802 60–64 0.829 65–69 0.806 70–74 0.747 75–79 0.731 80–85 0.699 85+ 0.676	EQ-5D for general population; hence, includes all sources of morbidity found in this population	TTO valuations of EQ-5D hypothetical states with full health and dead as reference states	General population (*n* = 3381)
'Established osteoporosis', i.e. history of broken wrist, spinal or hip fracture				
Gabriel, *et al.*, 1999[288]	0.84 (± 0.29)	Patients who experienced non-traumatic vertebral fracture in last 5 years but not multiple fractures	TTO valuation of own health anchored by best imaginable for age and dead	Patients (*n* = 75; mean age, 76 years)
	0.43 (± 0.40)	Valuation of hypothetical state constructed from clinician views and focus groups – these include reference to future risk	TTO valuation of hypothetical health state anchored by current health and dead transformed using valuation of own health against perfect health and dead	Non-fracture cases attending clinic in last 2 years (*n* = 199; mean age, 68 years)
Hip fracture				
NOF review[9]	First year: 0.3817	Assumes quality-of-life reduction from acute care, rehabilitation, home care, GP visits and ambulance	Judgement	Expert panel
	Subsequent years: 0.855	Assumes distribution across disability states		
Gabriel, *et al.*, 1999[288]	0.68 (0.18)	37 patients who had hip fracture in last 5 years completed HUI-II (mean age, 76 years)	HUI-II valued by SG (estimated from transformation of VAS)	HUI-II parents of school children from Hamilton, Canada (*n* = 203)
	0.61 (0.08)	Above patients completed QWB scale	QWB valued by VAS	Representative sample of general population of San Diego, USA
	0.72 (0.16)	Above patients valued their own health states	VAS	Patients (*n* = 37)
	0.70 (0.41)	Above patients valued their own health states	TTO anchored by perfect health and dead, where perfect health is best imaginable for their age	Patients (*n* = 37)
	0.65 (0.45)	Patients' own valuation of their hip fracture states, which they regarded as worse than hypothetical 'disabling' fracture state	TTO anchored by perfect health and dead, where perfect health is best imaginable for their age	Patients (*n* = 33; mean age, 76 years)
	0.28 (0.37)	Hypothetical 'disabling' hip fracture state	TTO anchored by own health state and dead, and latter transformed using their valuation of own health state (itself anchored against best imaginable for health and dead)	Recent clinic attendees who have never had a fracture (*n* = 198, mean age, 68 years)

continued

***TABLE 51* contd** *Empirical estimates of utility values for osteoporosis-related health states*

Source	Utility values	Methods		
		Health state description	**Valuation technique**	**Source of values**
***Hip fracture* contd**				
Salkeld, *et al.*, 2000[290]	0.31 (interquartile range, 0.0–0.65)	Based on description of life after 'good' hip fracture	TTO anchored by hypothetical health state in someone of similar age to respondent and death	Older people at risk of fracture (*n* = 194; mean age, 81 years)
Brazier, *et al.*, 2000[286]	at 6 months: 0.49 (0.32) at 12 months: 0.48 (0.38)	39 patients completed EQ-5D before fracture and then at 6 and 12 months after fracture (mean age, 76 years)	TTO valuations of EQ-5D hypothetical states with full health and dead as reference states	General population (*n* = 3381)
Confined to nursing home due to hip fracture				
NOF review[9]	0.4	Nursing home	Judgement	Expert panel
Salkeld, *et al.*, 2000[290]	0.05 (no range given)	Based on description of life after 'bad' hip fracture that included being in nursing home	TTO anchored by hypothetical health state of someone of similar age to respondent and death	Older people at risk of fracture (*n* = 194)
Vertebral fracture				
NOF review[9]	0.97	Assumes 33% experience no change; 57 % quality of life reduced by 0.5 for 1 month; 10% experience complete loss, then 0.5 loss for 7 weeks	Judgement	Expert panel
Gabriel, *et al.*, 1999[288]	0.80 (0.16)	94 patients who had vertebral fracture in last 5 years completed HUI-II	HUI-II valued by SG (estimated from trans-formation of VAS)	HUI-II parents of school children from Hamilton, Canada (*n* = 203)
	0.66 (0.09)	Above completed QWB	QWB valued by VAS	Representative sample of general population of San Diego, USA
	0.76 (0.17)	Above patients valued their own state	VAS	Patients (*n* = 94)
	0.81 (0.32)	Above patients valued their own state	TTO anchored by perfect health and death, where perfect health is best imaginable	Patients (*n* = 94)
	0.68 (0.4)	Patients' own valuation of their fracture state, which they regarded as worse than multiple vertebral fracture state	TTO anchored by perfect health and death, where perfect health is best imaginable	Patients (*n* = 24)
	0.31 (0.38)	Hypothetical multiple vertebral fracture state	TTO anchored by own health state and death, and latter transformed using their valuation of own health state (itself anchored against best imaginable for health and death)	Recent clinic attendees who had never had fracture (*n* = 199)
Oleksik, *et al.*, 2000[285]	0.744 (0.231)	130 patients who had experienced radiographically confirmed fracture in last 5 years completed EQ-5D	EQ-5D for general population; hence, includes all sources of morbidity found in this population	TTO valuations of EQ-5D hypothetical states with full health and dead as reference states

continued

***TABLE 51* contd** *Empirical estimates of utility values for osteoporosis-related health states*

Source	Utility values	Methods		
		Health state description	**Valuation technique**	**Source of values**
Wrist fracture				
NOF review[9]	1st year, 0.96; subsequent years, 0.98	Assumes 0.7 for 7 weeks Assumes long-term dependency for 2% of patients with QoL reduction to 0.7	Judgement	Expert panel
Dolan, *et al.*, 1999[297]	0.982	EQ-5D completed by 50 wrist fracture attendees (mean age, 72 years, range, 52–91) at outpatient clinic at first and final visit (average 48-day interval). Implied QALY loss over year, assuming linear progression between initial and last assessment, 0.018 (0.014)	TTO valuations of EQ-5D hypothetical states with full health and dead as reference states	General population (*n* = 3381)
Breast cancer				
Hutton, *et al.*, 1996[287]	0.62 0.33 0.84	Stable disease Progressive disease Partial response to therapy Hypothetical health state descriptions constructed from multi-disciplinary group; no variance data given	SG using McMaster pingpong method	UK oncology nurses (n = 30). Similar figures obtained from nurses in three other countries
Grann, *et al.,* 1998[a]	0.89 (interquartile range, 0.86–1.00)	No detail offered on descriptions used	TTO – no protocol detail provided	Convenience sample (*n* = 54)
De Haes, *et al.*, 1991[b]	0.65 0.17	Health state described as 3 months to 1 year after mastectomy Terminal illness	Crude VAS values, subject to TTO power function	*n* = 27, healthcare workers and cancer experts
CHD				
Oldridge, *et al.*, 1991[c]	0.717–0.767 0.872–0.864	MI patients at baseline MI patients at 12-month follow-up	TTO valuing current state versus full health	Patients
Tsveat, et al., 1995[d]	0.88 0.89	Treatment group Placebo group Valuing own health state	TTO: 10 years in current state versus shorter life in excellent health	Survivors of MI (*n* = 82)
Nease, *et al.*, 1995[e]	1.0 0.997 0.929	Angina class I class II class III/IV Valuing their own health	TTO (VAS and SG also available)	Patients
Kuntz, *et al.*, 1996[f]	0.89 0.85 0.82 0.78	Mild angina/no CHF Mild angina, CHF Severe angina Severe angina, CHF Valuing their own health	TTO: telephone survey but no further details on procedure	Patients (1051 overall states)

VAS, visual analogue scale; QWB, Quality of Well-Being [scale]; CHF, congestive heart failure

[a] *Grann,* et al. J Clin Oncol *1998;**16**:979–85*
[b] *De Haes,* et al. Int J Cancer *1991;**49**:538–44*
[c] *Oldridge,* et al. Am J Cardiol *1991;**67**:1084–9*
[d] *Tsevat,* et al. J Am Coll Cardiol *1995;**26**:914–19*
[e] *Nease,* et al. JAMA *1995;**273**:1185–90*
[f] *Kuntz,* et al. Circulation *1996;**94**:957–65*

from these studies to specific age groups of the model would be to assume a constant **absolute** reduction regardless of age; another would be to assume a constant **proportional** effect on health state values. In the absence of good evidence, it is not possible to say which approach is correct. The latter approach was used in the model since it assumes that the better your health status the more you have to lose – which was considered to be the most realistic assumption.

Valuation technique

Another important difference between estimates was the valuation technique used to elicit health state values, whether directly as part of the study or implicitly through the use of generic preference-based measures. It is currently recommended that health state utility values should be obtained using a choice-based technique such as SG or TTO rather than a rating scale.[293] This recommendation was used in selecting values for this model.

Anchor states

Different anchor states were also used by the studies in their valuation tasks. For SG or TTO, a health state is valued against two reference states, one better and the other worse. Although most studies used 'dead' as the worst state, different upper states were described, such as 'excellent' health, 'full health' (as defined by EQ-5D or HUI-II), 'best imaginable for your age', or ' your current' health. This had important implications for the interpretation of the estimates and their use in the model. By convention, death is given a value of zero and the upper anchor state is given a value of one. When a health state was valued in a study using, for example, 'best imaginable for your age' as the upper anchor, the values were higher than those that would be generated from using 'full health' as the upper anchor. In some studies, attempts were made to correct for this by transforming the results using valuations of the upper anchor, as in Gabriel and colleagues.[288] The model requires a common scale, regardless of age; thus the health state values must lie on a scale where a value of one is equivalent to full health.

Estimating the health loss from an event

The model estimates the health loss for each individual from a health event as the difference between the health state values before and after the event. Earlier models assumed that the pre-event health state value was either one or the average health state value for the individual's age and gender group. However, this assumes that those who have experienced an event such as a hip fracture would have experienced full or average health if the fracture had not taken place. Taking an age–gender matched sample from the general population as a control group at least corrects for the fact that most people who experience fracture, particularly hip fracture, are older than the general population. According to a recent general population survey of the UK, for example, people in the age group 70–74 years have a health state value of about 0.8. A related approach in a study by Oleksik and colleagues[285] was to recruit a matched sample of people who had not had a (vertebral) fracture and to use them as the control group.

These methods do not provide valid control groups for those avoiding a fracture, since those who have a fracture may have a different health status from the average and are very unlikely to have had a health state value of one prior to a fracture. This concern was borne out in a recent study by Brazier and colleagues[286] on patients recruited into a trial to reduce the rate of fracture. This study provided genuine prospective data on the impact of hip fracture on health. Health status was assessed at entry into the trial prior to fractures occurring and then, following fracture, at 6 months and 12 months. Such data were not available for other health states in the model.

Review

The health state values considered in this review are presented in *Table 52*, including their: health state descriptions, mean and SDs, the valuation technique employed and the source of the valuations for each of the osteoporosis-related conditions. For comparison, normative health state utility values for the UK are presented by age group. These values were obtained from the results of the EQ-5D being administered to over 3000 representative members of the UK general population. The values used by NOF are also presented for comparative purposes, since these are in common use in current economic evaluations.

The 23 empirically derived health state utility values for the four fracture conditions (i.e. hip, vertebral, wrist and established osteoporosis) differed considerably from the values obtained by a panel of experts for NOF. For example, the NOF value for vertebral fractures of 0.97 compares with empirical values that range from 0.31 to 0.80. There was also a considerable range of values for each condition, probably due to differences in the derivation of the estimates. Differences included what is being valued, the valuation technique used, and the anchor states

TABLE 52 *Health state utility values used in the model*

Health state	Value		Source
'Healthy' osteoporotic			
Age group (years)	45–49	0.840	Kind, *et al.*, 1998[296]
	50–54	0.850	
	55–59	0.802	
	60–64	0.829	
	65–69	0.806	
	70–74	0.747	
	75–79	0.731	
	80–85	0.699	
	85+	0.676	
Established osteoporotic (use values associated with the type of fracture)			
Hip fracture	0.797 (95% CI, 0.651 to 1.012)		Brazier, *et al.*, 2000[286]
Nursing home	0.4		NoF[9]
Vertebral fracture	0.909 (95% CI, 0.84 to 0.97)		Oleksik, *et al.*, 2000[285]
Wrist fracture in first year	0.981 (95% CI, 0.978 to 0.986)		Dolan, *et al.*, 1999[297]
Proximal humerus	0.981 (95% CI, 0.978 to 0.986)		Dolan, *et al.*, 1999[297]
Breast cancer	0.62 (assumed range 0.33–0.84)		Hutton, *et al.*, 1996[287]
CHD	0.85		Assumption

used in the valuation task. The results are discussed below in more detail for each condition.

Healthy osteoporosis

The model required a set of normative health state utility values. There were remarkably few studies with detailed normative data by age. In the USA, there was a set of normative data based on a random survey of the population of one city using the Quality of Well-being scale and the TTO valuation technique[294] and, in Canada, a version of HUI was used in a state-wide health survey.[295] The largest normative dataset of health state utility values available in the UK is based on the EQ-5D (administered to over 3000 representative members of the UK general population), and this was been used in the model.[296]

Established osteoporosis

Gabriel and colleagues[298] reported on patients' own valuation of states diagnosed with established osteoporosis and obtained values similar to those that would be expected for their age. They also reported on the valuation of a hypothetical state of 0.43 using a sample of non-fracture cases. However, this value suffers from being based on a description that does not clearly relate to any one type of fracture and includes references to future risk that are likely to distort the valuation of the state. Conceptually, a better approach would be to base the value of a case of established osteoporosis on the model estimate for the worst fracture experienced by each patient.

Hip fracture

There were nine different hip fracture values reported across three studies, ranging from 0.28 to 0.72. The HUI-II valuation of 0.68, for individuals who had fractured their hips in the last 5 years, was significantly below the age/gender norm of 0.82 found in Canada,[295] and suggests a multiplier of around 0.83. However, in the study by Brazier and colleagues,[296] better data were provided for use in the model as health state utility values were given for the sample population before they experienced fracture, thus offering a more valid estimate of the loss in health status associated with a fracture. The mean health state utility values at 6 and 12 months after hip fracture were 0.49 and 0.48, respectively, compared with 0.6 at baseline. These figures imply a multiplier of 0.8.

Nursing home

There was only one published estimate for hip fracture cases in a nursing home. Salkeld asked a group of elderly respondents to value a 'bad' hip fracture state that included 'being in a nursing home'. However, the upper anchor used in the TTO question was a hypothetical state of someone in good health for his or her age and no account was taken of the likely health state of someone at most risk of fracture. Furthermore, the description of the health state was based on quantitative evidence and, hence, its relevance to the cases in the model is not clear.[290] Hence, it was decided to use the NOF assumption of 0.4 in this model.

Vertebral fracture

The empirical estimates for vertebral fracture were considerably below the NOF assumption of 0.97. The lowest value was obtained from non-fracture respondents for a hypothetical state of 'multiple' fractures but this state is not used in the model. After allowing for the lower health state utility values expected in those age groups prone to vertebral fracture, the other apparent differences were considerably reduced. The HUI-II estimate for those who had a fracture in the last 5 years was 0.8, which compares with, for example, the normative value based on Canadian data of 0.82.[a] The best data for the model were provided by Oleksik and colleagues,[285] whose study was based on a sample of clinically diagnosed vertebral fracture cases using the EQ-5D and had a larger sample of patients than the study by Gabriel and colleagues.[288] The estimate for individuals who had experienced a fracture in the last 5 years compared with those who had not was 0.75–0.82, which generated a multiplier of 0.91. The adequacy of the cross-sectional control was of concern in this study. The control group had to meet the same inclusion criteria, including age and T score (< –2.5), but the authors found that the individuals in the control group were significantly younger (by 2.5 years), had a higher lumbar spinal BMD, and a lower prevalence of non-vertebral fractures. The consequences of these differences for the EQ-5D score are not known.

Wrist fracture

Some earlier models assumed that a wrist fracture had no impact on health status. The one empirical study in the field found a significant impact over short periods.[297] The researchers administered the EQ-5D at admission and at the final visit to the Accident and Emergency department, and were able to estimate a mean loss in health state utility value for the period since the wrist fracture by assuming a linear progression between the first and last visits. Whether the EQ-5D would be sensitive to some of the problems associated with wrist fracture was a cause for concern, particularly the longer-term complications found in a small proportion of patients. However, this is the only empirical estimate available at present.

Proximal humerus

On the advice of the clinical collaborators on this project, it was assumed that a fracture of the proximal humerus had the same impact on health status as a wrist fracture.

Breast cancer

There have been a number of studies presenting empirically derived estimates of the impact of breast cancer on health state utility values. The utility value depends on whether the disease is stable or progressive, whether it is being treated, and its stage. There was no average value for this disease and, hence, it was necessary to select a value that broadly represented the consequences of breast cancer for a person's health status. It was decided to use the value for stable disease estimated by Hutton and colleagues.[287]

CHD

This disease also suffers from the problem of being associated with more than one condition. There were estimates for patients following MI and other values for different severities of angina. An assumption of 0.85 was used in the model, with a range of 0.72–0.99 depending on the type of CHD and the study method.

A reference case set of values for the model

There were wide ranges of preference-based health state utility values for each condition, primarily because of differences in the descriptive systems and the sample of respondents used in the valuations. One recommended solution to such a situation is for all analysts to use a reference case of values. This does not imply that analysts should only use the reference case in any future economic evaluation but that they should be used in at least one analysis of each economic evaluation of an intervention for osteoporosis.

The influential Washington Panel on Cost-Effectiveness recommends the use of a generic instrument with social valuations of health states obtained using a preference-based instrument.[298] This allows comparison between healthcare programmes, such cardiac failure or cancer versus osteoporosis, as well as within programmes. The problem to date with the condition-specific approach has been that this has been limited to one or two vignettes, and these do not necessarily reflect the full range of states associated with each condition. Furthermore, they cannot be linked easily to patients in trials. Generic instruments can be administered to patients in trials or other clinical studies and thus provide a more accurate quantitative basis to the descriptive results. While accepting that there may be problems with generic

[a] See: Roberge R, Berthelot J-M, Cranswick K. Adjusting life expectancy to account for disability in the population: a comparison of three techniques. *Social Indicators Res* 1999;**48**:217–43.

health state classifications for some conditions, such as insensitivity to the consequences of wrist fracture, another approach would be to produce a preference-weighted condition-specific measure.

In this review, two generic preference-based measures were found to be in use, EQ-5D and HUI-II. There are few data on their relative performance in osteoporosis and no methodological basis for preferring one to the other. Currently, the EQ-5D has the advantage of being available for more osteoporosis-related conditions than the HUI-II and, hence, is preferred for the reference case set of values. Because of lack of evidence, it was not possible to distinguish between first and subsequent years, unlike NOF.

The final selection of health state utility values used in the model are presented in *Table 52,* including the mean 'multiplier' and 95% CIs estimated from the studies using Feiller's theorem. There are many uncertainties surrounding the appropriate estimates to use in the model for the reasons given above; hence it was important for a full sensitivity analysis to be undertaken, using 95% CIs to examine the robustness of any conclusions drawn to the health state utility values used.

Research agenda

Remarkably few studies were found relating to the impact of osteoporosis-related conditions on health state utility values. This finding was confirmed by a recently published listing of 1000 health state utility values,[299] which contained only six values for these conditions, five for hip and one for vertebral fracture, all of which were based on expert opinion rather than empirical evidence. The studies reviewed here had begun to use accepted methods for use in economic evaluation but were limited in terms of age range, sample size, the period since the event and poor control groups. To improve the reference-case value dataset would require the administration of a preference-based generic health status measure to a large prospective population cohort and long-term follow-up. Such preference-based measures could include the EQ-5D, HUI-III or the recently developed Short Form (SF)-6D that utilises SF-36 data. The choice should depend on evidence of their validity across these conditions. It would be possible and important to estimate by age the actual loss in health status utility values over time following each of the fractures (including multiple fractures) and to generate measures of variance. These data could be collected both as a part of large clinical trials and observationally. International studies would also allow for cross-national comparisons.

A longer-term agenda should look more critically at the instruments used for estimating health status utility values and, in particular, the generic preference-based measures for each of the fractures. If generic measures were found to be irrelevant or insensitive to important aspects of one or more of the conditions, then another approach would be to develop condition-specific vignettes, although these are difficult to apply to quantitative data from trials and other studies. A third approach would be to develop condition-specific, preference-based measures for use on patients in clinical studies (these could use existing measures of health-related quality of life). A fourth approach would be to estimate preference weights for condition-specific measures.

A review of costing

The model developed for this study required 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 was 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
- breast cancer
- death due to breast cancer
- CHD
- death due to CHD
- additional 'healthy' life-years.

The model also required that costs be disaggregated into year of incidence and subsequent year costs, and that costs be weighted for age. Potentially, the model required costs to be estimated for upwards of 120 variables. Ideally, they would be estimated using prospective resource use data collected alongside an appropriate UK-based randomised trial. Given the absence of such data, the method of deriving the best available cost estimates for use in the model is described below.

Methods

Drug formulation costs were estimated using published UK reference prices from the *British National Formulary* 2000 (no. 39). It was assumed there were no administration costs.

The published literature was searched for costs or information that would help in costing the

modelled health states. The review drew on papers identified from a series of systematic searches, including searches of papers reporting economic evaluations, using electronic databases including MEDLINE, NHS EED, HEED, EMBASE, and the Science Citation Index. Economics studies were identified using a search filter based on that developed by the NHS Centre for Reviews and Dissemination.[300] Details of the searching and selection strategy are outlined below and the search terms are presented in appendix 6. Generally, priority was given to the most recent UK-based analyses, as treatment pathways and unit costs can differ significantly between countries and over time.

The initial search resulted in over 2000 titles being returned. These were filtered by title and then abstract, in order to exclude irrelevant papers. The initial filtering by title reduced the number of papers to 200. In addition to the abstracts of those papers being reviewed, any non-UK papers plus those published before 1990 were set aside. Papers not explicitly addressing costing but analysing key resource-use variables, such as inpatient length of stay (LOS), were included. The resulting 29 papers were requested and reviewed. The costing analyses presented in the short-listed papers were assessed for quality, to identify whether the papers presented appropriate levels of detail for selected criteria (*Table 53*).[2,3,11,20,216,217,284,301–322] The results of the selection and quality assessment process were used to identify the most appropriate papers for the modelling exercise.

The very specific cost data requirements of the model meant that data gathered from the searched literature would only partially populate the model. In particular, information on age-related costs and the division of costs between year of incidence and subsequent years proved to be sparse. Also, because the economics literature search was specifically targeted at osteoporosis and related fractures, it was not a good source of information for costing adverse drug events, such as breast cancer and CHD. When costing information was not available from the literature, other sources, including publications from *ad hoc* searches and papers known to the authors, were used.

In view of the lack of information on age-related costs, a local patient database that included information on age, diagnosis codes, destination on discharge, and LOS was analysed. Inpatient LOS has been assumed to be a good proxy for resource use and has been used to determine the appropriateness of age weighting for modelled health state costs. In brief, age-specific, mean patient LOS was calculated by health state, allowing for destination on discharge (including death). Student *t*-tests were then performed. When the statistical analysis indicated evidence for age weighting, the literature was searched for appropriate age weights. If no age weights could be found, the ratio of the age-specific to all-age mean LOS, calculated using the local data, was used as a proxy age weighting. All age weighting estimates are presented in the appropriate sections of this report.

Results

Published literature

The searched papers predominantly reported costing analyses for osteoporotic fractures. Of the 29 papers, nine exclusively examined hip fracture costs. Only three papers included references to CHD and breast cancer, and none of these proved to be helpful in populating the model. The final selection of articles included six review articles. Only a handful of the papers fully satisfied the quality assessment criteria, although these criteria were not wholly appropriate for the review articles and those papers in which resource use (e.g. LOS) rather than costs were analysed. In summary, the published literature proved somewhat limited in terms of quantity, quality, and appropriateness for the model. That said, the paper by Dolan and Torgerson[20] was a key source for estimating costs for all osteoporotic fractures.

Cost estimates

When deriving the cost estimates for the model, the costing took, where appropriate, an NHS and social care perspective. Patient costs and indirect costs to the economy were not considered. In the analyses presented below, the costs quoted use the financial year currencies presented in the original sources. For modelling purposes, the derived costs estimates have all been inflated to 1999/2000 financial year prices using the Hospital and Community Health Service (HCHS) pay and prices index,[323] supplemented by the GDP [gross domestic product] deflator for years 1998/89 and 1999/2000.[324] The various costs estimates used in the model are presented in *Table 54*.

Drug costs

The estimated annual drug costs for the formulations under review in this report are presented in *Table 55*. The table shows the wide choice of HRT formulations on offer in the UK. Those drugs used in the model are indicated in bold type. Fluoride is not commercially available in the UK but is used by specialist centres. The cost used was the pharmacy price in France for Osteofluor® (Merck Pharmaceuticals), 50 mg daily (1.41 FF), equivalent to £48 per year in current prices using an exchange rate of £1 = 10.69 FF.

TABLE 53 *Summary analysis of costing papers found in the literature search*

Study	Procedures/ drugs analysed	Resource quantities identified separately from prices	Methods of estimating quantities given?	Methods of estimating prices given?	Year of prices given?	Sensitivity analysis performed?	Discount rate used	Summary notes
Beech, *et al.*, 1995[301]	Hip fracture	N/A	N/A	N/A	N/A	N/A	N/A	Good LOS data by type of hip fracture – see Withey.[322] Also quoted some orthopaedic costs/day
Best & Milne, 1998[302]	Hip fracture	No	No	No	Some	Yes	6%	Some local treatment costs for Wessex
Daly, *et al.*, 1992[2]	None	No	N/A	Yes	1989/90	Yes	6%	Potentially useful modelling paper for HRT and LYG but not much on costs
Daly, *et al.*, 1996[217]	All fractures and CHD	No	No	Yes	1992	Limited	6%	Expected cost and savings of HRT and treating side-effects
Dolan & Torgerson, 1998[20]	All fractures	Yes	Yes	Yes	1995/96	Limited	N/A	Good study. Data and methods rich for fractures
Drummond, *et al.*, 1993[303]	CHD	No	No	No	N/A	Yes	N/A	Methodological discussion paper on choice of outcome measures for drug therapy in hypercholesterolemia
Fox, *et al.*, 1993[304]	Hip fracture	Some LOS	Yes	No	N/A	No	N/A	Hip fracture LOS and location on discharge for two UK units
Francis, *et al.*, 1995[305]	Vertebral fracture	Yes	Yes	Yes	1994?	No	6%	Focus on costs of drugs for vertebral fracture
French, *et al.*, 1995[306]	Hip fracture	Only LOS	Yes	Yes	1993	No	None	Detailed costs for hip fracture – regression analysis
Hollingworth, *et al.,* 1995[307]	Hip fracture	Yes	Yes	Yes	1991/92	Limited	N/A	Hip fracture, age/sex resource use data
Hollingworth, *et al.*, 1993[308]	Hip fracture	Yes	Yes	Yes	1991/92	Yes	N/A	Focus on potential savings from early discharge
Morris, *et al.*, 1999[309]	HRT, raloxifene, hip fracture, CHD, breast cancer	No	Yes	Yes	1998	Yes	6%	Modelling paper with focus on cost-effectiveness analysis (LYG) of HRT and raloxifene; no primary data other than drug costs
O'Cathain, 1994[310]	Hip fracture	Only LOS	YES	Yes	1992	No	N/A	Focus on potential savings from hospital at home scheme
Parker, *et al.*, 1998[311]	Hip fracture, LOS	N/A	N/A	N/A	N/A	N/A	N/A	Analysis of variations in LOS after hip fracture
Pitt, *et al.*, 1990[3]	Hip and spine fracture	No	N/A	Yes	1989	Yes	6%	Costs of HRT and likely impact on fracture incidence
Reid & Torgerson, 1998[312]	Etridonate	Review	Review	Review	Review	Review	Review	Review paper with focus on likely cost-effectiveness of etridonate compared with other drugs. Notes lack of good quality costing data. Quotes some indicative drug and hip fracture costs

continued

***TABLE 53* contd** *Summary analysis of costing papers found in the literature search*

Study	Procedures/ drugs analysed	Resource quantities identified separately from prices	Methods of estimating quantities given?	Methods of estimating prices given?	Year of prices given?	Sensitivity analysis performed?	Discount rate used	Summary notes
Sculpher, *et al.*, 1999[284]	Prevention and treatment of osteoporosis	Review	Review	Review	Review	Review	Review	Critical structured review, drug costs presented, excludes costing studies, suggests US prices inappropriate
Taylor & Kirby, 1999[313]	Cardiac rehabilitation	Yes	Yes	Yes	Yes	Yes	5%?	Concentrates on cardiac rehabilitation but contains potentially useful more general cardiac costing information and sources
Torgerson & Dolan, 1998[314]	Osteoporotic fracture	N/A	N/A	N/A	N/A	N/A	N/A	Prescribing after osteoporotic fractures. No costing data. Some sources for drug papers
Torgerson & Kanis, 1995[11]	Oral and injected vitamin D, hip fracture	Yes	Yes	Yes	No	None	6%	Measures direct costs of hip fracture using Hollingworth results. Possible wrong decision criteria, i.e. average not marginal. Implies that addition of indirect costs would double costs
Torgerson & Reid, 1999[315]	HRT	Review	Review	Review	Review	Review	Review	Review article including cost of HRT
Torgerson & Reid, 1993[316]	Screening for prevention of osteoporosis	Review	Review	Review	Review	Review	Review	Focus on cost-effectiveness of screening for prevention of osteoporosis and hip fracture. No primary data; some assumptions and use of published data. Useful general discussion
Torgerson & Reid, 1997[216]	Osteoporosis	Review	Review	Review	Review	Review	Review	Review: no detailed costings but good summary of costing methodologies and quality-of-life methods
Torgerson, *et al.*, 1996[317]	Drug costs and fracture avoidance	Yes	Yes	Yes	No	Yes	6%	Case study in use of economics for prioritising research using cost-effectiveness of drugs to prevent hip fracture. No primary data
Torgerson, *et al.*, 1996[318]	BMD	No	Yes	No	No	N/A	Not stated	Discussion of value of BMD scans. Some drug and BMD scan costs
Torgerson, *et al.*, 1997[319]	Fracture prevention	Review	Review	Review	Review	Review	Review	Economics of prevention of osteoporosis. Potentially useful summary table of previously published economic analyses
Townsend, 1998[320]	HRT	Yes	Yes	Yes	1994	Yes	N/A	HRT cost trends. Considers total costs but some potentially useful break-down of types of HRT use in UK
Townsend & Buxton, 1997[321]	HRT	No	Yes	Yes	1992	No	Not stated	Cost-effectiveness scenario analysis for proposed trial of HRT

continued

***TABLE 53* contd** *Summary analysis of costing papers found in the literature search*

Study	Procedures/ drugs analysed	Resource quantities identified separately from prices	Methods of estimating quantities given?	Methods of estimating prices given?	Year of prices given?	Sensitivity analysis performed?	Discount rate used	Summary notes
Withey, *et al.*, 1995[322]	Hip fracture	N/A	N/A	N/A	N/A	N/A	N/A	No costings but potentially useful resource use information for costing of hip fracture by case-mix. Same data and team as Beech[301]

LYG, life-years gained

TABLE 54 *Final cost estimates by health state, age and time (year 1999/2000 prices)*

Health state	Costs per annum (£)									
	Base case		Age range (years)							
			45–64		65–74		75–84		85+	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
Suffered uncomplicated hip fracture	7,398	N/A	4,530	N/A	5,698	N/A	7,499	N/A	8,600	N/A
Confined to nursing home due to hip fracture	30,360	21,163	27,491	20,695	28,659	21,291	30,460	22,179	31,562	23,362
Death due to hip fracture	8,666	N/A	8,666	N/A	8,666	N/A	8,666	N/A	8,666	N/A
Suffered vertebral fracture	465	216	419	195	521	242	546	253	590	274
Suffered wrist fracture	522	N/A	316	N/A	316	N/A	516	N/A	1,609	N/A
Suffered 'other' fracture	1,492	N/A	902	N/A	902	N/A	1,474	N/A	4,601	N/A
Contracted breast cancer	7,949	N/A	7,949	N/A	7,949	N/A	7,949	N/A	7,949	N/A
Death due to breast cancer	10,981	N/A	10,981	N/A	10,981	N/A	10,981	N/A	10,981	N/A
Contracted CHD	2,577	619	1,915	619	2,454	619	2,930	619	3,360	619
Death due to CHD	2,160	N/A	2,160	N/A	2,160	N/A	2,160	N/A	2,160	N/A
Confinement to nursing home not due to hip fracture	21,163	21,163	20,695	20,695	21,291	21,291	22,179	22,179	23,362	23,362
Healthy life-years	776	N/A	416	N/A	874	N/A	1,558	N/A	2,468	N/A

Fracture costs

Dolan and Torgerson[20] presented detailed costings of hip, vertebral, wrist and 'other fractures' in their paper. They estimated costs by analysing resource use in terms of acute care, social and long-term hospital care, follow-up and drug use.

Hip fractures

Dolan and Torgerson[20] presented detailed costings for various categories of hip fracture patients and for various stages of treatment from acute to long-term domestic and residential home treatment. For modelling purposes, cost estimates needed to be constructed for hip fracture patients discharged home, hip fracture patients discharged to long-term residential or hospital care, and for hip fracture patients dying within the year of fracture. An acute care cost of £4808 per patient was estimated. This estimate has been included in all three of the model's hip fracture categories.

Dolan and Torgerson[20] also presented comprehensive estimates for social care costs, including an estimate of £1574 for care in the home following discharge from hospital. This estimate

TABLE 55 *Drug costs (entries in bold type are those used in the model)*

Drug class	Drug name	Dosage	Preparation	Unit cost (£)	Annual cost (£)
SERM	**Raloxifene® [a]**	**60 mg**	**28-tablet pack**	**19.76**	**257**
Calcitonin	**Calsynar® [b]**	**100 unit/ml**	**1-ml ampoule**	**6.34**	**2,314**
	Miacalcic® [c]	100 unit/ml	1-ml ampoule	7.13	2,602
Bisphosphonate	**Fosamax® [d]**		**28-tablet pack**	**25.69**	**334**
	Didronel PMO® [e]	**400 mg**	**90-tablet pack**	**40.20**	**163**
Calcium supplements	See vitamin D				
Calcium salts	**Calcichew® [f]**	**1.25 mg**	**100-tablet pack**	**10.97**	**40**
	Calcichew Forte® [f]	2.5 mg	100-tablet pack	21.94	80
Parenteral preparations	Gluconate injection 10%	8.9 mg 10-ml ampoule		0.57	
	Calcium chloride injection	100 mg/ml	10-ml disposable syringe	4.02	
Vitamin D	**Adcal-D3® [g]**	**CaCo 1.5 mg**	**100-tablet pack**	**7.50**	**55**
	Calcichew D3® [f]	1.25 mg, 200 units	100-tablet pack	13.65	100
	Calcichew D3 Forte® [f]	100-tablet pack	16.50	120	
	Calciferol	10,000 units (1.25 mg (50,000 units) may also be available)	20-tablet pack	4.65	
	Calciferol injection	7.5 mg (300,000 units)/ml	1-ml ampoule 2-ml ampoule	5.92	7.07
Calcitriol	Calcijex® [h]	Injection, 1 µg/ml	1-ml ampoule	5.71	
		Injection, 2 µg/ml	1-ml ampoule	11.42	
	Rocaltrol® [i]	**250 ng**	**20-tablet pack**	**4.31**	**157**
HRT for women without a uterus					
Conjugated oestrogens	Premarin® [j]	6.25 µg	3 x 28 tablets	7.36	32
		1.25 mg	3 x 28 tablets	9.99	43
Estradiol only	Organon implants	25 mg	per implant	9.59	19
		50 mg	per implant	19.16	38
		100 mg	per implant	33.40	67
	Elleste-solo® [k]	2 mg tablets	3 x 28 pack	5.34	23
	Elleste-solo MX 80® [k]	80 µg/24 hours	8-pack (two per week)	6.56	85
	Estraderm MX50® [c]	50 µg/24 hours	8-pack (two per week)	7.45	97
	Estraderm MX75® [c]	75 µg/24 hours	8-pack (two per week)	7.90	103
	Estraderm TTS50® [c]	50 µg/24 hours	8-pack (two per week)	7.45	97
	Evorel 50® patches[l]	50 µg/24 hours	8-pack (two per week)	7.45	97
	Evorel 75® patches[l]	75 µg/24 hours	8-pack (two per week)	7.90	103
	Evorel 100® patches[l]	100 µg/24 hours	8-pack (two per week)	8.20	107
	Fematrix® [m]	80 µg/24 hours	8-pack (two per week)	6.95	90
	Femseven 50® [d]	50 µg/24 hours	4-pack (one per week)	6.44	84
	Femseven 75® [d]	75 µg/24 hours	4-pack (one per week)	7.49	97
	Femseven 100® [d]	100 µg/24 hours	4-pack (one per week)	8.19	106
	Oestrogel® [n]	1.5 mg	64-dose pack	7.95	45
	Progynova® [o]	2 mg	3 x 28-pack	7.02	30
	Zumenon® [m]	2 mg	84-pack	7.65	33

continued

***TABLE 55* contd** *Drug costs (entries in bold type are those used in the model)*

Drug class	Drug name	Dosage	Preparation	Unit cost (£)	Annual cost (£)
***HRT for women without a uterus* contd**					
Estradiol, estriol andestrone only	Hormonin® [f]	600 µg	90-tablet pack	6.44	26
	Hormonin® [f]	600 µg	90-tablet pack	6.44	52
Estropipate	Harmogen® [f]	1.5 mg	28-tablet pack	3.14	41
Oestrogens and HRT	Tibolone	2.5 mg daily	28-tablet pack	13.66	178
HRT for women with uterus					
Conjugated oestrogens	Premique® [j]		3 x 28-pack	22.62	98
	Prempak-C® [j]	**625 µg**	**3 x 40-pack**	**13.38**	**58**
Estradiol with progestogen	Climesse® [c]	2 mg	28-pack	7.90	103
	Cyclo-progynova® [p]	2 mg	28-day pack	3.50	46
	Elleste-Duet® [k]	2 mg	3 x 28-day pack	9.72	42
	Estracombi® [c]	50 µg/24 hours	8-patch pack	11.14	145
	Estrapak® [c]	50 µg/24 hours	One-month pack	9.48	123
	Evorel conti patch® [l]	50 µg/24 hours	8-patch pack	12.90	168
	Evorel pak® [l]	50 µg/24 hours	8-patch pack	8.45	110
	Femapak80® [m]	80 µg/24 hours	8-patch pack	8.95	116
	Femoston 2/10® [m]	Estradiol, 2 mg	28-tablet pack	4.99	65
	Femoston 2/20® [m]	Estradiol, 2 mg	28-tablet pack	7.48	97
	Kliofem® [q]	2 mg	3 x 28-tablet pack	25.95	112
	Nuvelle® [o]	2 mg	3 x 28-tablet pack	13.77	60
	Tridesta® [r]	2 mg	91-tablet pack	24.90	100
	Trisequens® [q]	2 mg	3 x 28-tablet pack	20.55	89

[a] Eli Lilly & Company; [b] Rhone-Poulenc Rorer; [c] Novartis Pharmaceuticals; [d] Merck Sharp & Dohme; [e] Procter & Gamble Pharmaceuticals; [f] Shire Pharmaceuticals; [g] Straken; h Abbott Laboratories; [i] Roche Products; [j] Wyeth Laboratories; [k] Searle; [l] Janssen-Cilag; [m] Solvay Healthcare; [n] Hoechst-Marion Roussel; [o] Schering Health Care; [p] ASTA Medica; [q] Novo Nordisk Pharmaceuticals; [r] Orion Pharma

was derived from a synthesis of patient survey data and other published sources.[325,326] The total annual social care cost for hip fracture patients was estimated to be £370.9 million. This figure has been apportioned across the model's three hip fracture patient groups by assuming that 'discharged to home' patients form one patient group, that the two patient groups dying in the year following fracture form a second patient group, and that patients assumed to remain in long-term hospital care or residential care after discharge form a third group. Thus the social care costs per patient for the three defined groups for the year immediately following treatment are estimated to be as follows.

Patients discharged home (45%)	£1,574
Patients dying within the year (30%)	£2,964
Long-term care patients (25%)	£22,218

The total cost estimate of £8.5 million for additional general practitioner (GP) and follow-up outpatient visits estimated by Dolan and Torgerson[20] have been apportioned to all patients discharged from hospital care within the first 12 months after fracture. Thus GP and outpatient average annual costs are estimated to be as follows.

Patients discharged home	£253
Patients dying within the year	£0
Long-term care patients	£202

Aggregating these hip fracture cost estimates, gives year-of-fracture cost estimates per patient as follows.

Patients discharged home	£6,635
Patients dying within the year	£7,772
Long-term care patients	£27,228

These figures represent the year one cost estimates for the defined hip fracture patient groups, 'suffered an uncomplicated hip fracture', 'died from hip fracture' and 'confinement to nursing home due hip fracture', respectively.

Costs for subsequent years were not estimated by Dolan and Torgerson,[20] and very little information to help in the estimation of these was found in the published literature. Consequently, a number of simplifying assumptions were made. Given that all patients who died of their hip fracture were assumed to die within the year of fracture, subsequent year costs were not an issue for this patient group. It was also assumed that patients in the 'uncomplicated hip fracture' group incurred no costs beyond the year of fracture. A possible justification for this simplifying assumption is the prescribing work by Torgerson and Dolan,[314] which indicated a return to control levels of prescribing for hip fracture patients in the year following the year of fracture.

In the analysis by Dolan and Torgerson,[20] all long-stay hospital and residential care patients were assumed to have been discharged to private nursing homes for the second and subsequent years following their fracture. Consequently, they were assumed to incur subsequent year costs of £18,980 per annum, with no additional costs for hip fracture care. This figure has also been used as the cost estimate for any patient confined to a nursing home in the model.

Analysis of local LOS data indicated some justification for age-weighting costs for hip fracture patients discharged home but not for those who died following hip fracture. On the basis of the latter, no age weights were applied to this patient group. Hollingworth and colleagues[307] presented secondary care hip fracture costs by age and gender. Using their results for female hip fracture patients, the analysis by Hollingworth and colleagues implied the following hip fracture age weightings:

- age 45–64 years, 0.61
- age 65–74 years, 0.77
- age 75–84 years, 1.01
- age 85+ years, 1.16.

These weights were applied to the year 1 cost estimates for the 'uncomplicated hip fracture' patient group in the model.

For the group of hip fracture patients discharged to residential care, it was assumed that the costs of medical care were the same in year 1 as for patients discharged home (£6635), and that this cost element for this patient group had the same Hollingworth age weightings.[307] The remainder of the £27,228 was assumed to be invariable by age.

The final group of hip fracture patients for whom age weightings needed to be considered were those living in nursing homes beyond the year of fracture. Dolan and Torgerson[20] estimated costs for nursing home care using data from Netten and Dennett,[326] who indicated that 5% of private nursing home costs comprised fees for external services such as district health authority and GP services. On this basis, it was assumed that 5% of the estimated cost should vary by age. The weightings applied were determined using HCHS *per capita* expenditure figures (see below for details).[327] The model used the same age weightings as for those patients confined to nursing homes for reasons other than hip fracture.

Wrist fracture

Dolan and Torgerson estimated the cost per wrist (Colles) fracture as £468 per annum.[20] This was comprised of £368 for acute care costs, £64 for GP costs and £36 for outpatient costs. This figure has been used for the year-of-incidence cost estimate for wrist fracture in the model. Because of the nature of wrist fractures, it was assumed that all costs associated with wrist fractures are consumed in the year of fracture; hence, there are no subsequent year costs. Statistical analysis of local patient data indicated that there were significant differences in LOS for the different age groups who sustained a Colles fracture. These data were used to derive the following age weightings:

- age 45–74 years, 0.60
- age 75–84 years, 0.99
- age 85+ years, 3.08.

Vertebral fracture

De Laet and colleagues acknowledged that costing information for vertebral fractures was sparse.[328] Although short-term costs are not large compared with, for example, hip fracture, vertebral fractures are more chronic in nature. Despite this, the published evidence for long-term resource use is poor.

Dolan and Torgerson estimated an annual cost of £479 (1995/96) per patient for the year of fracture.[20] This included £62 for costs of bone drugs administered after the fracture. Because costs of bone drugs are modelled separately in the current report, the £62 was deducted to avoid double counting. Vertebral fracture costs were therefore assumed to be £417 per patient in the first year.

Given the chronic nature of vertebral fractures, subsequent year costs will be relatively more

significant than the other fractures modelled. Dolan and Torgerson did not explicitly present longer-term costs for vertebral fractures;[20] however, in a separate paper, Torgerson and Dolan reported that vertebral fracture patients (unlike hip and wrist fracture patients) showed a significant increase in prescribing of bone drugs in the year subsequent to the year of fracture.[314] Given that such prescribing is likely to be accompanied by additional GP and outpatient visits, subsequent year resource use from vertebral fractures is reasonably assumed. Acute costs associated with vertebral fracture were assumed to be confined to the year of fracture. Looking beyond UK-based evidence, the Dutch-based analysis by De Laet and colleagues[328] indicated that, compared with a control group, costs of visits to physicians fell by 40% in the year following a first vertebral fracture. Consequently, it was assumed that 60% (£193) of Dolan and Torgerson's[20] estimated costs of GP and outpatient follow-up visits persist as subsequent-year costs in the model.

None of the reviewed UK-based papers indicated the appropriateness of age weighting for vertebral fractures. In an analysis based in the USA, Chrischilles and colleagues modelled the costs of vertebral fracture for defined age groups.[329] The results of this analysis imply weightings of 0.90, 1.12, 1.17 and 1.27, respectively, for our four age groups. These weights were applied to both year 1 and subsequent year costs in the model.

Other fractures

Dolan and Torgerson[20] quoted an acute cost of £1200 for 'other' fractures, using closed upper limb fracture as a proxy for 'other' fractures. GP and outpatient follow-up costs, including rib, humerus and leg fracture data, were estimated at £138 per patient per annum. The estimated total cost per patient was, therefore, £1338. The age weighting and subsequent year assumptions used for Colles' fracture were also applied to the estimate for 'other' fracture costs.

Adverse drug reactions

Breast cancer

Based on earlier work by Wolstenholme and colleagues,[330] Dolan and colleagues presented a detailed costing analysis that covered all aspects of treatment for breast cancer in the UK.[331] Using 1995/96 prices, costs were analysed using the four recognised stages of cancer development. Individual estimates of treatment costs were required by the model for patients who survived and those that died from cancer. In the model, the simplifying assumption was made that the costs identified by Dolan and colleagues[331] for Stages I–III comprised the costs for cancer survivors. Stage IV costs formed the basis for costing death from breast cancer.

Dolan and colleagues reported individual costs for secondary, primary, hospice and nursing residential care.[331] Their secondary care cost analysis also included estimated costs for breast reconstruction surgery. These costs (£2046 per patient) were apportioned to the survivor group in the model.

The costs of additional GP visits for breast cancer patients were estimated to be £141 per patient by Dolan and colleagues.[331] These costs were apportioned across both defined patient groups. The costs of hospice and nursing residential care were estimated by Dolan and colleagues at £1.1 million for 443 terminally ill patients.[331] This cost was apportioned across all 1456 Stage IV patients in our analysis, implying a mean cost of £781 per patient. Thus, before allowing for inflation, cost estimates for breast cancer patients of £7129 for survivors and £9848 for those who died were used in the model.

According to Dolan and colleagues,[331] the incremental costs of breast cancer tended to occur in the 2 years following onset of disease. On the basis of this evidence, the simplifying assumption that all costs for breast cancer occur in the year of incidence was made. Local LOS data analysis implied no need for age weighting for the costs of surviving or dying from breast cancer.

CHD

The costing assumptions for CHD were based on the work of Pickin and colleagues[332] and Piercy and Pledger.[333] Pickin and colleagues estimated secondary care costs for major CHD events: that is, coronary artery bypass graft £5500; percutaneous transluminal coronary angiography £3517; emergency MI £1887; emergency ischaemic heart disease £1471 (1995/96 prices assumed). Based on the distribution of such events for a UK population, as quoted by Piercy and Pledger,[333] a weighted average cost of £1937 has been calculated for major CHD events. Increasing this by 5% to allow for outpatient events[333] gave an estimated average total cost for CHD of £2034. In addition, it was assumed that CHD patients consumed 6 months' supply of simvastatin in the year of incidence (27.4 mg daily @ £1.52 = £277.40), thereby implying an estimated average total cost of £2311 for year 1. It was assumed in the model that CHD patients would consume simvastatin for

the remainder of their lives, implying annual subsequent year costs of £555 (1995/96 prices).

Estimates of the costs for patients who died from CHD were also required. The simplifying assumption was made that patients who died in the year of a CHD event did so at the end of the acute inpatient episode. Consequently, a cost of £1937 (1995/96 prices) was estimated for death from CHD.

Statistical analysis of local patient data implied that LOS did vary with age for patients discharged home but not for patients dying from CHD. As such, no age weightings were applied to those patients dying from CHD. Using the results of the LOS analysis, the following age weightings were assumed:

- age 45–64 years, 0.60
- age 65–74 years, 0.60
- age 75–84 years, 0.99
- age 85+ years, 3.08.

Given that it is assumed in the model that subsequent year costs for CHD patients comprised only the costs of simvastatin, no age weightings were assumed for these costs.

Healthy life-years

There is an option in the model to consider the costs of healthy life-years for the modelled population. Also, some modelled patient groups (e.g. those discharged to residential care) have required age-related cost weightings. Age-related costs for this population have been estimated using general health expenditure data. In the Office of Health Economics compendium of health statistics,[327] the following age-related *per capita* expenditure (1996/97 prices) for HCHS for England are quoted:

- age 45–64 years, £383
- age 65–74 years, £805
- age 75–84 years, £1435
- age 85+ years, £2274.

Using mid-1996 age group population estimates for England,[334] the weighted average *per capita* expenditure for all individuals over 44 years of age has been estimated at £715. As such, the following cost weightings were estimated for the HCHS *per capita* expenditure figures:

- age 45–64 years, 0.54
- age 65–74 years, 1.13
- age 75–84 years, 2.01
- age 85+ years, 3.18.

The model also contains assumptions about GP visits and BMD scanning activity for patients who were alive and being treated for osteoporosis. Netten and Curtis indicated costs per GP consultation ranging from £13 to £18 (1999/2000).[335] Torgerson and colleagues[318] quoted a BMD scan cost of £25 from a paper by Garton and colleagues,[336] which quoted total scanning costs varying from £21 to £25. Precise timings of costings were not made explicit in the paper, hence, 1991/92 prices were assumed. Applying an HCHS inflator, the estimated 1999/2000 cost was £27.61–32.87. Based on these findings, costs of £16 per GP consultation and £30 per BMD scan were used in the model.

Uncertainties surrounding cost estimates

Taking account of the model's requirements that health state costs were estimated by age and broken down by year of incidence and subsequent-year costs, the analysis presented here required estimation of well over 50 health states costs. Inevitably, these estimates were subject to uncertainty around the central estimates. The drug costs presented in *Table 55* include a range of formulations and, hence, cost estimates. The age- and condition-related cost variations for health states (*Table 54*) could be used as a basis for sensitivity cost estimates for the modelled health states. It is unfortunate that the papers used as a basis for calculating the cost estimates used here presented very limited or, more usually, no sensitivity analyses. In view of this, and in view of the considerable time implications of having to undertake such an analysis, further estimations of costing sensitivity ranges were considered to be beyond the scope of this study. The model was, however, used to test the sensitivity of cost-effectiveness to changes in drug prices.

Summary

The costing data requirements of the model stretched the available literature to their limits. Only a handful of papers proved to be of use in terms of providing information for estimating costs for modelled health states. In particular, evidence for longitudinal and age-related costs was sparse. In view of the lack of published evidence, the authors were forced to take a pragmatic approach to costing by making the best use of the available information.

Chapter 5

Health economics model

Information on effectiveness of interventions (chapter 2), and the risk functions, health states and costs (chapter 4) have been used to populate a cost–utility health economics model. The principles of the model and its inherent assumptions are described below.

Model approach

The approaches used previously were based on cohort analyses using decision-analysis and Markov models.[337,338] The present model is an individual patient-based, transition state, osteoporosis model created in Excel 97© (Microsoft Corporation). In this type of approach, patients are modelled as individuals and whether or not an event will occur in the forthcoming year is simulated for each patient. A full patient history is recorded and thus factors such as prior fractures and current residential status can be used to determine the likelihood of events in the next period. Following a simulated event, the quality of life of the patient and the costs incurred are calculated. Any residual costs of quality-of-life impacts from previous fractures are taken into account for both these factors. The model continues to simulate at 1-year intervals until either the patient dies or the user-defined analysis period (e.g. 10 years) is reached. The process is repeated until all patients have been simulated. The rationale for using the individual patient approach is that it provides more accuracy and flexibility than a cohort approach, which is bounded by a limited number of transition states. Some examples are reviewed briefly below.

The first example relates to the accuracy with which the probability of fractures can be calculated, based on the patient's history. There is a breadth of published literature that indicates that an initial fracture greatly increases the risk of subsequent fractures[263] (see chapter 4). Given this, it would be inaccurate to structure a cohort-based transition state model. Consider the example of two identical patients with osteoporosis at the cohort model initiation, for whom 5 years of life are simulated. Patient A may suffer no fractures in the first 4 years and a wrist fracture in the fifth year. Patient B suffers no fractures in the first 2 years and then suffers a hip, vertebral and wrist fracture in the next 3 years. In a simple cohort model, both patients would now reside in the wrist fracture state. However, if the values from the available data are used, patient B would be at much greater risk of vertebral fracture and at increased risk of hip fracture compared with patient A. Without adjusting for this increased probability of fracture, the model would underestimate the number of fractures that occurred.

As a further example, a large component of costs are those associated with nursing home care following hip fracture. If the model does not track the residential status of a patient, there is a probability that additional nursing home costs would be added for patients already in nursing homes, whose marginal care costs could be zero.

Finally, a patient-based model can accommodate new information. For future modelling uses, when data on the duration of the elevated risk of fracture become available, the ability to know in which periods the fractures occurred may affect the results. This can be incorporated into a model based on an individual patient but would be difficult to undertake in a cohort model and still retain accuracy.

In addition, the reviews described in chapters 2 and 4 have highlighted several uncertainties relating to costs and quality-of-life changes associated with fractures, largely because of the multiple outcomes that are possible in real life. It is uncertain whether the costs of fractures are dependent on the number of previous fractures at a site – for example, whether the cost of treating a second hip fracture is significantly different from treating the first hip fracture. Similarly, the ongoing costs of treating vertebral fractures may differ following a second vertebral fracture. Indeed, interaction of all prior fractures in determining the initial and follow-up treatment costs are not quantified. In order that such costs are accurately totalled, a full patient history would need to be recorded through an individual patient-based method.

Similar considerations pertain to the accuracy with which the quality-of-life changes caused by fractures can be calculated when gaps in our current knowledge are bridged.

Data are required to determine whether the quality-of-life decrements associated with a given fracture are dependent upon the number of previous fractures at that site or elsewhere. For example, it may be shown that the decrease in quality of life is different for a first hip fracture than for a second. Similarly, the loss of quality of life associated with a first vertebral fracture may be different, depending on whether a patient had previously suffered a hip fracture. If these relationships are shown to wane with time then the time at which the fractures occurred needs to be noted. These factors can only be incorporated into an individual-based patient model.

The only alternative method by 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 require 4^{10} branches over a 10-year period, in order that all conceivable combinations of events are recorded – resulting in over 1 million branches at year 10! 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). Hence, 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 unmanageable.

Overview of model

In this study, the transition states between which patients could move were limited to fracture states (hip, wrist, vertebral, proximal humerus, and death due to hip fracture), CHD states (non-fatal and fatal events), breast cancer states (non-fatal and fatal breast cancer) and death from other causes. The probability of a hip fracture causing a patient to reside in a nursing home has been estimated, together with the substantial annual costs that would be incurred.

The CHD and breast cancer states were included because there is published literature reporting that treatments for osteoporosis may also influence the probability of these diseases. The assumptions that are used concerning breast cancer risk with HRT and SERMs were given in chapter 2. In the case of CHD, there is considerable uncertainty over the effects of HRT. The epidemiological data consistently indicate a protective effect but the only prospective RCT showed little or no benefit in women at risk from CHD.[153] For the base case, no cardiovascular risk or benefit has been assumed but the assumptions can be changed for sensitivity analysis. Diseases in which there may be possible links with osteoporosis treatments, such as Alzheimer's disease, and venous thrombolic events, that is, cancer, were excluded from this study, although the model has been written with spare transition state capacity. Thus, when appropriate, further disease areas may be investigated in the future.

The characteristics of the population to be analysed were flexible. The age, T-score and prior history of the population are all user-defined. Here the focus was upon patients with established osteoporosis, defined as having suffered a prior fragility fracture; however, the model also has the facility to analyse patients with low bone mass but without prior fracture. In this study, selected patient groups were chosen for analysis – for example, 60-year-old patients with established osteoporosis and a T-score of –2.5 SD – although the user may choose to enter whatever patient groups are desired.

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

Having established the transition probabilities, the model simulates the experiences of the cohort under 'no treatment'. Outputs are the numbers of life-years gained (discounted at a flexible rate), the numbers of QALYs gained (also discounted at a flexible rate), the discounted costs incurred, and the numbers of each transition state event suffered.

As a patient moves into a transition state, an initial one-off cost is incurred and an ongoing cost 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 in which all the costs are incurred in the initial year. In circumstances in which 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 plus a recurrent cost of £500 annually, a further vertebral fracture in the same individual would cost a further £2000

but the recurrent costs would not increase from £500 per 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, it affects 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 at least the second time, only the initial 1-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 the opposite side to the first, or a second vertebral fracture. However, because of lack of data, the approach taken was to assume no extra residual QALY loss from a second incident.

Having established a baseline, 'no treatment' cost for the cohort, the incremental effects from pharmaceutical treatments have been 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 on 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 have been subjected to meta-analysis for each treatment whenever possible, using published RCTs with the number of fractures as an endpoint (chapter 2). The effectiveness of each treatment has relatively large uncertainties but the meta-analyses have provided distributions and 95% CIs.

In addition to the RRs for efficacy of treatment, the model incorporates offset times, defined as the time from when treatment is stopped to when the RR returns to unity compared with 'no treatment'. It is assumed that the RR returns to unity in a linear manner during the offset time. The incorporation of offset times is crucial in accurately modelling those treatments that are considered to have long residual effects.

Each treatment option has also been assigned costs additional to drug acquisition, namely GP visits, assumed to be two per annum, and BMD scans, assumed to occur in years 2 and 5 of treatment. In sensitivity analyses, when treatment was given for 10 years, the second BMD scan was assumed to occur at year 10. Lack of compliance was also modelled, assuming that the patient incurs 3 months of drug costs but receives no health benefits. It has been assumed that, for the year in which death occurred, the QALYs gained are half those for the prior year, the costs incurred are equal to half of the ongoing annual costs, and only 50% of the drug acquisition cost is paid.

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

The basic design of the Sheffield Health Economics Model for Osteoporosis (SHEMO) is similar, in many ways, to the conventional Markov models used in osteoporosis, in which patients pass through states using a set of transition probabilities, and each state has its associated costs, mortality rates and health state utility values. However, SHEMO differs in two crucial respects to the conventional cohort Markov design. First, individual cases pass through the model one at a time and then a mean estimate is taken of costs, mortality and QALYs for each cohort. The advantage of this individual level approach is that it is able to take account of a patient's history in terms of factors, such as prior fracture (a key factor in fracture rates) and residential status, that can be used to determine the likelihood of an event occurring in the next period. Also, by recording the number of events, and the period in which they occur, the model can provide additional output, once new data become available, on factors such as the interaction of fractures in terms of costs and QALYs, and for how long the increased risk of subsequent fractures persists.

SHEMO also differs from cohort Markov models in that it is a stochastic model that formally incorporates the uncertainties that underlie key parameters. The distribution of values for clinical efficacy is used to reflect current uncertainty, based on the 95% CIs estimated from a systematic review of the published literature. The model works by undertaking the individual level simulations in cohorts and, for each cohort, the RRs are re-sampled using a Monte Carlo simulation.

The key features are:

- an individual patient approach
- accommodation of multiple states: for example, prior fracture, residential status, change in status
- account taken of uncertainty: for example, in efficacy.

The process of estimation is in two parts. The first estimates the relationship between the inputs of the model and the outputs, in terms of costs and QALYs. To do this, approximately 80 different combinations of RR values for each clinical condition (the fractures, CHD and breast cancer) were selected for each age group. For each combination, 8000 patients were simulated to give mean costs and QALY estimates. By undertaking runs that simulated 8000 patients, it was possible to remove a large proportion of 'noise'. The relationship between these model inputs and costs and QALYs was estimated using a non-parametric technique called a Gaussian process.[339] This effectively produces a formula that allows instant calculation of the expected QALY and costs for any parameter set.

The second phase of the estimation process examines the consequences of the uncertainty around the efficacy estimates for each treatment. For each treatment, 1000 values of efficacy for each type of fracture (plus CHD and breast cancer for some treatments) were selected using Monte Carlo methods. From the 1000 samples of parameter points, the model formulated in the first phase was used to generate estimates of 1000 costs and QALYs. These formed the basis of the estimated mean cost per QALY, and the associated CIs, compared with 'no treatment'.

The mean cost per QALY was calculated as the mean cost difference divided by the mean QALY difference for the 1000 points and for 'no treatment'. The CIs were calculated by ranking the cost per QALY from each of the 1000 parameters and ascertaining the 90% and 80% CIs. These CIs reflect the genuine uncertainty around the estimate rather than random noise. As the results have been generated from a formula, any differences in the mean cost per QALY and the CIs between treatments are due solely to the RRs around efficacy.

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

Population of the model

Population start age

The model had 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 our purposes, women were chosen at ages 50, 60, 70 or 80 years of age.

Osteoporotic fracture

The present study considers fractures of the spine, hip, proximal humerus and distal forearm. Established osteoporosis is defined as an individual with one or more of these fractures, having a T-score at the femoral neck that is 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 and summarised in *Table 56*. For each year over age 50 years, the expected cumulative number of fractures per site was calculated.

These were then proportioned to provide the percentages shown in *Table 57*. 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 age 80 years. Thus, in each cohort of 100 individual patients at age 70, 11% were assumed to have had hip fractures, 19% vertebral fractures, 56% wrist fractures and 14% proximal humerus fractures.

This approach is likely to produce some bias, caused by patients with more than one prior osteoporotic fracture. For example, in an extreme case in which all 80-year-old patients 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 previously (in chapter 2), 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, (number of SDs below the BMD of a young female adult) can be user defined. Osteoporosis is defined as a T-score of –2.5 SD unless otherwise indicated.

TABLE 56 *Annual fracture risk by age at the sites shown*

Age range (years)	Annual fracture risk (%)			
	Hip	Spine	Wrist	Proximal humerus
50–54	0.041	0.160	0.255	0.058
55–59	0.050	0.087	0.374	0.085
60–65	0.083	0.139	0.467	0.136
65–69	0.157	0.178	0.573	0.126
70–74	0.485	0.461	0.699	0.246
75–79	0.707	0.467	0.697	0.306
80–84	1.437	0.503	0.749	0.372
85–89	2.761	0.884	1.001	0.362
90+	3.851	1.232	0.919	0.391

TABLE 57 *The estimated starting distributions of established osteoporosis at various ages*

Fracture site	Estimated starting distributions of osteroporosis (%) at ages (years)			
	50	60	70	80
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 at 6% per annum, in accordance with published guidelines.[340] The default discount rate for QALYs was set at 1.5% per annum.[341] However, because of debate about the value that should be used, a sensitivity analysis, run in parallel, used a discount value of 6% per annum.

Default state transition probabilities

In this study, the following transition states were used in the model.

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. Sustained a wrist fracture
7. Sustained a proximal humerus fracture
8. Contracted breast cancer
9. Death due to breast cancer
10. Sustained a non-fatal CHD incident
11. Death due to a CHD incident
12. Death due to other causes

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

The model could accommodate 25 different states, so that conditions that were suspected but currently unproven to have RRs associated with osteoporosis treatment could be entered into a future model if new evidence was obtained.

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

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

Osteoporotic

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

For patients in this state, the probability is zero, with 'no event' signifying that a patient remains healthy although osteoporotic. As the focus of this study is on patients with established osteoporosis, this state was not populated in this model.

Fracture risks

The estimated figures for the average population are shown in *Table 56*. The average population risks were adjusted for a population with osteoporosis. The risk of fracture in 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 a meta-analysis[16] that was similar to those derived from the SOF study.[9] The predicted number of wrist and vertebral fractures was slightly lower than those predicted by use of the SOF figures.

The fracture risks were computed for individuals with a T-score of –2.5 using these gradients and the pattern of change of BMD with age described in chapter 4.

Death due to hip fracture

It was assumed that 48% of all deaths in the first year associated with hip fracture are causally related to the fracture and would therefore be avoided by preventing hip fracture (chapter 4). 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.

Death due to vertebral fracture

No excess mortality was assumed other than that accounted for by low BMD. It was assumed that interventions that increase the BMD of a patient will not change the T-score (BMD)-adjusted risk of death from other causes.

Developed breast cancer

The risks of breast cancer, taken from the cancer registrations in England and Wales, were adjusted downwards to accommodate the evidence that low BMD is associated with a lower breast cancer risk.

Death due to breast cancer

Risks of death for the UK were used. It was assumed that the risk of death following breast cancer in women with osteoporosis was similar to that in the general population.

Death due to CHD

Risks of death for the UK were used. It was assumed that the risk of death from CHD in women with osteoporosis is similar to that in the general population.

Sustained a non-fatal CHD event

Data were derived from those for England. It was assumed that the probability of CHD in patients with osteoporosis is similar to that in the general population.

Death due to other causes

These were computed from interim life tables and adjusted for deaths due to CHD and breast cancer. It should be noted that excess mortality was assumed for low values of BMD.

Adjustments to the default transition probabilities

The model had the facility to allow prior patient states to influence the transition matrix. This was needed since the risk of a secondary fracture is higher than the risk of an initial fracture.

A summary of each state is given 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 from Klotzbeucher and colleagues has been used with some additional assumptions.[263] It was assumed that future fractures at the proximal humerus were equivalent to future fractures that were in the non-spinal category. It was also assumed that the proximal humerus had the predictive power equal to that of the 'other' category. All populations were assumed to be peri/postmenopausal. There were no prior studies on the future effect that hip fractures might have on wrist fractures. As a conservative estimate, this risk was set at 1.4, equivalent to the lowest RR of all other fracture sites.

It was assumed that, for individuals who suffered fractures at two different sites, only the greatest risk adjustment would 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 for a

second wrist fracture would be 3.3 (from the wrist fracture).

Contracted breast cancer

The model has the facility to increase the risk of contracting breast cancer following an earlier non-fatal breast cancer incident. Because of a paucity of prospective data, this was set to RR = 1 in the base case but altered for the sensitivity analyses. A change in risk was assumed to revert to 1.0 when treatment was stopped (i.e. offset time = 0).

Suffered a CHD incident

The model has the facility to increase the risk of a CHD incident following an earlier non-fatal CHD incident. Because of lack of data, this was set to RR = 1 in the base case but altered for sensitivity analyses. A change in risk was assumed to revert to 1.0 as soon as treatment stopped.

Compliance

It was assumed, in consultation with clinicians, that the patient, if non-compliant, would 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 RR derived by meta-analysis (chapter 2). 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 (see chapter 2) and thus, as the duration of treatment increases, the assumption of a consistent risk reduction becomes unsafe. This was one of the reasons for selecting a 5-year treatment time that corresponded to the duration of exposure in RCTs, particularly those undertaken in the past 10 years.

The treatment effect was 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 individuals drawn from the cohort according to the probability density. For many treatments, the 95% CI for efficacy exceeded a value of 1. 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 when 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 hip fracture risk is related to the expense of undertaking such studies and the regulatory framework, which does not encourage such studies for registration. For this reason, sensitivity analyses were undertaken in two ways relating to the effectiveness of treatment. When there was a small effect or no effect on hip fracture risk, the RR was set at an absolute value of 1.0. When there was a substantial effect on hip fracture risk but the CIs exceeded 1.0, the estimate was set at the point estimate without CIs.

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 2). The offset time was assumed to be 5 years for all interventions except calcium and calcitonin. For these agents, a 3-year offset time was assumed. 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 the sensitivity analyses.

In the base case no interaction was assumed between treatment and non-skeletal outcomes. As mentioned previously, patients with osteoporosis were assumed to have a lower risk of breast cancer. Such data were derived from epidemiological estimates and may therefore be subject to bias. When treatments had an effect on breast cancer risk, this assumption was tested by sensitivity analysis. In the case of HRT, epidemiological evidence also indicated that it might afford substantial cardiovascular protection (see chapter 2). Again, this was derived from epidemiological data so was not considered in the base case. Base-case assumptions and sensitivity analyses for efficacy are shown in *Tables 58* and *59*.

All of the agents under consideration have been shown to have side-effects. In most instances, the prevalence was not well documented, nor were the consequences known for quality of life expressed in utilities (chapter 2). Also, the impact of side-effects on compliance is conjectural. Adverse effects have not been included in the analysis, although it should be recognised that even small gains or decrements in quality of life caused by side-effects could have a marked impact on cost-effectiveness.

TABLE 58 *Efficacy of agents on fracture risk at the sites shown for the base case (A) and sensitivity analyses (B/C)*

Agent		RR (0.95% CI)			
		Spine	**Hip**	**Forearm**	**Humerus**
Alendronate	A	0.544 (0.448 to 0.659)	0.611 (0.392 to 0.951)	0.866 (0.672 to 1.115)	0.825 (0.736 to 0.926)
Bisphos-phonates[a]	A	0.526 (0.445 to 0.637)	0.672 (0.459 to 0.983)	0.833 (0.659 to 1.054)	0.824 (0.745 to 0.913)
	B[b]	0.575 (0.490 to 0.675)	0.620 (0.368 to 1.042)	0.566 (0.377 to 0.848)	0.813 (0.693 to 0.954)
Alfacalcidol	A	0.459 (0.149 to 1.414)	0.249 (0.009 to 6.768)	1.042 (–[c])	0.193 (0.007 to 5.068)
	B	0.459 (0.149 to 1.414)	1.0	1.0	1.0
Calcitonin	A	0.308 (0.113 to 0.838)	0.681 (0.145 to 3.198)	0.947 (0.197 to 4.565)	0.553 (0.224 to 1.254)
	B	0.308 (0.113 to 0.838)	1.0	1.0	0.553
	C	0.308 (0.113 to 0.838)	0.63 (0.440 to 0.900[d])	1.0	0.553
Fluoride	A	0.350 (0.253 to 0.486)	1.778 (0.758 to 4.170)	0.766 (0.371 to 1.583)	0.975 (0.782 to 1.217)
	B	0.350 (0.253 to 0.486)	1.0	1.0	1.0
Calcium	A	0.550 (0.330 to 0.930)	1.0	1.0	1.0
	B[e]	0.550 (0.330 to 0.930)	0.738 (0.600 to 0.908)	0.739 (0.687 to 0.917)	0.739 (0.687 to 0.917)

[a] *Aggregate of bisphosphonate data*
[b] *Patients with prior fracture*
[c] *Confidence estimate not modelled due to high range of risk (0.021 to 51.993)*
[d] *Observational estimate*
[e] *Calcium plus vitamin D*

TABLE 59 *Efficacy (RRs and 95% CIs) of raloxifene and HRT on fracture risk, CHD and breast cancer showing the base case and sensitivity analyses*

Base case (A) or sensitivity analysis (B, C, D, E)	RR (95% CI) of fracture				RR (95% CI) of CHD[a]	RR (95% CI) of breast cancer[a]
	Spine	**Hip**	**Forearm**	**Humerus**		
Raloxifene						
A	0.596 (0.516 to 0.688)	1.141 (0.663 to 1.966)	0.887 (0.684 to 1.151)	0.920 (0.792 to 1.068)	1.00	0.35 (0.21 to 0.58)
B	0.596 (0.516 to 0.688)	1.00	1.00	1.00	1.00	0.35 (0.21 to 0.58)
C	0.596 (0.516 to 0.688)	1.00	1.00	1.00	0.80[b]	0.35 (0.21 to 0.58)
Oestrogen						
A	0.583 (0.262 to 1.301)	1.00	1.00	1.00	1.00	1.00
B	0.583 (0.262 to 1.301)	0.86[c] (0.42 to 1.75)	0.32[c] (0.13 to 0.78)	0.63[c] (0.45 to 0.89)	1.00	1.00
C	0.583	0.86[c]	0.32[c] (0.13 to 0.78)	0.63[c] (0.45 to 0.89)	1.00	1.00
D	0.583	0.86[c]	0.32[c] (0.13 to 0.78)	0.63[c] (0.45 to 0.89)	0.66[c] (0.53 to 0.84)	1.00
E	0.583 (0.262 to 1.301)	0.86[c] (0.42 to 1.75)	0.32[c] (0.13 to 0.78)	0.63[c] (0.45 to 0.89)	0.66[c] (0.53 to 0.84)	1.35[c] (1.21 to 1.49)

[a] *Offset time = 0*
[b] *Computed from lipid changes*
[c] *Observational estimate*

The failure to include beneficial effects on symptoms is most problematic in the case of HRT, since HRT has been proven to reduce symptoms associated with the menopause. Indeed, health economics analyses suggest that treatment for this indication alone is cost-effective.[2] It was decided not to include such effects for several reasons. First, the use of HRT for menopausal symptoms is given for months rather that the several years required for the management of osteoporosis. Second, a very small minority of patients at menopause are expected to have osteoporosis. Third, the assumptions concerning efficacy were based on epidemiological estimates with their own uncertainties, so that the inclusion of an effect on menopausal symptoms provided an unnecessary level of complexity for uncertain gains. The additional potential extra-skeletal benefits of HRT (and SERMs) on cardiovascular disease were accommodated in a sensitivity analysis.

All analyses are based on the 10-year time frame rather than over a lifetime, unless otherwise stated. In the context of treatments that are presently developed for 3–5 years, a 10-year interval was considered to be more appropriate. It takes account of the intervention period as well as the offset time of therapeutic effect once treatment is stopped.[44] In addition, the predictive value of risk factors such as low BMD becomes less over intervals greater than 10 years.[42] A time frame of 15 years was used in sensitivity analysis to model a change in the assumption relating to offset time.

Chapter 6
Results

Analytical approach

The results for each drug at each age group are presented in terms of a central estimate of cost per QALY gained and a cumulative frequency distribution represented in the tables by the 90% CIs. Note that the CI is not that of the central estimate of cost-effectiveness but of the range of costs per QALY gained that is incurred by 90% of runs sampled over the range of efficacy for the intervention. An example is provided in *Figure 19* that shows the cost-effectiveness ratio of a hypothetical agent in women aged 60 years. The mid-point estimate of cost-effectiveness was £22,557. The cost-effectiveness ratio varied between £13,562 and £546,604. In 90% of the estimates, the cost-effectiveness ratio lay between £17,362 and £40,779.

In cases where the cost-effectiveness curve intersects with 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 for the *y*-axis denotes the proportion of estimates that are dominating (i.e. 'increasing costs' and 'detrimental to health').

Because of the very wide CIs generated by analysis of trials of calcitriol (RR = 0.87; 95% CI, 0.00 to 218.4 for hip fracture), and because there was no effect on vertebral fracture risk, this intervention was omitted from the analyses. However, alfacalcidol has been included, although this agent is not a licensed treatment for osteoporosis in the UK.

Costs for different interventions are summarised in *Table 60*.

The results from the base-case assumptions are described below. These discount costs 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

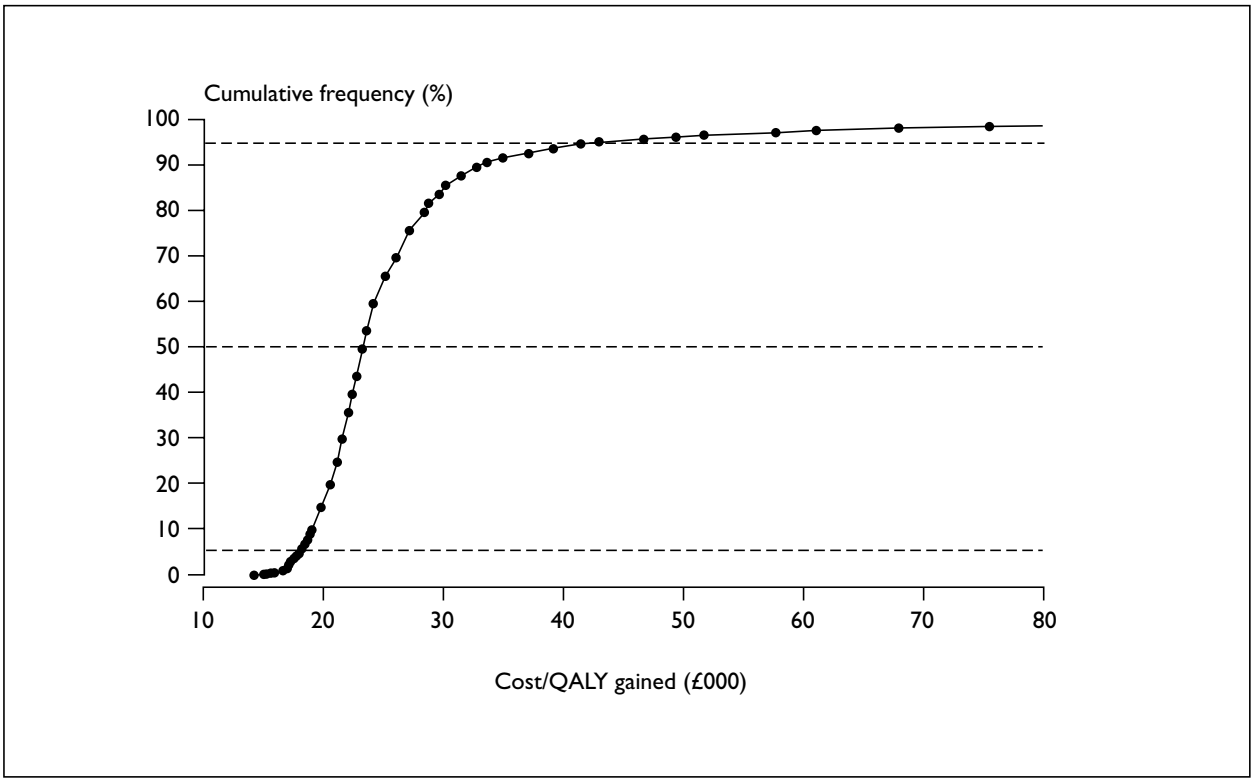

FIGURE 19 *Distribution of cost-effectiveness of a hypothetical agent in women aged 60 years with established osteoporosis. Horizontal lines denote the cost-effectiveness ratio of 5%, 50% and 95% of the cohort (£17,362, £22,557 and £40,779, respectively)*

TABLE 60 *Costs of different interventions*

Intervention	Annual cost (£)
No treatment	0
Calcium	40
Fluoride	48
Calcium plus vitamin D	55
HRT	58
Alfacalcidol	157
Etidronate	163
Raloxifene	257
Alendronate	334
Calcitonin	2314

presented in *Table 61* to derive the marginal costs and QALYs. Each treatment was given to a population of women with osteoporosis, that is, with a predetermined ratio of individuals with prior fractures of different types. Results of cohorts with specific fracture types are shown subsequently in sensitivity analyses and as clinical vignettes.

In this study, a threshold of £30,000/QALY gained for cost-effectiveness has been used:

TABLE 61 *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	92.0	702.5
60	133.1	669.4
70	285.3	530.1
80	645.6	366.7

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

that is, treatments that have a cost–utility ratio of £30,000 or less are considered cost-effective.[342] Since the methodology gives 'CIs' for cost-effectiveness, this permits several categories to be derived, based on the 90% interval, as shown in *Table 62*. Note that the 90% CI describes the cost-effectiveness ratio computed in 90% of the samples and not the confidence estimate of the mid-point estimate. A grade of A or B was considered to be cost-effective for the purposes of this study.

Specific treatments

Raloxifene

Raloxifene significantly reduced the risk of vertebral fracture (RR = 0.60) but had no significant effect on appendicular fractures. For the base case, a significant effect on breast cancer was assumed (RR = 0.35), in line with RCT evidence and, in the absence of RCT data, a neutral effect on CHD.

It was not cost-effective to treat women with established osteoporosis. At age 50 years, the cost per QALY gained was £572,125 (*Table 63*). The cost per QALY decreased at age 60 years but thereafter increased with age. This is because the assumed effectiveness on hip fracture is negative (RR = 1.14). The adverse effect of hip fracture risk with age was not compensated by additional dividends from breast cancer prevention, at least over the 10-year time frame modelled.

When the assumption was made that the effects of raloxifene on appendicular fractures were neutral (i.e. RR set to 1.0), then cost-effectiveness improved, and improved with advancing age except at age 80 years (*Table 64*). Cost-effectiveness remained on average above the threshold of £30,000/QALY gained in 90% of the treated cohort at all ages.

TABLE 62 *Classification of cost-effectiveness*

Grade	Description	Cost-effectiveness (£/QALY gained) 90% CI		
		Mid-point	Lower	Upper
A*	Always cost-effective	< 0	< 0	< 0
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 63 *Cost-effectiveness of using of raloxifene in women with established osteoporosis according to age: base case*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
50	235.1	702.8	572.1	61.6	dominated	D
60	280.2	670.9	94.7	29.6	dominated	D
70	441.1	530.9	187.0	11.6	dominated	D
80	815.0	366.0	dominated	dominating	dominated	D

[a] *Discounted at 6%;* [b] *discounted at 1.5%*

TABLE 64 *Cost-effectiveness of using of raloxifene in women with established osteoporosis according to age (raloxifene is assumed not to affect the risk of appendicular fracture)*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
Neutral effect on appendicular fracture						
50	232.2	703.5	148.5	126.8	180.8	D
60	273.0	672.3	47.8	35.2	71.0	D
70	411.8	532.8	46.4	31.4	59.0	D
80	754.0	368.2	76.1	50.0	223.0	D
Effect on cardiovascular disease						
50	232.2	703.5	148.1	126.8	180.8	D
60	273.1	672.4	46.6	31.9	70.1	D
70	414.7	535.1	25.6	20.2	32.0	B
80	754.1	373.9	15.2	11.2	20.6	A

[a] *Discounted at 6%;* [b] *discounted at 1.5%*

Since RCTs showed that raloxifene had significant effects on surrogate markers of CHD, a 20% RR reduction in cardiovascular disease was examined. This resulted in a marked improvement in cost-effectiveness (see *Table 64*) that improved with age. At age 70 years or more, raloxifene was cost-effective in nearly 90% of treated women. The cost-effectiveness acceptability curve for this scenario is shown in *Figure 20*.

Cost-effectiveness ratios improved when patients at higher risk were treated (T-score < 2.5 SD; see page 100).

A focus of the brief for raloxifene was to examine its cost-effectiveness for prevention as well as for treatment of established osteoporosis. Raloxifene was not found to be cost-effective except in the very elderly, so that prevention would be even less cost-effective, since the risks of fracture are lower in patients without prior fractures.

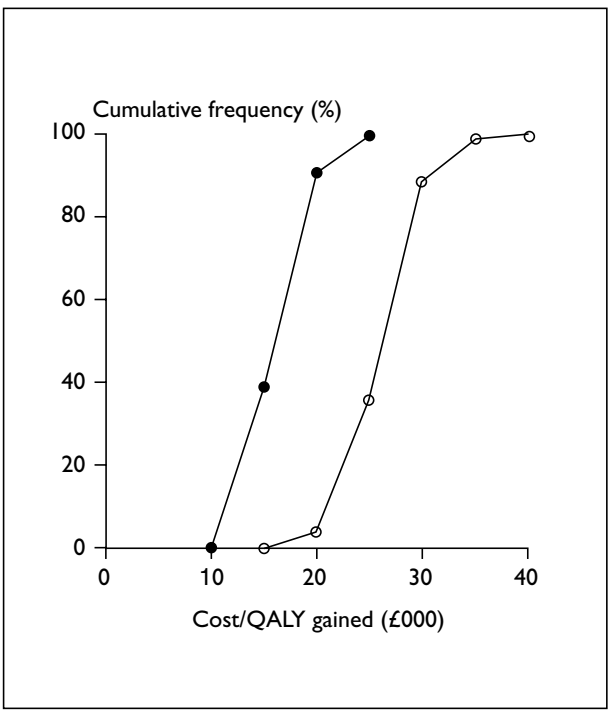

FIGURE 20 *Distribution of cost-effectiveness of raloxifene in women aged 70 and 80 years with established osteoporosis (○, 70 years; ●, 80 years)*

HRT

The base case for HRT assumed efficacy only on vertebral fracture risk (RR = 0.58) and, in

TABLE 65 *Cost-effectiveness of using HRT in women with established osteoporosis according to age*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
50	144.5	703.4	61.9	30.9	dominated	D
60	186.7	671.3	27.8	17.2	dominated	B
70	330.6	532.0	24.1	13.3	dominated	B
80	681.8	368.6	19.9	6.1	dominated	B

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

line with RCT data, no effect on appendicular fractures or CHD. Note that the 95% CI for vertebral fracture efficacy crossed unity. Under these assumptions, it was not cost-effective in women aged 50 years (*Table 65*). At age 60 years or more, the mid-point estimate for cost per QALY gained was less than £30,000.

The assumptions on effectiveness were varied in sensitivity analyses. The first analysis was to assume that HRT decreased the risk of appendicular fractures in line with the extensive epidemiological data. Note that the RR of hip fracture was reduced but the 95% CI crossed unity (RR = 0.86; 95% CI, 0.42 to 1.75). Under this assumption, cost-effectiveness improved (*Table 66a*). On average, cost-effectiveness scenarios were found at all ages. Cost-effectiveness improved still further when point estimates of efficacy were used to model hip fracture outcomes (*Table 66b*), that is, for this purpose, the RR was pegged at 0.86 without the use of confidence estimates. In this way, the risk of hip fracture could not increase over the control risk. The improvement in cost-effectiveness was more marked with advancing age and the grading of cost-effectiveness improved from B to A at age 70 years and from B to A* at age 80 years.

In the absence of RCT data, the model above assumed neutral effects on CHD and breast cancer. Population of the model with effects of HRT on CHD, as observed in epidemiological studies, improved cost-effectiveness (*Table 66c*). Little improvement was observed at age 50 years because of the low absolute risk of cardiovascular disease. At age 60 years or more, treatment was always cost-effective.

The addition of a significant increase in the risk of breast cancer (RR = 1.35) had a modest impact on the central estimate of cost-effectiveness (*Table 66d*). Overall, the principal effect of adding cardiovascular plus breast cancer risk was to improve the cost-effectiveness ratio marginally: that is, the benefits of cardiovascular protection largely offset the risks of breast cancer. In the cost-effectiveness curves shown in *Figure 21*, it is assumed that HRT has both cardiovascular benefits and breast cancer risks. Note that cost-effectiveness was not observed in all patients.

Calcium

In the base case for calcium, only effects on vertebral fracture were considered, in accordance with the methodology chosen for the meta-analysis of RCTs (RR = 0.55). It was assumed, therefore, that calcium had no effect on appendicular fractures. An offset time of 3 years was modelled. On average, calcium was cost-effective from age 60 years (*Table 67a*). Cost-effectiveness acceptability curves are shown for the cost-effective scenario in *Figure 22*.

The evidence from RCTs indicated, however, that calcium given with vitamin D decreased the risk of appendicular fractures in women. In these studies, BMD was not systematically assessed and was therefore omitted from the meta-analysis and base-case analysis. When these effects were included in the model (using a price for calcium and vitamin D), it was, on average, cost-effective to use calcium with vitamin D at all ages. Cost-effectiveness was below the threshold of £30,000/ QALY gained in > 90% of patients aged 60 years or more (*Table 67b*). Cost-savings occurred at age 80 years.

Cost-effectiveness acceptability curves are shown for all ages in *Figure 23*. Cost savings occurred in 43% of individuals at age 70 years and in 98% at age 80 years.

TABLE 66 *Sensitivity analysis of cost-effectiveness of using HRT in women with established osteoporosis according to age*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
(a) HRT affects appendicular fractures						
50	140.4	704.2	29.3	10.7	dominated	B
60	176.7	672.8	12.7	3.6	dominated	B
70	313.5	534.3	6.7	dominating	dominated	B
80	633.1	373.2	dominating	dominating	dominated	B
(b) HRT has fixed effect on appendicular fracture						
50	139.3	704.4	25.1	16.8	65.1	B
60	174.0	673.1	10.9	7.7	20.7	A
70	304.7	534.4	4.5	2.5	12.0	A
80	611.7	373.7	dominating	dominating	dominating	A*
(c) Additional benefits in CHD included						
50	139.3	704.4	25.1	16.8	65.1	B
60	174.1	673.3	10.6	7.6	20.5	A
70	304.8	536.4	3.1	1.8	7.9	A
80	611.8	377.9	dominating	dominating	dominating	A*
(d) Additional risk of breast cancer included						
50	140.4	704.2	29.4	10.7	dominated	B
60	176.7	672.9	12.4	3.6	dominated	B
70	313.6	535.7	5.0	dominating	dominated	B
80	633.1	376.4	dominating	dominating	dominated	B

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

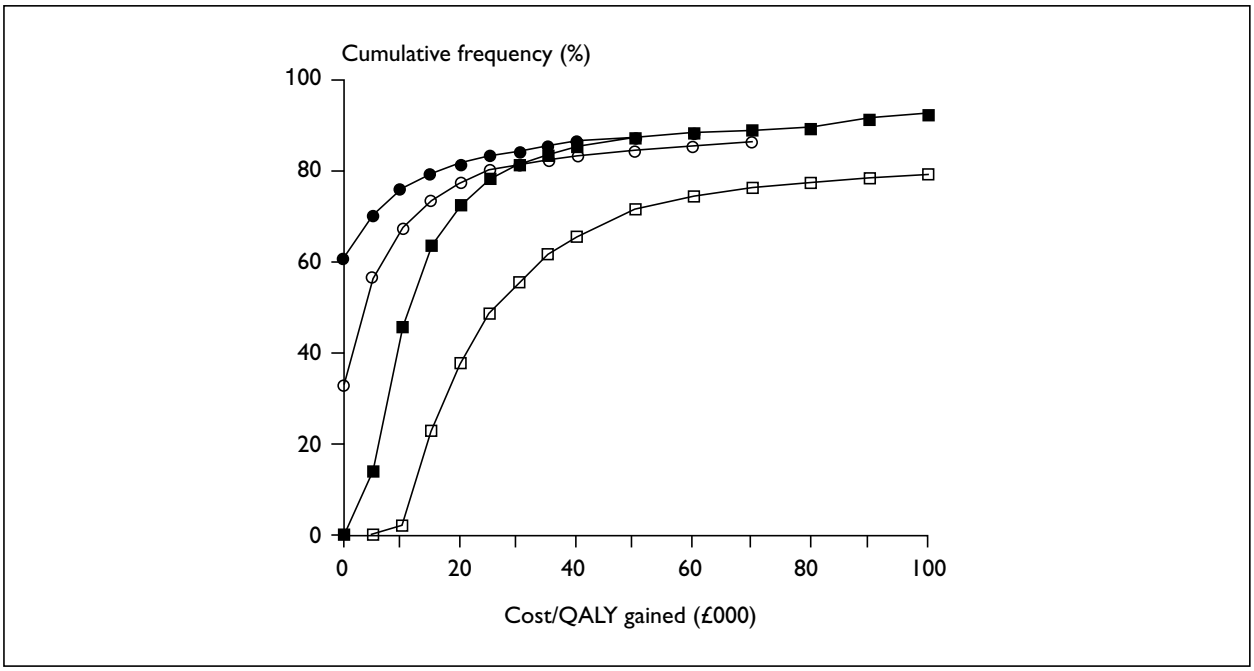

FIGURE 21 *Distribution of cost-effectiveness of HRT in women aged 50–80 years with established osteoporosis (□, 50 years; ■, 60 years; ○, 70 years; ●, 80 years)*

TABLE 67 *Cost-effectiveness of using calcium or calcium with vitamin D in women with established osteoporosis according to age*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
(a) Calcium: effects on vertebral fractures only						
50	136.1	703.5	44.0	28.5	121.4	C
60	178.5	671.5	21.4	15.0	44.7	B
70	322.0	532.4	15.9	10.8	41.5	B
80	671.5	368.3	16.3	5.1	124.3	B
(b) Calcium + vitamin D: effects on appendicular fractures also						
50	136.7	704.8	19.8	14.2	33.6	B
60	169.9	673.4	9.2	6.0	16.1	A
70	287.9	535.6	0.4	dominating	6.7	A
80	570.9	374.0	dominating	dominating	dominating	A*

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

Calcitonin

It was not cost-effective to use calcitonin for long-term treatment of established osteoporosis, according to the data derived from the meta-analysis (*Table 68a*). An offset time of 3 years was used in the model. The fact that the assumed effects on hip fracture (RR = 0.68) ranged from 0.15 to 3.20 is relevant. When neutral effects on hip fracture were assumed, only minor effects were noted and cost-effectiveness was still not seen at any age (*Table 68b*). As reviewed earlier in chapter 2, the mid-point estimate for the effects of calcitonin on hip fracture risk from RCTs is similar to that from the epidemiological data, that is, 0.63. The confidence estimate for the case–control analysis indicates a significant association between exposure to calcitonin and hip fracture risk (95% CI, 0.44 to 0.90). The inclusion of this effect in the model improved cost-effectiveness but not sufficiently to impact on the grade of cost-effectiveness (*Table 68c*).

Alendronate

The most extensive RCT information base exists for alendronate. The agent has been shown to significantly reduce hip fracture (RR = 0.61), vertebral fracture (RR = 0.54) and humeral fracture (RR = 0.83). The effect on forearm fractures (RR = 0.87) was not significant. The cost-effectiveness ratio improved with age. Treatment with alendronate became cost-effective at age 70 years or more. At age 80 years, treatment was always cost-effective (*Table 69* and *Figure 24*).

Bisphosphonate

There was little evidence of differences in efficacy between the bisphosphonates (see chapter 2), and for this reason, data were pooled. Mid-point estimates were comparable to those of alendronate for spine and humeral fractures but slightly less favourable for hip fracture and slightly more favourable for forearm fracture (see *Table 60*). With a treatment cost of £163 yearly (the price of etidronate), treatment was not cost-effective at age 50 years but became

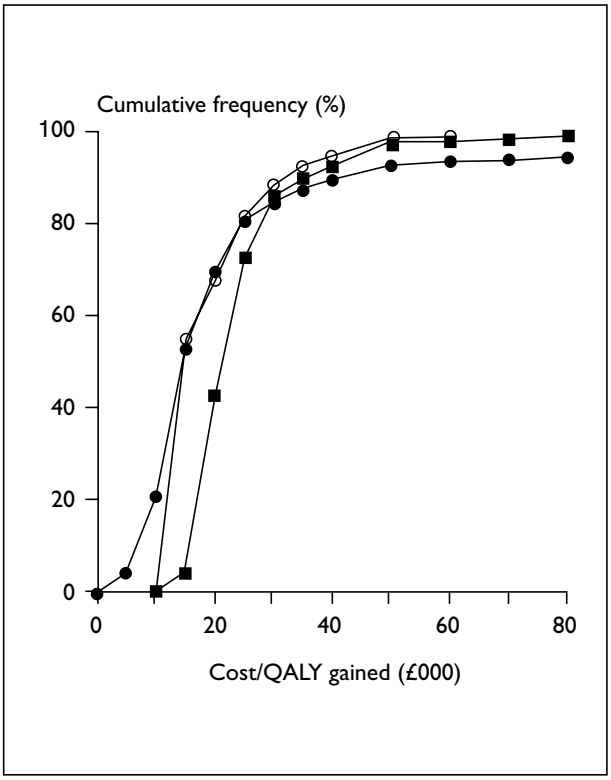

FIGURE 22 *Distribution of cost-effectiveness of calcium in women aged 60–80 years with established osteoporosis (■, 60 years; ○, 70 years; ●, 80 years)*

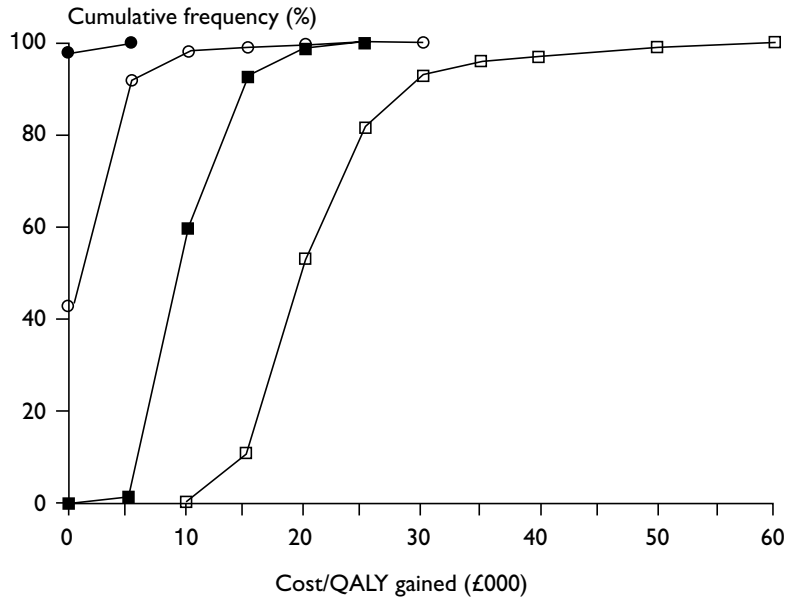

FIGURE 23 *Distribution of cost-effectiveness of calcium plus vitamin D in women aged 50–80 years with established osteoporosis (□, 50 years; ■, 60 years; ○, 70 years; ●, 80 years)*

TABLE 68 *Cost-effectiveness of using calcitonin in women with established osteoporosis according to age*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
(a) Results of meta-analysis						
50	1138	704.1	641	205	dominated	D
60	1161	672.6	301	118	dominated	D
70	1256	535.9	168	55	dominated	D
80	1472	373.4	124	27	dominated	C
(b) Assuming neutral effect on hip fracture						
50	1138	704.1	685	512	1413	D
60	1162	675.6	323	248	551	D
70	1263	534.2	235	159	777	D
80	1490	370.2	245	142	533	D
(c) Effects on hip fracture from epidemiological data						
50	1132	705.6	341	247	1450	D
60	1147	675.0	182	175	1207	D
70	1210	538.6	108	78	190	D
80	1363	377.0	70	44	146	D

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

TABLE 69 *Cost-effectiveness of using alendronate in women with established osteoporosis according to age*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
50	258.2	705.2	61.4	45.5	111.6	D
60	287.2	673.8	35.3	24.4	63.7	C
70	387.0	537.8	13.3	6.2	37.0	B
80	633.4	376.5	dominating	dominating	21.3	A

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

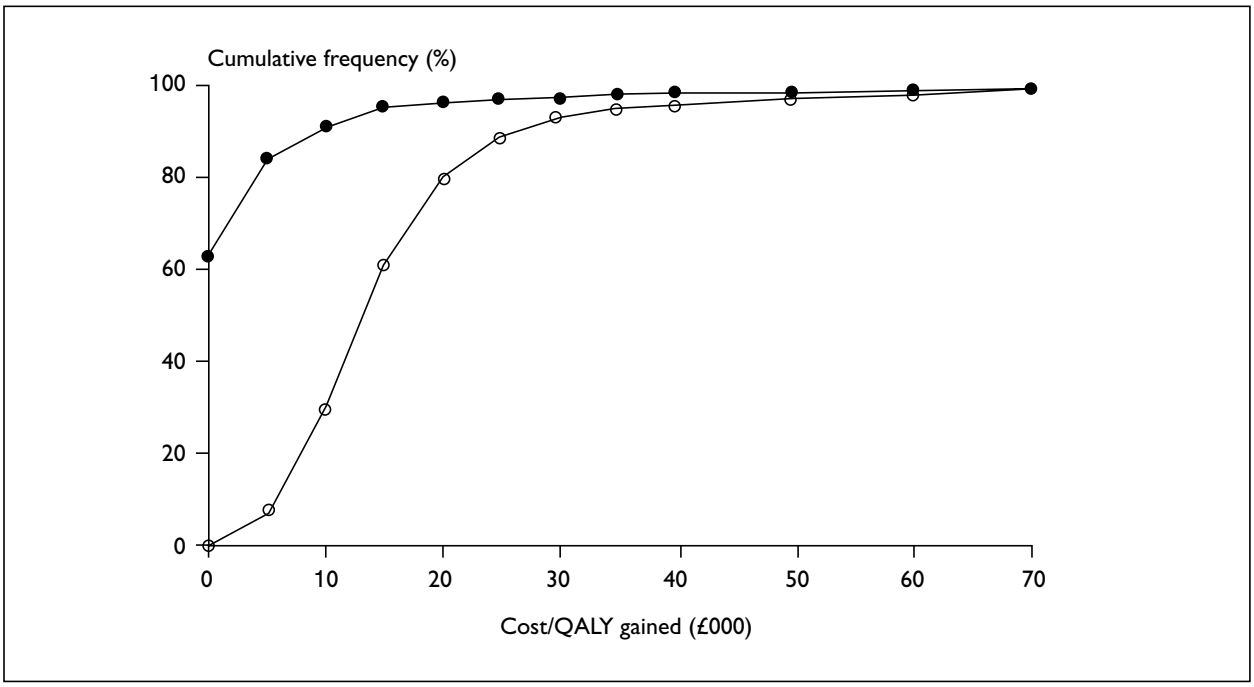

FIGURE 24 *Distribution of cost-effectiveness of alendronate in women aged 70 and 80 years with established osteoporosis (○, 70 years; ●, 80 years)*

TABLE 70 *Cost-effectiveness of using bisphosphonate in women with established osteoporosis*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
Intervention costs £163/year						
50	183.5	705.1	36.1	26.0	66.1	C
60	215.2	673.5	19.8	13.0	36.4	B
70	324.5	536.9	5.7	0.9	21.1	A
80	590.5	375.4	dominating	dominating	10.4	A
Intervention costs £334/year						
50	259.0	705.1	65.8	48.4	117.8	D
60	289.5	673.5	37.8	26.0	66.5	C
70	395.3	536.9	16.1	7.9	40.1	B
80	653.7	375.4	0.9	dominating	28.2	A

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

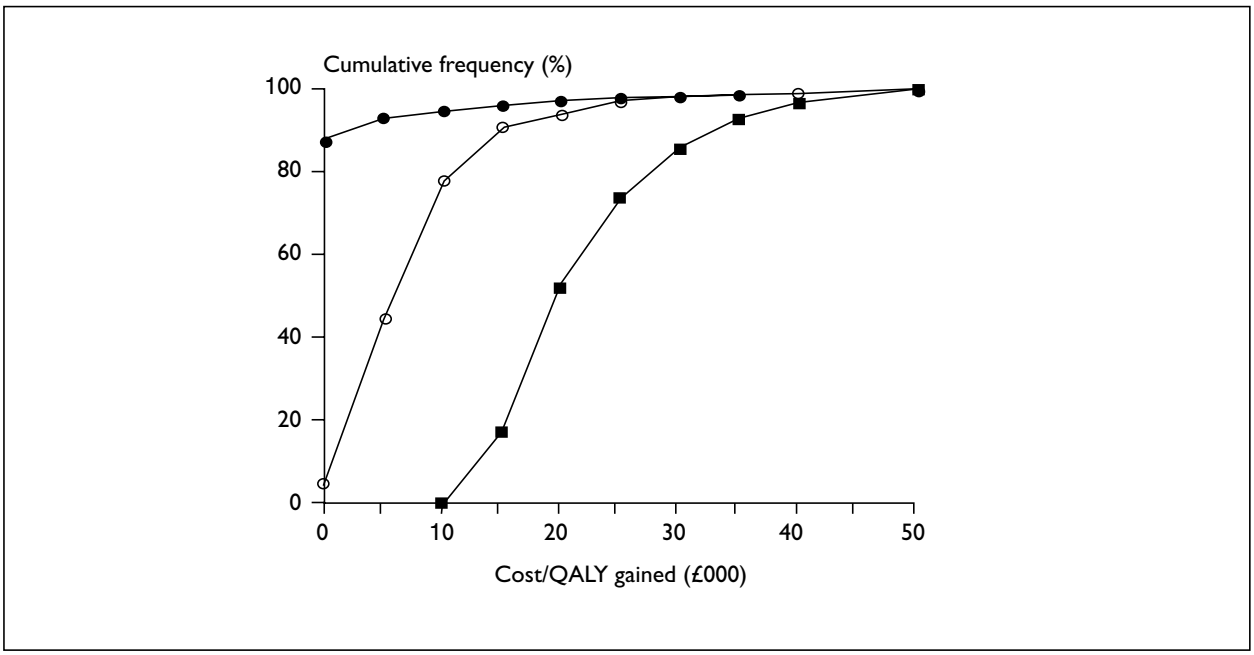

FIGURE 25 *Distribution of cost-effectiveness of bisphosphonate in women aged 60, 70, and 80 years with established osteoporosis (■, 60 years; ○, 70 years; ●, 80 years)*

cost-effective at age 60 years and above. Cost-savings occurred from age 80 years (*Table 70*). The cost-effectiveness acceptability curves for the cost-effective scenario are shown in *Figure 25*.

With a higher cost of treatment (£334 annually, equivalent to alendronate), cost-effectiveness was seen at age 70 years and above (*Table 70*).

An analysis using risk estimates confined to patients with established osteoporosis had slightly lower cost-effectiveness ratios but did not affect the grading (*Table 71*).

Fluoride

Fluoride significantly decreased the risk of vertebral fracture (RR = 0.35) but appeared to increase the risk of hip fracture (RR = 1.78), although this was not statistically significant. Fluoride was not cost-effective at any age using the RCT data (*Table 72*). When it was assumed that the effect of fluoride on hip and other appendicular fractures was neutral (RR = 1.0),

TABLE 71 *Cost-effectiveness of using bisphosphonate in women with established osteoporosis based on meta-analysis of women only with prior fracture*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
Intervention costs £163/year						
50	182.2	705.3	32.5	22.5	71.4	C
60	212.1	673.9	17.6	10.9	33.8	B
70	289.9	537.8	0.6	dominating	17.9	A
80	572.3	376.8	dominating	dominating	11.8	A
Intervention costs £334/year						
50	257.8	705.3	59.7	42.4	127.2	D
60	286.5	673.9	34.1	22.8	60.7	C
70	360.7	537.8	9.8	3.4	39.7	B
80	635.6	376.8	dominating	dominating	27.1	A

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

TABLE 72 *Cost-effectiveness of using fluoride in women with established osteoporosis*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
Results of meta-analysis						
50	155.4	700.2	dominated	20.8	dominated	C
60	222.8	667.1	dominated	11.1	dominated	C
70	486.7	523.3	dominated	4.2	dominated	C
80	1012.0	357.3	dominated	dominating	dominated	C
No effects on hip fracture						
50	138.3	704.0	30.8	26.9	36.6	C
60	180.8	672.1	17.4	14.7	21.5	A
70	324.0	532.9	13.5	11.2	16.9	A
80	665.4	369.7	6.8	4.1	11.8	A

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

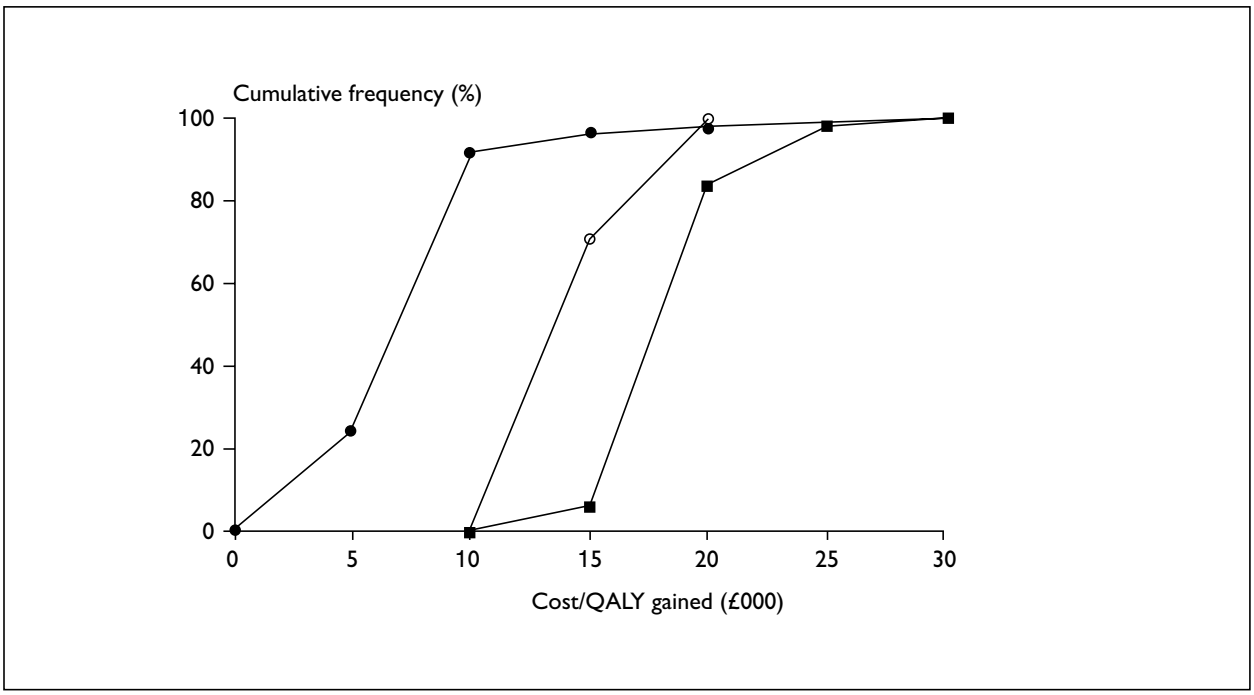

FIGURE 26 *Distribution of cost-effectiveness of fluoride in women aged 60, 70 and 80 years with established osteoporosis (■, 60 years; ○, 70 years; ●, 80 years)*

then treatment from age 60 years was cost-effective (*Figure 26*).

Alfacalcidol

The meta-analysis of alfacalcidol RCTs suggested a marked decrease in vertebral fracture risk (RR = 0.46). The data were similar for hip fracture risk (RR = 0.25) and humeral fracture risk (RR = 0.19). However, the confidence estimates were wide and the risk reduction was not significant for any of these fractures.

Cost-effectiveness improved with age but the cost-effective scenario was confined to women aged 70 years or more (*Table 73a*). When neutral effects on appendicular fractures were assumed, it was not cost-effective to treat at any age (*Table 73b*).

Incremental cost-effectiveness

Incremental cost-effectiveness, using £30,000 cost per QALY gained, was undertaken for all cost-effective scenarios shown in *Table 74* as grade B or better. Fluoride was not included

TABLE 73 *Cost-effectiveness of using alfacalcidol in women with established osteoporosis*

Age (years)	Cost (£000)[a]	Total QALYs[b]	Cost/QALY gained (£000)			Grade
			Midpoint	90% CI		
(a) Results of meta-analysis						
50	187.8	703.5	100.8	13.3	dominated	C
60	229.0	671.7	41.6	4.7	dominated	C
70	375.1	534.0	22.7	dominating	dominated	B
80	716.5	371.4	15.2	dominating	dominated	B
(b) No effects on appendicular fractures						
50	187.6	703.6	87.5	49.1	dominated	D
60	229.9	671.9	39.0	25.8	dominated	C
70	370.4	532.4	36.5	22.3	dominated	C
80	713.0	369.0	30.1	4.6	dominated	C

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

TABLE 74 *Summary of grading of cost-effectiveness by agent and age*

Agent	Cost-effectiveness grade by age (years)			
	50	60	70	80
Raloxifene[a]	D	D	B	A
HRT[b]	B	B	B	B
Calcium	C	B	B	B
Calcium and vitamin D	B	A	A	A*
Calcitonin	D	D	D	C
Alendronate	D	C	B	A
Bisphosphonate[c]	C	B	A	A
Fluoride[d]	C	A	A	A
Alfacalcidol	C	C	B	B

[a] *Only when an effect on cardiovascular disease is assumed, plus no adverse effect on hip fracture*
[b] *Adverse effects on breast cancer and beneficial effects on cardiovascular diseases are assumed*
[c] *Price of £163/year; all osteoporotic patients*
[d] *Assumed not to affect appendicular fractures*

since it is not available in the UK and alfacalcidol was also not considered since it is not licensed for use in osteoporosis in the UK. Treatments were ranked in ascending order of QALY gained. Marginal costs, QALYs and costs/QALY are shown in *Table 75* for ages 50, 60, 70 and 80 years. At age 50 years, there were two cost-

TABLE 75 *Marginal cost-effectiveness of interventions compared with no treatment*

Intervention	Marginal cost (£000)	Marginal QALY
Age 50 years		
HRT	48.4	1.65
Calcium and vitamin D	44.7	2.26
Age 60 years		
Calcium	45.4	2.13
HRT	43.6	3.53
Calcium and vitamin D	36.8	3.98
Bisphosphonate	82.1	4.14
Age 70 years		
Calcium	36.7	2.31
Raloxifene	140.1	3.01
Calcium and vitamin D	2.7	5.55
HRT	28.4	5.63
Bisphosphonate	39.2	6.82
Alendronate	101.7	7.67
Age 80 years		
Calcium	26.0	1.60
Raloxifene	108.6	7.13
Calcium and vitamin D	–74.7	7.27
Bisphosphonate	–55.1	8.66
HRT	–12.4	9.69
Alendronate	–12.2	9.73

effective scenarios (calcium plus vitamin D, assuming effects on appendicular fractures and HRT in rank order). At age 60 years, the rank order of incremental cost-effectiveness was calcium plus vitamin D, HRT, bisphosphonate and calcium. At age 70 years, the rank order was bisphosphonate, calcium plus vitamin D, HRT, alendronate, calcium and raloxifene. At 80 years, the rank order was bisphosphonate, alendronate, HRT, calcium plus vitamin D, raloxifene and calcium.

Sensitivity analysis

As discussed above, sensitivity analyses for variations in effectiveness were included when appropriate. Here, further analyses are confined to treatments that have been shown to be cost-effective, as shown in *Table 74*, unless otherwise indicated. Important drivers of cost-effectiveness that are evident from the preceding analyses include age and costs of the intervention.

Age

Age is clearly an important determinant of cost-effectiveness since the risk of fractures increases with age. It is clearly illustrated in the case of alendronate (see *Table 69*), for which the range of cost-effectiveness varied more than 60-fold between the ages of 50 and 80 years. It should be noted that improving cost-effectiveness with age is not invariant when extraskeletal risks and benefits are included (e.g. raloxifene, see *Table 63*) or when neutral effects on hip fracture are assumed (e.g. calcium, see *Table 67a*).

Costs of intervention

As expected, high costs of intervention are associated with poorer cost-effectiveness since, in general, the variation in cost is greater than any proven variation in efficacy. This, however, is a generalisation: for example, the effects of alendronate were better than those for fluoride despite a sevenfold higher intervention cost (*Table 76*). This clearly rests on the assumptions that alendronate lowers the hip fracture rate (proven by RCT in established osteoporosis) and that fluoride does not (shown to increase hip fracture risk in epidemiological studies).

Confidence in mid-point estimates

The sampling process using 1000 estimates of RRs permits an estimate of the 95% CI of all estimates for a given treatment at a given age against a fixed estimate of no treatment. For all agents, the 95% CI lay within £1000/QALY gained at the thresholds of cost-effectiveness (data not shown).

Criteria for cost-effectiveness

In this study, the criteria for cost-effectiveness were based on cost-effectiveness being shown in 90% of cohorts. For example, grade A was allocated to a treatment scenario in which, in 90% of the model runs, cost-effectiveness was less than £30,000/QALY gained (see *Table 64*). Decreasing the range to 80% of runs had a modest effect on the range of cost-effectiveness, particularly the lower estimate (*Table 77*). A greater effect was seen on the upper estimate, such that the grading of cost-effectiveness changed in a favourable manner. In the case of alendronate at the age of 70 years, grading would change

TABLE 76 *Yearly costs and cost-effectiveness of different treatments*

Agent	Cost/year (£)	Cost/QALY (£000)	
		Aged 70 years	Aged 80 years
Calcitonin	2314	168	124
Alendronate	334	13.3	dominating
Raloxifene[a]	257	46.4	76.1
Bisphosphonate	163	5.7	dominating
Vitamin D derivatives[a]	157	36.5	30.1
HRT[b]	58	5.0	dominating
Calcium and vitamin D	55	dominating	dominating
Fluoride[a]	48	13.5	6.8
Calcium	40	15.9	16.3

[a] *Assumes for appendicular fractures that RR = 1*
[b] *Assumes benefit in CHD and increased risk of breast cancer*

TABLE 77 *Range of cost-effectiveness estimates according to percentiles of the population used*

Age (years)	Cost-effectiveness estimate	
	90% CI	**80% CI**
Alendronate[a]		
50	45.5 to 111.6	47.7 to 86.6
60	24.3 to 63.7	25.8 to 56.0
70	6.2 to 37.0	7.3 to 26.0
80	dominating to 21.3	dominating to 9.1
Bisphosphonate[a]		
50	26.0 to 66.1	27.4 to 51.7
60	13.0 to 36.4	14.0 to 32.9
70	0.9 to 21.1	1.6 to 14.0
80	dominating to 10.4	dominating to 0.9
Calcium[a]		
50	28.5 to 121.4	30.5 to 81.4
60	15.0 to 44.7	15.3 to 34.5
70	10.8 to 41.5	11.0 to 31.1
80	5.1 to 124.3	6.3 to 40.0
HRT[a]		
50	30.9 to dominated	33.7 to dominated
60	17.2 to dominated	17.6 to dominated
70	13.3 to dominated	14.4 to dominated
80	6.1 to dominated	7.2 to dominated
Calcium + vitamin D[a]		
50	14.2 to 33.6	14.9 to 28.2
60	6.0 to 16.1	6.5 to 13.6
70	dominating to 6.7	dominating to 4.4
80	dominating to dominating	dominating to dominating

[a] *Base-case scenario*

TABLE 78 *Grading of cost-effectiveness using a threshold of £20,000 for cost/QALY (gradings using £30,000 threshold shown in parentheses if this differs from lower threshold)*

Agent	Cost-effectiveness grade by age (years)			
	50	**60**	**70**	**80**
Raloxifene[a]	D	D	D (B)	B (A)
HRT[b]	C (B)	B	B	B
Calcium[c]	D (C)	B	B	B
Calcium and vitamin D	B	A	A	A*
Calcitonin	D	D	D	D (C)
Alendronate	D	D (C)	B	B (A)
Bisphosphonate	D (C)	B	B (A)	A
Fluoride[c]	D (C)	B (A)	A	A
Alfacalcidol	C	C	C (B)	B

[a] *Only when an effect on cardiovascular disease is assumed with no adverse effect on hip fracture*
[b] *When adverse effects on breast cancer and beneficial effects on cardiovascular diseases are assumed*
[c] *Assumed not to affect appendicular fractures*

from B (probably cost-effective) to A (always cost-effective). For calcium and vitamin D, a change of grade (from B to A) occurred at age 50 years.

Altering the threshold value for cost-effectiveness from £30,000 to £20,000 had a modest effect on the grading of cost-effectiveness (*Table 78*). A decrement in grading was observed for raloxifene at ages 70 and 80 years, for HRT at age 50 years, for calcium and vitamin D at age 80 years, for calcitonin at 80 years, for alendronate at 60 and 80 years, for bisphosphonate at 50 and 70 years, for fluoride at 50 and 60 years, and for alfacalcidol at 70 years.

Discounting

The base case used a discount rate of 6% for costs and 1.5% for QALYs gained. The effect of discounting the latter at 6% was significant. The effects of variations in discount rate for cost-effective treatments in women aged 60 years are shown in *Table 79*. The higher discount of benefits increased the cost-effectiveness ratio by approximately 25% at age 60 years. The higher discount value for QALYs increased cost-effectiveness by approximately 63% at age 50 years and by 43% at age 70 years (data not shown). Thus, differences in discount rates modify the conclusions concerning cost-effectiveness using the £30,000 threshold value.

Compliance

Patients were said to be non-compliant if they received 3 months of drug treatment and accrued no health benefit. With this definition, variations in compliance had a modest effect on cost-effectiveness, since costs as well as effectiveness change in the same direction. The effect of assuming 70% compliance was quantitatively much less than for the variation in discount rate. Cost-effectiveness rose by less than 5% and did not alter the overall conclusions on cost-effectiveness. For HRT, cost-effectiveness rose by 1% or less assuming compliance to be 70%, and by 5–10% assuming compliance to be 30%. Further base-case examples are shown in *Table 80*.

Since the cost-effectiveness ratio increases with decreasing compliance, an alternative way of assessing the impact of non-compliance on cost-effective treatments is to determine at what level of compliance interventions no longer remain

TABLE 79 *Effect of variable discount rates for QALYs on cost-effectiveness at age 60 years*

Agent	Cost/QALY gained (£000) with QALY discounted at:		Increment (%)
	1.5%	6%	
Alendronate	35.2	41.9	19
Bisphosphonate[a]	19.8	23.3	18
Bisphosphonate[b]	37.8	44.3	17
Bisphosphonate[c]	17.6	21.5	22
Bisphosphonate[d]	34.1	41.7	22
Calcium	21.3	27.4	29
Calcium and vitamin D	9.2	11.7	27
HRT[e]	27.7	34.5	25
HRT[f]	12.7	16.6	31
HRT[g]	10.6	14.3	35
HRT[h]	12.4	16.6	34

[a] *Aggregated effect, price of agent £163 p.a.*
[b] *Aggregated effect, price of agent £334 p.a.*
[c] *As [a] in patients with prior fractures*
[d] *As [b] in patients with prior fractures*
[e] *Effects on vertebral fractures*
[f] *Effects on vertebral fracture and non-vertebral fracture*
[g] *As [e] with additional effects on CHD*
[h] *As [f] with additional effects on breast cancer and fixed effects on appendicular fractures*

cost-effective (i.e. exceed the £30,000/QALY threshold). The compliance threshold is low, in that a very significant majority of patients would need to be non-compliant to make treatment scenarios no longer cost-effective (*Table 81*). For example, if in women aged 80 years more than 5% were compliant, then treatment with alendronate would remain cost-effective within the limitations of the assumptions on compliance.

Offset time

It was assumed in the base case that in most instances (but not calcitonin or calcium) the effects of treatment wear off in a linear fashion over 5 years. Thus, 5 years of treatment incurs some benefit when treatment is stopped. Reducing the offset time to zero has a marked effect on cost-effectiveness. In *Table 82*, three scenarios are shown for offset time following bisphosphonate treatment in women.

It should be noted that these simulations were undertaken on a single run of 8000 patients (rather than the smoothed approximation given by the Gaussian process), so that these central point estimates differ somewhat from values previously given and the errors (not given) are substantially greater.

Using a 10-year analytic time frame, cost/QALY gained increased at all ages when the offset time was changed from 5 to 0 years.

In order to explore the effects of a longer offset time, a 15-year analytic time frame was used. As expected, changing from a 5-year to a 10-year offset time improved cost-effectiveness. At age 50 years, the cost/QALY was above the £30,000 threshold for cost-effectiveness but decreased from £49,000 to £25,100 with an offset time of 10 years.

Effect of changing T-score

Treating women with a T-score lower than –2.5 SD had a very marked effect on cost-effectiveness (*Table 83*). For bisphosphonate treatment, the intervention was not cost-effective at age 50 years. Increasing the stringency of the cut-off value for the T-score from –2.5 to –3.5 SD made treatment cost-effective at age 50 years and cost savings were made at age 70 years or more.

Similarly, other treatments of borderline cost-effectiveness became cost-effective with increasing stringency of the T-score threshold. In women aged 70 years treated with raloxifene, the cost-effectiveness ratio fell from £26,500 at a T-score of –2.5 to £7538 at a T-score of –3.5 SD.

TABLE 80 *Cost-effectiveness (£000) of interventions according to age and compliance years*

Age (years)	Cost-effectiveness (£000) according to compliance		
	100	70	30
Alendronate[a]			
50	61.4	62.8	68.6
60	35.3	36.1	39.7
70	13.3	13.7	15.8
80	–1.3[b]	–0.9[b]	0.7
Bisphosphonate[a]			
50	36.1	36.8	39.8
60	19.8	20.3	22.1
70	5.7	6.0	7.3
80	–6.4[b]	–6.2[b]	–5.3[b]
Calcium[a]			
50	44.0	44.5	46.4
60	21.4	21.6	22.5
70	15.9	16.1	16.9
80	16.3	16.5	17.7
HRT[a]			
50	61.9	62.7	65.9
60	27.8	28.1	29.5
70	24.1	24.4	25.9
80	19.9	20.2	21.7
Calcium and vitamin D[a]			
50	19.8	20.1	21.2
60	9.2	9.4	10.1
70	0.5	0.6	1.1
80	–10.3	–10.2	–9.8

[a] *Base-case scenario*
[b] *Dominating*

Costs of added years of life

As expected, the inclusion of future years of medical costs had effects on cost-effectiveness ratios over the analytic time frame (10–15 years) but the effect at all ages was small and most deviations were the result of sampling errors (*Table 84*).

Duration of intervention

Cost-effectiveness improved as expected when the duration of treatment was increased from 5 to 10 years (modelled in both cases over a 15-year interval). The effect can be judged indirectly by changing the offset time from 5 to 10 years. For bisphosphonate at age 50 years, the cost/QALY decreased from £36,700 to £17,800 with the increased offset time (see *Table 84*). At greater

TABLE 81 *Thresholds of compliance at which a cost-effective intervention exceeds a cost–utility of £30,000/QALY gained*

Age (years)	Cost/QALY gained (£000)	Compliance threshold (%)
Alendronate		
70	13.3	5–10
80	–1.3	1–5
Bisphosphonate[a]		
60	19.8	5–10
70	5.7	1–5
80	–6.4	1–5
Bisphosphonate[b]		
60	17.6	5–10
70	0.6	1–5
80	–7.3	1–5
Calcium		
60	21.4	5–10
70	15.9	1–5
80	16.3	1–5
Calcium and vitamin D[c]		
50	19.8	5–10
60	9.2	1–5
70	0.5	< 1
80	–10.3	< 1
HRT[d]		
60	27.8	20–30
70	24.1	10–20
80	19.9	5–10
HRT[e]		
50	29.4	80–90
60	12.7	10–20
70	6.7	5–10
80	–1.9	1–5
HRT[f]		
50	25.1	40–50
60	10.6	10–20
70	3.1	1–5
80	–3.0	1–5
HRT[g]		
50	29.4	80–90
60	12.4	5–10
70	5.0	1–5
80	–1.3	< 1

[a] *Aggregate of bisphosphonate data; costs £163 p.a.*
[b] *Effectiveness in patients with prior fracture*
[c] *Effectiveness on appendicular fractures (calcium with vitamin D)*
[d] *Assumed effect on vertebral fracture alone*
[e] *Effects on vertebral and non-vertebral fracture*
[f] *As* [e] *but fixed effects on appendicular fractures and effects on CHD*
[g] *As* [e] *but effects on CHD and breast cancer*

TABLE 82 *Effects of offset time on cost-effectiveness of a bisphosphonate*

Age (years)	Offset time (years)	Cost/QALY gained (£000)	
		10-year time frame	15-year time frame
50	0	71.0	
	5	36.1	49.0
	10		25.1
60	0	22.9	
	5	19.8	15.3
	10		16.7
70	0	12.1	
	5	5.7	3.2
	10	1.7	
80	0	–2.2	
	5	–6.4	–24.9
	10		–19.2

TABLE 83 *Effects of differences in BMD T-score on cost-effectiveness of bisphosphonate*

Age (years)	Cost/QALY gained (£000)	
	T-score = –2.5 SD	T-score = –3.5 SD
50	36.1	13.9
60	19.8	8.2
70	5.7	–2.1
80	–6.4	–14.5

ages, the effect was smaller because of higher mortality rates.

Mortality attributed to hip fracture

In the base case, it was assumed that 67% of all deaths up to 90 days following hip fracture were causally related to the hip fracture. If deaths beyond 90 days were considered, the rate of causally related deaths modelled fell to 42%. When all deaths within 90 days were assumed to be causally related (approximately 63% of deaths in the first year), the cost-effectiveness ratio increased, although the effect was small and the overall conclusions (i.e. grade of cost-effectiveness) did not markedly change. For example, treatment of a patient with bisphosphonate at age 60 years gave a cost-effectiveness ratio of £25,453. When all deaths were assumed to be causally related, the cost-effectiveness improved to £22,392. The effect is likely to be less at younger ages since fewer women would sustain hip fractures and even fewer would be admitted to nursing homes. Conversely, the effect is more marked at older ages. At age 70 years, the cost-effectiveness ratio fell from £7710 to £5748, assuming the higher mortality rate.

Effects on CHD

Both raloxifene and HRT may decrease the risk of CHD. These assumptions are based on epidemiological information in the case of HRT and on surrogate markers in the case of raloxifene. The inclusion of these effects improves cost-effectiveness, particularly in the elderly, because of a marked increase in marginal QALY gained. In the case of both HRT and raloxifene, the cost-effectiveness improved in the elderly but remained little changed at younger ages (*Table 85*).

Effect on breast cancer

The concern that HRT may increase the risk of breast cancer is largely derived from an epidemiological database. In this study, HRT was assumed variously to have no effect or to have an adverse effect on breast cancer. The inclusion of an increase in risk of 35% over 5 years increased the marginal costs and decreased the QALYs gained. As for CHD, the effect was most marked in the elderly (see *Table 85*). Indeed, a 35% increase in breast cancer risk more or less negated a 34% decrease in CHD risk.

Prior fracture

The cohort modelled is a population of women with osteoporosis. Within this population, there is a mixed pattern of prior fragility fractures. The

TABLE 84 *The effect of adding cost of added years to cost-effectiveness of bisphosphonates*

Age (years)	10-year analysis		15-year analysis	
	Base case	+ Cost of added years	Base case	+ Cost of added years
50	36.1	39.1	49.0	48.5
60	19.8	22.5	15.3	16.5
70	5.7	9.4	3.2	6.9
80	–6.4	–8.7	–24.9	–7.2

TABLE 85 *Effects on cost-effectiveness of changing assumptions relating to CHD and breast cancer risk*

Age (years)	RR reduction (%)	Marginal cost (£000)	Marginal QALY	Cost/QALY gained (£000)	Grade
Raloxifene and CHD					
50	0	140.2	0.94	148.5	D
80	0	108.4	1.43	76.1	D
50	20	140.2	0.95	148.1	D
80	20	108.6	7.13	15.2	A
HRT and CHD					
50	0	47.3	1.89	25.1	B
80	0	–33.8	6.98	–4.8	A*
50	34	47.3	1.89	25.1	B
80	34	–33.8	11.4	–3.0	A*
HRT, CHD (at +34%) and breast cancer					
50	0	48.4	1.65	29.4	B
80	0	–12.5	6.44	–1.9	A*
50	-35	48.4	1.65	29.4	C
80	-35	–12.4	9.69	–1.3	B

TABLE 86 *Cost-effectiveness of bisphosphonate treatment in women aged 60 years according to site of prior fracture*

Site of fracture	Cost/QALY gained (£)	Marginal QALY
Base case	19,842	4.14
Wrist	22,823	4.53
Proximal humerus	30,157	3.09
Spine	15,394	5.22
Hip	26,524	3.07

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 fracture on treatment outcomes, viz.:

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

The effect of bisphosphonate treatment in women at age 60 years with a BMD T-score of –2.5 SD in the presence of specific prior fractures is shown in *Table 86* compared with a base-case scenario (a population with a given distribution of prior fractures).

At this age, vertebral and forearm fractures are the most common, and the treatment of patients with these fractures yields dividends in terms of marginal QALYs greater than the base case. The dividend is less than the base case for hip and shoulder fractures.

Criteria for vertebral fracture

Our estimates suggested that vertebral fractures that come to clinical attention comprised approximately 25% of all vertebral fractures. Clinically covert fractures diagnosed by vertebral morphometry are associated with significant morbidity and their exclusion will underestimate cost-effectiveness. In this sensitivity analysis, it was assumed that the utility loss was half that of a clinically overt fracture, based on estimates of hospital stay and changes in activities of daily living.[343] If the utility loss is half that of a clinically overt fracture then, for every 100 fractures on X-ray, 25 will be clinically overt and the utility loss of 100 patients would be equivalent to 62.5 overt fractures, or 2.5 times greater than our estimates.

Increasing the apparent incidence of vertebral fracture by a factor of 2.5 improved cost-effectiveness, an effect more marked with increasing age. At age 60 years, treatment with bisphosphonate decreased the cost-effectiveness ratio from £25,453 to £21,548. At age 70 years, the ratio fell from £7710 to £775.

Clinical vignettes

From this review it can be seen that it is possible to deliver some treatments for established osteo-

porosis cost-effectively. The limitations of the analyses for clinical care rest not only on the many assumptions to be made, but also on the analytical approach. For example, as shown earlier, cost-effectiveness depends critically upon age, the type of prior fracture and the T-score. Moreover, even though there was no RCT evidence for a hierarchy of treatment efficacy, differences in cost and in apparent effectiveness, particularly on hip fracture risk, have marked implications for cost-effectiveness. Of particular therapeutic interest are the effects of calcium, bisphosphonates and HRT, since these are widely used in the UK, and cost-effective scenarios are identified in this report. HRT is commonly targeted at the menopause, whereas calcium and vitamin D are most commonly used later in life in the elderly. The bisphosphonates are most widely used at intermediate ages, typically following a vertebral fracture.

Current practice guidelines adopted in the UK follow a case-finding strategy in which potential candidates for treatment are identified by the presence of strong risk factors for osteoporotic fracture. These risk factors include low body mass index, a family history of hip fracture and prior fragility fractures. These risk factors capture an element of fracture risk over and above that explained by BMD. Treatment is indicated in individuals subsequently found to have osteoporosis. The present analysis provides a suitable framework for examining the cost-effectiveness of a major independent risk factor – namely, a prior fragility fracture. Common clinical situations are described here briefly and questions raised relating to the cost-effectiveness of given approaches against the background of current practice guidelines.

Forearm fracture

Forearm fractures commonly occur at the peri-menopause. Mrs X presented at age 50 years with a forearm fracture. She was at the peri-menopause but had no menopausal symptoms. A subsequent BMD measurement identified her to be on the threshold for osteoporosis. Can she be offered cost-effective treatment with HRT?

Inspection of *Table 65* indicates that at age 50 years, treatment of patients with established osteoporosis is not cost-effective in the majority of women, using a threshold value of £30,000/QALY gained. The mid-point estimate is £61,921 but falls within the threshold to £29,399, assuming cardiovascular benefits and breast cancer risks (see *Table 66*). At this age, the majority of the burden of osteoporosis is accounted for by fractures of the distal forearm. The mean cost-effectiveness ratio at this age for women with forearm fractures is £26,403, which is close to the mid-point estimate of a population of women at this age with established osteoporosis and a T-score of –2.5 SD. When the threshold for BMD is set at a T-score of –3.5 SD, treatment becomes very cost-effective, with a cost per QALY gained of £14,424. Thus there are cost-effective scenarios to be found and, using more stringent criteria than the WHO threshold for osteoporosis, treatment is very cost-effective.

Vertebral fracture

The mean age for vertebral fracture is in the mid-60s. Mrs Y sustained a vertebral fracture at age 60 years. A BMD examination showed her to have osteoporosis, with a T-score of –3.0 SD. Can she be given a bisphosphonate (etidronate or alendronate) cost-effectively?

The cost-effectiveness ratio with bisphosphonate at age 60 years at the threshold of osteoporosis (T-score = –2.5) is £36,000 but decreases to £6100 with a T-score of –3.5 (see *Table 83*). In the presence of a prior vertebral fracture and a T-score of –3.0 SD, the intermediate ratio is £17,584. The value lies within the threshold for cost-effectiveness. Note that the combined bisphosphonate effect is modelled on the price of etidronate (£163 annually). When the higher treatment cost of alendronate is used, the cost-effectiveness ratio increases to £31,178.

Hip fracture

The average age for hip fracture in Northern Europe is 80 years. Mrs Z lived alone and sustained a hip fracture at age 85 years. Could she be treated cost-effectively with calcium and vitamin D without recourse to a BMD measurement?

Here it is assumed that calcium plus vitamin D decreases the risk of appendicular fractures to an extent described for women in sheltered accommodation. In this scenario, treatment of all women with established osteoporosis is cost saving at age 80 years (see *Table 67*). The average T-score of women aged 85 years is –2.5 SD so that it will, on average, also be cost-effective to intervene, even without the assessment of BMD. Note that at this age, bisphosphonate and alendronate are even more cost-effective.

Chapter 7

Discussion and conclusions

A cost-effectiveness analysis was undertaken of interventions in established osteoporosis. The approach was to review systematically the evidence for efficacy from RCTs, costs and health-state utility values. A model was constructed that was populated with hazard functions drawn whenever possible from the UK. A novel feature of the model is that ranges of cost-effectiveness could be determined which take account of the uncertainties surrounding the effectiveness of intervention.

The principal findings show that there are effective treatments for established osteoporosis in women and that some of these treatments can be given cost-effectively. However, not all treatments were shown to be effective and, even when efficacy was demonstrated, they were not invariably cost-effective. No single agent was cost-effective over the entire age range relevant for post-menopausal osteoporosis, with exception of HRT and the possible exception of calcium (with vitamin D), as shown in *Table 74*.

The incremental cost-effectiveness suggests that calcium is the agent of choice at ages 50–70 years and bisphosphonate at age 80 years. There are, however, difficulties in assigning a rank order of preference. First, the meta-analysis of effectiveness could not distinguish significant differences in effectiveness between agents, although the mid-point estimates vary. Second, untested assumptions were made for efficacy. For example, calcium and vitamin D were assumed to decrease appendicular fractures in the general population (as shown by an RCT for women in sheltered accommodation). Moreover, the efficacy has not been tested in women aged 50 years. The effectiveness of bisphosphonate is an aggregate effect but the intervention cost was modelled for etidronate. These various considerations suggest that it would be unwise at present to recommend a hierarchy of preferred treatments.

The observation that most interventions are not cost-effective at all ages indicates that conclusions are very sensitive to the assumptions used to populate the model and to the modelling technique. Many of these assumptions have been identified; only those of particular importance to the conclusions or recommendations are reviewed below. However, the vast majority of the assumptions used are conservative. This, in turn, should modulate the interpretation of health economics analyses, in the sense that scenarios that demonstrate cost-effectiveness are likely to be robust but scenarios without, or 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 giving rise to uncertainties of major importance include:

(a) treatment effects
(b) health states in established osteoporosis
(c) the hazard function in established osteoporosis
(d) the constraints of the model.

Treatment effects

Hip fracture accounts for the greatest morbidity and costs of osteoporosis, and drives health economics considerations. In the absence of any assumed effect on hip fracture, cost-effective scenarios using base-case assumptions from RCTs are confined to the very elderly (e.g. HRT, calcium plus vitamin D). There is a paucity of available information from RCTs on hip fracture outcomes in established osteoporosis. Indeed, at the cut-off date for this analysis, only for alendronate had a significant effect on hip fracture rates been demonstrated by RCT. There was information from RCTs on hip fracture with the use of vitamin D with or without calcium and hip protectors, but these studies did not specifically examine women with osteoporosis. For this reason, such studies were excluded from the meta-analysis of efficacy. Moreover, there were epidemiological data suggesting that a number of other interventions decrease the risk of hip fracture. These included HRT, calcitonin, anabolic steroids, thiazide diuretics and etidronate. Because these findings were unsupported by RCTs, they were not considered in the meta-analysis but were included in sensitivity analyses of cost-effectiveness when beneficial effects on other fracture outcomes had been proven. In the summary of cost-effectiveness, some of these assumptions are embraced.

The logic of this approach is that osteoporosis is a systemic disease affecting all regions of the skeleton. It may, therefore, be counter-intuitive to assume that, when agents acting systematically have demonstrated efficacy on vertebral fracture, there is no effect on hip fracture risk, particularly when this is supported by observational studies. On the other hand, precedents discussed in chapter 2 indicate that caution is required, in that RCTs suggest that raloxifene and fluoride have little or no effect on hip fracture risk, despite RCT evidence for significant effects on vertebral fracture risk. In such cases, a neutral effect (RR = 1.0) has been conservatively assumed in the sensitivity analyses.

As mentioned, the absence of RCT data on hip fracture outcome should not necessarily be taken to mean that agents do not favourably affect hip fracture risk. Indeed, the balance of probabilities suggests otherwise. There is also a lack of convincing RCT data about the effects of HRT or raloxifene on cardiovascular outcomes. These absences limit interpretation of the data. When hip fracture effects have been assumed from epidemiological data, it is important to acknowledge that the quantum of effect is uncertain, due to intrinsic population biases that are unquantifiable. A good example is HRT, for which large effects on hip fracture risk are shown in many observational studies but the only RCT (albeit in patients without osteoporosis) showed no significant effect. For these reasons, the hip fracture effect used in the sensitivity analysis was modest. These considerations suggest that many of the conclusions relating to efficacy will be conservative.

A further problem relating to the treatments identified here is that the responses to intervention in terms of vertebral fracture outcome may be non-linear, as the greatest risk reduction is seen in the early years of intervention. If true, this suggests that for some treatments, the longer the duration of treatment, the lower the RR reduction. Until these uncertainties are resolved, analyses of treatments for more than 5 years become progressively more speculative; this is the principal reason why the treatment time frame was restricted to 5 years. Conversely, however, shorter intervention times might usefully be modelled when more information becomes available on offset times.

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 WHO in drug development,[50] a view that is endorsed. A review of the available evidence suggests that the chosen 3–5 year offset time might be conservative for some agents. The offset time has been shown to be a critical component of apparent cost-effectiveness.

Also, the vast majority of studies compared the test agent plus calcium and/or vitamin D with a placebo with calcium and/or vitamin D. In effect, these are trials of superiority. On the assumption that calcium with or without vitamin D has intrinsic therapeutic effects, then the efficacy of the test agent 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 test agent alone. Such data are not available. Moreover, the effects of calcium and/or vitamin D appear to be greater in individuals with a poorer nutritional status, so that in RCTs of new agents, any effect of calcium and vitamin D alone is uncertain. For these reasons, the observed effects of test agents 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.

There are additional considerations for several of the therapeutic modalities discussed and for which cost-effectiveness has not been demonstrated.

1. **Raloxifene has not been shown to be cost-effective below the age of 60 years (even when beneficial effects on CHD are assumed).**
   The major reason for this conclusion is the absence of effect on the risk of appendicular fractures. There were no RCTs that examined non-vertebral fractures as a primary endpoint. Direct information on cardiovascular outcomes is likely to be available shortly, which might significantly temper our conclusions. Since raloxifene is generally not cost-effective in established osteoporosis, it will not be cost-effective in the prevention of osteoporosis. It is relevant that the time frame modelled was 10 years and, if longer-term effects on breast cancer mortality were assumed, it is likely that cost-effective scenarios at younger ages would be found.
2. **Calcitonin has not been shown to be cost-effective at any age.**
   The cost of calcitonin rather than its efficacy is the principal determinant of this outcome. It may be relevant that intranasal calcitonin has just been approved in the UK and, from precedents elsewhere in Europe, may have a more favourable pricing structure. If so, then further analyses would be of considerable interest.

Health state utility values in established osteoporosis

The systematic review has highlighted the paucity of data available on health state utility values in established osteoporosis. The health state values for each fracture are based on a critical review of the literature but, clearly, further work needs to be done in this area, using standardised methodology over the different health states. Since the completion of this study, further empirical data have become available on health state values in established osteoporosis in patients referred to a hospital accident department in Malmö, Sweden.[344] If such data are applicable to all patients with symptomatic vertebral fractures, they suggest that the disutility used here might be doubled and substantially alter the conclusions on cost-effectiveness.

There is a particular problem in patients with established osteoporosis. Such individuals have already sustained a fragility fracture. Thus, the relevant question is the impact of a second fracture on existing health states – and there is absolutely no literature available on this. This has posed problems in modelling. It has been 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 value equivalent to that of a hip fracture multiplied by the remaining disutility of the Colles' fracture. It has also been 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 woman with a vertebral fracture would sustain no further disutility from a second vertebral fracture other than in the first year. This may well be a conservative scenario and, again, underestimate the utility losses in osteoporosis.

It has not been possible to quantify the impact of side-effects on cost–utility apart from in CHD and breast cancer. Many of the agents evaluated have the additional unwanted effects identified in this review. The health state consequences are unknown and are not considered here. This is an important omission since risks that have effects on the treated population as a whole are likely to affect cost–utility markedly.

Hazard functions in established osteoporosis

The principal modelling exercise was undertaken in cohorts of women at the boundary of osteoporosis (i.e. with a T-score of –2.5 SD). In practice, few individuals diagnosed as having established osteoporosis would have a T-score of exactly this value. Indeed, distribution theory indicates that the RR for patients with osteoporosis is approximately twice that of individuals at the threshold for osteoporosis (see *Table 40*). The excess risk is approximately equivalent to a T-score of –3.5 SD. As shown here, cost-effectiveness is critically dependent on the T-score.

With respect to outcomes, the major uncertainty in the analysis related to vertebral fracture risk, with its problematic epidemiology. Uncertainties arose because of multiple methods of diagnosis and their uncertain relevance to patients. In this study, the incidence of vertebral fractures that come to clinical attention has been computed using data derived from Sweden rather than the UK. Although the estimates are likely to be reasonably accurate, there is increasing evidence that vertebral deformities that do not present to clinical attention occasion a substantial morbidity. They also presage future fractures. As shown by the sensitivity analysis, this exclusion has a substantial impact on intervention thresholds based on cost-effectiveness. Against this background, the approach used is conservative.

Constraints of the model

Multiple outcomes are a major problem in the evaluation of osteoporosis. These include not only the many different fractures, each with different morbid consequences, but also non-skeletal outcomes. There is, for example, evidence that the risk of breast cancer is lower in women with osteoporosis than in those without. Moreover, several interventions may affect non-skeletal outcomes. Classic examples are HRT and raloxifene, both of which may affect the risk of breast cancer and CHD. One of the strengths of the modelling approach is that it can accommodate, on a patient-by-patient basis, the multiple transitions that the disorder demands. It also indicates the need to use a cost–utility approach.

Although the model is very flexible and can handle many transition probabilities, it was impeded by a lack of information on many of the transitions that arise in such a complex disorder with multiple outcomes. Whenever possible, conservative assumptions were used. An exception was the relationship between BMD and fracture

risk. It was assumed that the average risk of fracture (i.e. in the general population) occurs with an average BMD. This is a simplification because BMD is normally distributed, whereas the risk of many fractures, hip fracture in particular, increases exponentially with decreasing BMD. Thus, a given BMD will overestimate the risk of fracture when the fracture hazard is derived from the average fracture rate. However, not all osteoporotic fractures (although a substantial majority) were accommodated, largely because of the lack of relevant information to populate these transition states. This is clearly an area for further research.

Although the first phase of modelling was based on 8000 patients for each set of parameters, this may not eliminate noise for infrequent events. For example, the probability of some events, such as hip fracture and entry to nursing home following a hip fracture is low, being less than 0.6% and 0.04%, respectively, at age 60 years. It is likely that more than 8000 patients would be required to significantly reduce noise. With such small values, the reduction in events because of treatment, assuming RR = 0.5 for hip fracture, is small compared with the probability of death due to natural causes (approximately 0.9% at age 60 years).

Implications for practice

The results presented in chapter 6 and the summary of findings presented in *Table 74* provide important information for policy makers on the cost-effective treatment of established osteoporosis. The principal findings are that there are effective treatments for established osteoporosis in women and that some of these can be cost-effective. However, not all treatments were shown to be effective and, even when efficacy was shown, they were not invariably cost-effective. Few agents are cost-effective over the entire age range relevant for post-menopausal osteoporosis, as shown in *Table 74*.

However, it was not possible to identify with confidence a hierarchy of interventions based on effectiveness. An incremental cost-effectiveness analysis by age group was undertaken but great caution is required in suggesting the order in which treatments should be considered.

Important areas of further research (outlined below) have been identified that will, when the results become available, inform policy more accurately in the future.

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 upon 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, as well as for practice guidelines.[9,141,345] It is evident, however, that the same T-score has different significance at different ages and in different clinical contexts. As shown here, 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. For example, the incidence of hip fracture in women from the UK with a T-score of –2.5 SD varies from 0.25% at ages 50–54 years to 3.2% at age 90 years or more (see *Table 38*). It is evident, therefore, that diagnostic thresholds should differ from intervention thresholds, even without health economics considerations. Indeed, it is the view of both WHO and the International Osteoporosis Foundation that, in the future, intervention thresholds should be based upon absolute fracture probabilities, such as 10-year risk.[346] As assessment guidelines develop, it will be important to change the analytical framework of health economics assessments to accommodate these concepts.
2. ***Adverse effects***. Because of lack of resources, the impact of adverse effects other than breast cancer or CHD has not been considered. However, common adverse effects in the treated population would have a marked negative effect on cost-effectiveness. A systematic review of side-effects and their associated utility states would determine whether these might be included in further health economics analysis.
3. ***Prior fractures***. The cohorts of women modelled had a range of osteoporotic fractures. However, different prior fractures have different future consequences, as shown in the sensitivity analysis. For example, treatment of patients with a prior vertebral fracture is more worthwhile than treatment of women with a prior forearm fracture. The analysis of this is not exhaustive and is amenable to further research.
4. ***Health state utility values***. There is a dearth of empirical data on these values in established

osteoporosis using standardised methodology. Of particular concern is that the health utility states in second and subsequent years may have been seriously mis-estimated. Again, this is bounded by the lack of empirical data and hence is recommended as an area for further research. 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. ***Symptomatic vertebral fractures***. There is increasing evidence that these are associated with significant mortality. In addition, it is likely that health utility states are underestimated. These deficiencies will affect conclusions concerning cost-effectiveness. However, the consideration of morphometric deformities and attendant morbidity is likely to have a much greater impact. More precise information on the incidence of vertebral deformities and their associated impact on quality of life is likely to become available within the next year, and its inclusion in health economics models will be an important area for further research.
6. ***Costs and effectiveness of interventions***. The evidence base for these is changing rapidly. New agents are undergoing clinical development, for example, parathyroid hormone, risedronate and other SERMs. In addition, new formulations are now available in the UK with lower intervention costs than those used here, such as the oestrogens, alendronate, and calcium with vitamin D. Since the completion of this data analysis, intranasal calcitonin has become available in the UK and is likely to be priced more competitively than other forms. Outcomes on hip fracture are expected from intervention with vitamin D, calcium and HRT. As further information become available, it will be important to update the present analysis.

Acknowledgements

This report was commissioned by the NHS R&D HTA Programme (project number 95/11/04). The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

The authors are grateful to Professor David Barlow (John Radcliffe Hospital, Oxford), Professor Cyrus Cooper (Southampton General Hospital, Southampton) and Dr Eugene McCloskey (WHO Collaborating Centre for Metabolic Bone Disease, Sheffield) for acting as consultants during this work.

The authors are also indebted to the referees for their perseverance in reading the report and the quality of their comments.

References

1. Office of Technology Assessment. Effectiveness and costs of osteoporosis screening and hormone replacement therapy. Pittsburgh: Office of Technology Assessment; 1995.

2. Daly E, Roche M, Barlow D, Gray A, McPherson K, Vessey M. HRT: an analysis of benefits, risks and costs. *Br Med Bull* 1992;**48**:368–400.

3. Pitt FA, Lloyd Jones M, Brazier JE, McGrother CW, Kanis JA, Wallace WA, *et al.* The costs and benefits of screening and preventing post-menopausal osteoporosis in Trent RHA. Sheffield: Trent Osteoporosis Working Group; 1990.

4. Pitt FA, Brazier JE, Kanis JA, Wallace WA, McGrother C, Radley H, *et al.* Guidance for the prevention of osteoporosis in general practice. Sheffield: Trent Osteoporosis Working Group; 1991.

5. Whittington R, Faulds D. Hormone replacement therapy: 1. Pharmacoeconomic appraisal of its therapeutic use in menopausal symptoms and urogenital oestrogen deficiency. *Pharmacoeconomics* 1994;**5**:419–45.

6. Whittington R, Faulds D. Hormone replacement therapy: 2. Pharmacoeconomic appraisal of its role in the prevention of postmenopausal osteoporosis and ischaemic heart disease. *Pharmacoeconomics* 1994;**5**:513–54.

7. Weinstein MC. Estrogen use in postmenopausal women – costs, risks and benefits. *N Eng J Med* 1980;**6**:308–16.

8. Weinstein MC, Tosteson ANA. Cost-effectiveness of hormone replacement. *Ann NY Acad Sci* 1990;**592**:162–72,185–9.

9. National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Status report. *Osteoporos Int* 1998;**8** Suppl 4:1–88.

10. Jonsson B, Christiansen C, Johnell O, Hedbrandt J. Cost effectiveness of fracture prevention in established osteoporosis. *Osteoporos Int* 1995;**5**:136–42.

11. Torgerson DJ, Kanis JA. Cost-effectiveness of preventing hip fractures in the elderly population using vitamin D and calcium. *QJM* 1995;**88**:135–8.

12. Consensus Development Conference. Diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med* 1991;**90**:107–10.

13. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical Report Series no 843. Geneva: WHO; 1994.

14. Kanis JA, Melton LJ, Christiansen C, Johnston C, Khaltaev A. The diagnosis of osteoporosis. *J Bone Miner Res* 1994;**9**:1137–41.

15. Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. *Osteoporos Int* 2000;**11**:192–202.

16. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;**312**:1254–9.

17. Kanis JA, Pitt F. Epidemiology of osteoporosis. *Bone* 1992;**1**:S7–15.

18. Report on osteoporosis in the European Community. Action for prevention. Luxembourg. Office for Official Publications of the European Communities; 1998.

19. Kanis JA. Textbook of osteoporosis. Oxford: Blackwell Science; 1996.

20. Dolan P, Torgeson DJ. The cost of treating osteoporotic fractures in the United Kingdom female population. *Osteoporos Int* 1998;**8**:611–17.

21. Melton LJ, Kan SH, Wahner WA, Riggs BL. Lifetime fracture risk: an approach to hip fracture risk assessment based on bone mineral density and age. *J Clin Epidemiol* 1988;**41**:989–94.

22. Oden A, Dawson A, Dere W, Johnell O, Jonsson B, Kanis JA. Lifetime risk of hip fracture is underestimated. *Osteoporos Int* 1998;**8**:599–603.

23. Lauritzen JB, Shorts P, McNair P, Lurid B, Transbol I. Radial and femoral fractures as predictors of subsequent hip, radial or humeral fractures, and their seasonal variations. *Osteoporos Int* 1993;**3**:133–7.

24. Kanis JA, Johnell O, Oden A, Sernbo I, Redlund-Johnell I, Dawson A, *et al.* Long term risk of osteoporotic fracture in Malmo. *Osteoporos Int* 2000;**11**:669–74.

25. Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15,000 adults. *J Bone Joint Surg Br* 1998;**80**:243–8.

26. Ellfors L, Allander E, Kanis JA, Gullberg B, Johnell O, Dequeker A, *et al.* The variable incidence of hip fracture in southern Europe: the MEDOS study. *Osteoporos Int* 1994;**4**:253–63.

27. Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. How many women have osteoporosis? *J Bone Miner Res* 1992;**7**:1005–10.

28. Melton LJ, O'Fallon WIM, Riggs BL. Secular trends in the incidence of hip fractures. *Calcif Tissue Int* 1987;**41**:57–64.

29. Spector TD, Cooper C, Lewis AF. Trends in admission for hip fracture in England and Wales 1968–1985. *BMJ* 1990;**3**:1173–4.

30. Lancaster HO. Expectations of life. Berlin: Springer-Verlag; 1990. p.33.

31. Hoffenberg R, Jarnes OFW, Brocklehurst JC, Green ID, Horrocks P, Kanis JA, *et al.* Fractured neck of femur. Prevention and management. *J R Coll Physicians Lond* 1989;**23**:8–12.

32. Cooper C, Campion C, Melton LJ. Hip fractures in the elderly: world-wide projections. *Osteoporos Int* 1992;**2**:285–9.

33. Gullberg B, Johnell O, Kanis JA. Worldwide projection for hip fracture. *Osteoporos Int* 1997;**7**:407–13.

34. Riggs BL, Melton LJ. The prevention and treatment of osteoporosis. *N Eng J Med* 1992;**327**:620–7.

35. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of cholecalciferol treatment for three years on hip fracture in elderly women. *BMJ* 1994;**308**:1081–2.

36. Kannus P, Parkkari J, Pasanen SNM, Palvanen M, Jarvinen M, Vuori L. Prevention of hip fracture in elderly people with use of a hip protector. *N Eng J Med* 2000;**343**:1506–13.

37. Kanis JA. The use of calcium in the management of osteoporosis. *Bone* 1999;**24**:279–90.

38. Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, *et al.* Risk factors for hip fracture in European women: the MEDOS study. *J Bone Miner Res* 1995;**10**:1802–15.

39. Kanis, JA. Screening of post-menopausal osteoporosis. A review. London: Department of Health; 1992.

40. Osteoporosis after fractures. Clinical guidelines for management amongst older people. London: Royal College of Physicians of London; 1996.

41. Kanis JA, Johnell O, Oden A, de Laet C, Jonsson B, Dawson A. Ten year risk of osteoporosis fracture and the effect of risk factors on screening strategies. *Bone* 2001;**30**:251–8.

42. Kanis JA, Johnell O, Oden A, Jonsson B, de Laet C, Dawson A. Prediction of fracture from low bone mineral density overestimates risk. *Bone* 2000;**26**:387–91.

43. Kanis JA. Treatment of osteoporosis in elderly women. *Am J Med* 1995;**98** Suppl 2A:S60–6.

44. Jonsson B, Kanis JA, Dawson A, Oden A, Johnell O. Effect and offset of effect of treatments for hip fracture on health outcomes. *Osteoporos Int* 1999;**10**:193–9.

45. Barlow D. Report of Department of Health Advisory Group on Osteoporosis. London: Department of Health; 1994.

46. Compston JE, Cooper C, Kanis JA. Bone densitometry in clinical practice. *BMJ* 1995;**310**:1507–10.

47. Kanis JA, Geusens P, Christiansen C. Guidelines for clinical trials in osteoporosis. A position paper for the European Foundation for Osteoporosis and Bone Disease. *Osteoporos Int* 1991;**1**:182–8.

48. Note for guidance on involutional osteoporosis in women. CMPM/EWP/552/95. London: Committee for Proprietary Medicinal Products; 1997.

49. Guidelines for preclinical and clinical evaluation of agents used in the prevention or treatment of postmenopausal osteoporosis. Rockville, MD: Food and Drug Administration, Division of Metabolism and Endocrine Drug Products; 1994.

50. World Health Organization. Guidelines for preclinical evaluation and clinical trials in osteoporosis. Geneva: WHO; 1998.

51. Tosteson AN, Rosenthal DI, Melton LJ 3rd, Weinstein MC. Cost effectiveness of screening perimenopausal white women for osteoporosis: bone densitometry and hormone replacement therapy. *Ann Intern Med* 1990;**113**:594–603.

52. Kanis JA. What constitutes evidence for drug efficacy in osteoporosis? *Drugs Aging* 1993;**3**:391–9.

53. Cummings SR, Black DM, Vogt TM. Changes in BMD substantially underestimate the anti-fracture effects of alendronate and other antiresorptive agents. *J Bone Miner Res* 1996;**11**:S102.

54. van Staa TP, Abenhaim L, Cooper C. Use of cyclical etidronate and prevention of non-vertebral fractures. *Br J Rheumatol* 1998;**37**:87–94.

55. Kanis JA, Johnell O, Gullberg B, Allander E, Dilsen G, Gennari C, *et al.* Evidence for efficacy of drugs affecting bone metabolism in preventing hip fracture. *BMJ* 1992;**305**:1124–8.

56. Shiraki M. [Vitamin K2. In Japanese] *Nippon Rinsho* 1998;**56**:1525–30.

57. Nakatsuka K, Inaba M, Aratani H, Iba K, Sato T, Koike T, *et al.* [Effects of long-term administration of alfacalcidol on bone mass and bone metabolism in patients with primary osteoporosis – comparison with calcium preparations. In Japanese.] *Nippon Ronen Igakkai Zasshi* 1997;**34**:569–76.

58. Fujita T, Orimo H, Inoue T, Kaneda K, Sakurai M, Morita R, *et al.* [Double-blind multicentre comparative study with alfacalcidol of etidronate disodium (EHDP) in involutional osteoporosis. In Japanese] *Rinsho Hyoka* 1993;**21**:261–302.

59. Overgaard K, Ravn P, Hansen MA, Christiansen C. [Salmon calcitonin in osteoporosis. The effect of intranasal application on bone mineral content and fracture frequency in postmenopausal women with manifest osteoporotic changes. In Dutch.] *Ugeskr Laeger* 1993;**155**:2387–91.

60. Overgaard K, Hansen MA, Jensen SB, Christiansen C. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose–response study. *BMJ* 1992;**305**:556–61.

61. Agrawal R, Wallach S, Cohn S, Tessier M, Verch R, Hussain M, *et al.* Calcitonin treatment of osteoporosis. In: Calcitonin 1980: proceedings of an international symposium; Milan, October 1980. Amsterdam: Excerpta Medica; 1981 p.237–46.

62. Buckle RM. Three year study of sodium fluoride treatment on vertebral fracture incidence in osteoporosis. *J Bone Miner Res* 1989;**4**:S186.

63. Dykman TR, 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.

64. Fujita T, Fukase M, Shimada T, Yamamoto H. Treatment of established osteoporosis with 1 alpha (OH) vitamin D3 and low dose intermittent elcatonin (eel calcitonin derivative). *J Bone Miner Metab* 1992;**10**:37–40.

65. Gennari C, Chierichetti SM, Bigazzi S, Fusi L, Gonnelli S, Ferrara R, *et al.* Comparative effects on bone mineral content of calcium and calcium plus salmon calcitonin given in two different regimes in postmenopausal osteoporosis. *Curr Therapeut Res* 1985;**38**:455–64.

66. Hayashi Y. Investigation of fracture frequency of Japanese osteoporosis patients: effects of drug therapy. *J Bone Miner Metab* 1988;**6**:120.

67. Hayashi Y, Fujita T, Inoue T. Decrease of vertebral fracture in osteoporotics by administration of 1 alpha-hydroxy-vitamin D3. *J Bone Miner Metab* 1992;**10**:184–8.

68. Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K_2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. *J Bone Miner Res* 2000;**15**:515–21.

69. Dilsen G, Gulbaba G, Sindel D. Calcitriol in the treatment of osteoporosis. *Osteoporos Int* 1998;**8**:101.

70. Ebeling PR, Wark JD, Yeung S, Poon C, Salehi N, Nicholson GC, *et al.* Effects of calcitriol or calcium on bone mineral density and fractures in men with idiopathic osteoporosis. *Osteoporos Int* 1998; **8** Suppl 3:114.

71. Gallagher JC. Treatment of postmenopausal osteoporosis with fluoride plus either calcium or calcitriol. *J Bone Miner Res* 1992;**7**:S318.

72. Rozhinskaya L, Marova E, Sazonova N. Effectiveness of monofluorophosphate in established steroid osteoporosis. *Osteoporos Int* 1999;**9**(4 Suppl 1):S11–12.

73. Brockstedt H, Melsen F, Mosekilde L. Double-blind, randomized study comparing the therapeutic effects of continuous and pulse dosing sodium monofluorophosphate (NaMFPh) in spinal crush fracture osteoporosis [abstract]. *Osteoporos Int* 1996;**6** Suppl 1:254.

74. Gallagher JC. Effect of fluoride in osteoporosis [abstract]. *J Bone Miner Res* 1990;**5** Suppl 1:S230.

75. Guañabens N, Farrerons J, Perez-Edo L, Monegal A, Renau A, Roca M, *et al.* Comparison of the efficiency and safety of cyclic etidronate versus sodium fluoride in postmenopausal osteoporosis [abstract]. *Osteoporos Int* 1996;**6**:255.

76. Leidig-Bruckner G, Eberwein S, Bruckner T, Wolf S, Ziegler R. Long term follow-up of lumbar and femoral bone mineral density and vertebral fractures in patients with manifest postmenopausal osteoporosis after fluoride therapy alone or combined with estrogens or anabolica [abstract]. *Exp Clin Endocrinol Diabetes* 1997;**105**:A58.

77. McClung M, Bensen W, Bolognese M, Bonnick S, Ettinger M, Harris S, *et al.* Risedronate increases bone mineral density at the hip, spine and radius in postmenopausal women with low bone mass. *Osteoporos Int* 1998;**8**:111.

78. Chesnut CH 3rd, Baylink DJ, Doyle D, Genant H, Harris S, Kiel DP, *et al.* Salmon calcitonin nasal spray prevents vertebral fractures in established osteoporosis: further interim results of the "PROOF" study. *Osteoporos Int* 1998;**8** Suppl 3:13.

79. Gutteridge DH, Drury PH, Stewart GO, Prince RL, Price RI, Retallack RW, *et al.* Cyclic Na fluoride + HRT in postmenopausal osteoporosis – more vertebral fractures with NaF: less with HRT and NaF [abstract]. *Osteoporos Int* 1996; **6** Suppl 1:263.

80. Gutteridge DH, Kent GN, Prince RL, Nicholson GC, Stewart GO, Jones CE, *et al.* Fluoride treatment of osteoporosis: cyclical non-blinded or continuous blinded studies? *Osteoporos Int* 1993;**3** Suppl 1:215–17.

81. Gutteridge DH, Price RI, Prince RL, Jones CE, Stewart GO, Nicholson GC, *et al.* Fluoride ± estrogen in osteoporosis – spinal bone gain, lower limb bone loss and stress fractures. *J Bone Miner Res* 1993;**8** Suppl 1:S341.

82. Begg CB. Publication bias. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York: Russell Sage Foundation 1994. p.339–409.

83. Windeler J, Lange S. Events per person year – a dubious concept. *BMJ* 1995;**310**:454–6.

84. Ross PD, Davis JW, Epstein RS, Wasnich RD. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. *Ann Intern Med* 1991;**114**:919–23.

85. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. *J Bone Miner Res* 1999;**14**:821–8.

86. Meunier PJ. Evidence-based medicine and osteoporosis: a comparison of fracture risk reduction data from osteoporosis randomised clinical trials. *Int J Clin Pract* 1999;**53**:122–9.

87. Cucherat M. EasyMA 97b. Software for meta-analysis of clinical trials. Lyon, France: 1992–97. Available from: http://www.spc.univ-lyon1.fr/~mcu/easyma/

88. Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, l'Abbe KA. Incorporating variations in the quality of individual randomized trials into meta-analysis. *J Clin Epidemiol* 1992;**45**:255–65.

89. Gillespie WJ, Henry DA, O'Connell DL, Robertson J. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis [Cochrane review]. In: The Cochrane Library. Issue 1. Oxford: Update Software: 1999.

90. Prendiville W, Elbourne D, Chalmers I. The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* 1988;**95**:3–16.

91. Berlin JA. Does blinding of readers affect the results of meta-analyses? *Lancet* 1997;**350**:185–6.

92. Clark HD, Wells GA, Huet C, McAlister FA, Salmi LR, Fergusson D, *et al.* Assessing the quality of randomized trials: reliability of the Jadad scale. *Control Clin Trials* 1999;**20**:448–52.

93. Adami S, Passeri M, Ortolani S, Broggini M, Carratelli L, Caruso I, *et al.* Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *Bone* 1995;**17**:383–90.

94. Bone HG, Downs RW Jr, Tucci JR, Harris ST, Weinstein R, Licata AA, *et al.* Dose-response relationships for alendronate treatment in osteoporotic elderly women. *J Clin Endocrinol Metab* 1997;**82**:265–74.

95. Carfora E, Sergio F, Bellini P, Sergio C, Falco D, Zarcone R. Effect of treatment of postmenopausal osteoporosis with continuous daily oral alendronate and the incidence of fractures. *Gazzetta Med Ital Arch Sci Med* 1998;**157**(4):105–9.

96. Chesnut CH 3rd, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST, *et al.* Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995;**99**:144–52.

97. Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. *Osteoporos Int* 1997;**7**:488–95.

98. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, *et al.* Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;**348**:1535–41.

99. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, *et al.* Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;**280**:2077–82.

100. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, *et al.* Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999;**282**: 1344–52.

101. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, *et al.* Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;**333**:1437–43.

102. Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE, *et al.* Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab* 1999;**84**: 3076–81.

103. Montessori ML, Scheele WH, Netelenbos JC, Kerkhoff JF, Bakker K. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. *Osteoporos Int* 1997;**7**:52–8.

104. Pacifici R, McMurtry C, Vered I, Rupich R, Avioli LV. Coherence therapy does not prevent axial bone loss in osteoporotic women: a preliminary comparative study. *J Clin Endocrinol Metab* 1988;**66**:747–53.

105. Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Wilkin TJ, *et al.* Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. *Osteoporos Int* 1999; **9**:461–8.

106. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, *et al.* Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000;**11**:83–91.

107. Reid IR, Wattie DJ, Evans MC, Gamble GD, Stapleton JP, Cornish J. Continuous therapy with pamidronate, a potent bisphosphonate, in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 1994;**79**:1595–9.

108. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990;**322**:1265–71.

109. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, *et al.* Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;**323**:73–9.

110. Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with post-menopausal osteoporosis. *Am J Med* 1998;**104**:219–26.

111. Harris ST, Watts NB, Jackson RD, Genant HK, Wasnich RD, Ross P, *et al.* Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. *Am J Med* 1993;**95**:557–67.

112. McCloskey EV, Spector TD, Eyres KS, Fern ED, O'Rourke N, Vasikaran S, *et al.* The assessment of vertebral deformity: a method for use in population studies and clinical trials. *Osteoporos Int* 1993; **3**:138–47.

113. de Groen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, Freedholm D, *et al.* Esophagitis associated with the use of alendronate. *N Engl J Med* 1996;**335**:1016–21.

114. Miller PD, Watts NB, Licata AA, Harris ST, Genant HK, Wasnich RD, *et al.* Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment. *Am J Med* 1997;**103**:468–76.

115. Thiébaud D, Burckhardt P, Melchior J, Eckert P, Jacquet A, Schnyder P, *et al.* Two years' effectiveness of intravenous pamidronate (APD) versus oral fluoride for osteoporosis occurring in the postmenopause. *Osteoporos Int* 1994;**4**:76–83.

116. Ettinger B, Pressman A, Schein J, Silver P, Chan J Connolly N. Survey of women taking alendronate: prevalence of non-compliance with instructions and discontinuation. *Osteoporos Int* 1997;**7**:46.

117. Aloia JF, Vaswani A, Yeh JK, Ellis K, Yasumura S, Cohn SH. Calcitriol in the treatment of post-menopausal osteoporosis. *Am J Med* 1988;**84**:401–8.

118. Gallagher JC, Riggs BL, Recker RR, Goldgar D. The effect of calcitriol on patients with post-menopausal osteoporosis with special reference to fracture frequency. *Proc Soc Exp Biol Med* 1989;**3**:287–92.

119. Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol. A randomized controlled study. *Ann Intern Med* 1990;**113**:649–55.

120. Orimo H, Shiraki M, Hayashi T, Nakamura T. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D3. *Bone Miner* 1987;**3**:47–52.

121. Orimo H, Shiraki M, Hayashi Y, Hoshino T, Onaya T, Miyazaki S, *et al.* Effects of 1-alpha-hydroxyvitamin D3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. *Calcif Tissue Int* 1994;**54**:370–6.

122. Ott SM, Chesnut CH 3rd. Calcitriol treatment is not effective in postmenopausal osteoporosis [see comments]. *Ann Intern Med* 1989;**110**:267–74.

123. Shiraki M, Kushida K, Yamazaki K, Nagai T, Inoue T, Orimo H. Effects of 2 years' treatment of osteoporosis with 1 alpha-hydroxy vitamin D3 on bone mineral density and incidence of fracture: a placebo-controlled, double-blind prospective study. *Endocrine J* 1996;**43**:211–20.

124. Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992;**326**:357–62.

125. Levernieux J, Julien D, Caulin F. The effect of calcitonin on bone pain and acute resorption related to recent osteoporotic crush fractures – result of a double-blind and an open study. In: Cecchettin M, Segre G, editors. Calciotropic hormones and calcium metabolism. Amsterdam: Elsevier; 1986. p.171–8.

126. Lyritis GP, Tsakalakos N, Magiasis B, Karachalios T, Yiatzides A, Tsekoura M. Analgesic effect of salmon calcitonin in osteoporotic vertebral fractures: a double-blind placebo-controlled clinical study. *Calcif Tissue Int* 1991;**49**:369–72.

127. Lyritis GP, Paspati I, Karachalios T, Ioakimidis D, Skarantavos G, Lyritis PG. Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures. A double-blind, placebo-controlled clinical study. *Acta Orthop Scand Suppl* 1997;**275**:112–14.

128. Cristallini S, Pedetti M, Donatelli C, Gregorio F, Filipponi P. [The effect of different "coherent"-type therapeutic plans on bone mineral density and on the incidence of vertebral fractures in advanced osteoporosis. In Italian.] *Recent Prog Med* 1993;**84**:336–45.

129. Ellerington MC, Hillard TC, Whitcroft SI, Marsh MS, Lees B, Banks LM, *et al.* Intranasal salmon calcitonin for the prevention and treatment of postmenopausal osteoporosis. *Calcif Tissue Int* 1996;**59**:6–11.

130. Hizmetli S, Elden H, Kaptanoglu E, Nacitarhan V, Kocagil S. The effect of different doses of calcitonin on bone mineral density and fracture risk in postmenopausal osteoporosis. *Int J Clin Pract* 1998;**52**:453–5.

131. Hodsman AB, Fraher LJ, Watson PH, Ostbye T, Stitt LW, Adachi JD, *et al.* A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 1997;**82**:620–8.

132. Pontiroli AE, Pajetta E, Calderara A, Alberetto M, Pozza G, Manganelli V, *et al.* Intranasal and intramuscular human calcitonin in female osteoporosis and in Paget's disease of bones: a pilot study. *J Endocrinol Invest* 1991;**14**:47–51.

133. Stock JL, Avioli LV, Baylink DJ, Chesnut C, Genant HK, Maricic MJ, *et al.* Calcitonin-salmon nasal spray reduces the incidence of new vertebral fractures in post-menopausal women: three year interim results of the PROOF study. *J Bone Miner Res* 1997;**12**:S149.

134. Rico H, Hernandez ER, Revilla M, Gomez-Castresana F. Salmon calcitonin reduces vertebral fracture rate in postmenopausal crush fracture syndrome. *Bone Miner* 1992;**16**:131–8.

135. Rico H, Revilla M, Hernandez ER, Villa LF, Alvarez de Buergo M. Total and regional bone mineral content and fracture rate in postmenopausal osteoporosis treated with salmon calcitonin: a prospective study. *Calcif Tissue Int* 1995;**56**:181–5.

136. Ringe JD, Welzel D. Salmon calcitonin in the therapy of corticoid-induced osteoporosis. *Eur J Clin Pharmacol* 1987;**33**:35–9.

137. Ringe JD. [Treatment of primary osteoporosis with calcium and salmon calcitonin. In German.] *Dtsch Med Wochensch* 1990;**115**:1176–82.

138. Kanis JA, McCloskey EV. Effect of calcitonin on vertebral and other fractures. *QJM* 1999;**92**:143–9.

139. Abellan Perez M, Bayina Garcia FJ, Calabozo M, Carpintero Benitez P, Figueroa Pedrosa M, Fernandez Crisostomo C, *et al.* [Multicentre comparative study of synthetic salmon calcitonin administered nasally in the treatment of established postmenopausal osteoporosis. In Spanish.] *An Med Interna* 1995;**12**:12–16.

140. Grazioli I, Strumia E. Drug surveillance concerning calcitonin: preliminary findings on efficacy and tolerability. *Clin Ter* 1988;**127**:289–95.

141. Osteoporosis: clinical guidelines for prevention and treatment. London: Royal College of Physicians of London; 1999.

142. Recker RR, Hinders S, Davies KM, Heaney RP, Stegman MR, Lappe JM, *et al.* Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* 1996;**11**:1961–6.

143. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kptpwocz MA, Lane AW, *et al.* Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;**117**:1–9.

144. Zarcone R, Carfora E, Sergio F, Bellini P, Longo M, Tartaglia E, *et al.* [Oestrogen therapy in women with postmenopausal osteoporosis. In Italian.] *Minerva Ginecol* 1997;**49**:355–9.

145. Barrett-Connor E. Fortnightly review – hormone replacement therapy. *BMJ* 1998;**317**:457–61.

146. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999;**106**:574–82.

147. Sherwin BB. Hormones, mood, and cognitive functioning in postmenopausal women. *Obstet Gynecol* 1996;**87**:20–6S.

148. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998;**279**:688–95.

149. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;**350**:1047–59.

150. Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, *et al.* Postmenopausal hormone therapy increases risk for venous thromboembolic disease. *Ann Intern Med* 2000;**132**:689–96.

151. Grady D, Rubin SM, Pettiti DB. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;**117**:1016–37.

152. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Pettiti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;**85**:304–13.

153. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs BL, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**280**:605–13.

154. Wallace WA, Price VH, Elliot CA, MacPherson MB, Scott BW. Hormone replacement therapy acceptability to Nottingham post-menopausal women with a risk factor for osteoporosis. *J R Soc Med* 1990;**83**:699–701.

155. Torgerson DJ, Donaldson C, Russell IT, Reid DM. Hormone replacement therapy: compliance and cost after screening for osteoporosis. *Eur J Obstet Gynecol Reprod Biol* 1995;**59**:57–60.

156. Ryan PJ, Harrison R, Blake GM, Fogelman I. Compliance with hormone replacement therapy (HRT) after screening for post menopausal osteoporosis. *Br J Obstet Gynaecol* 1992;**99**:325–8.

157. Maugeri D, Panebianco P, Russo MS, Motta M, Tropea S, Motta L, *et al.* Ipriflavone-treatment of senile osteoporosis: results of a multicenter, double-blind clinical trial of 2 years. *Arch Gerontol Geriatr* 1994;**19**:253–63.

158. Passeri M, Biondi M, Costi D, Bufalino L, Castiglione GN, di Peppe C, *et al.* Effect of ipriflavone on bone mass in elderly osteoporotic women. *Bone Miner* 1992;**19** Suppl 1:S57–62.

159. Passeri M, Biondi M, Costi D, Dall'Aglio E, Pedrazzoni M, Bufalino L, *et al.* Effects of 2-year therapy with ipriflavone in elderly women with established osteoporosis. *Ital J Miner Electrolyte Metab* 1995;**9**:137–44.

160. Agnusdei D, Bufalino L. Efficacy of ipriflavone in established osteoporosis and long-term safety. *Calcif Tissue Int* 1997;**61** Suppl 1:S23–7.

161. Chesnut CH 3rd, Ivey JL, Gruber HE, Matthews M, Nelp WB, Sisom K, *et al.* Stanozolol in postmenopausal osteoporosis: therapeutic efficacy and possible mechanisms of action. *Metabolism* 1983;**32**:571–80.

162. Geusens P. Nandrolone decanoate: pharmacological properties and therapeutic use in osteoporosis. *Clin Rheumatol* 1995;**14** Suppl 3:32–9.

163. Geusens P, Dequeker J. Long-term effect of nandrolone decanoate, 1-alpha-hydroxy vitamin D3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: a double-blind controlled study. *Bone Miner* 1986;**1**:347–57.

164. Birkenhager JC, Erdtsieck RJ, Zeelenberg J, van Kuik C, van Veen LC, Birkenhager-Frenkel DH, *et al.* Can nandrolone add to the effect of hormonal replacement therapy in postmenopausal osteoporosis? *Bone Miner* 1992;**18**:251–65.

165. Need AG, Horowitz M, Walker CJ, Chatterton BE, Chapman JC, Nordin BE. Crossover study of fat-corrected forearm mineral content during nandrolone decanoate therapy for osteoporosis. *Bone* 1989;**10**:3–6.

166. Lyritis GP, Androulakis C, Magiasis B, Charalambaki Z, Tsakalakos N. Effect of nandrolone decanoate and 1-alpha-hydroxy-calciferol on patients with vertebral osteoporotic collapse. A double-blind clinical trial. *Bone Miner* 1994;**27**:209–17.

167. Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. *Calcif Tissue Int* 1987;**40**:315–17.

168. Kleerekoper M, Peterson EL, Nelson DA, Phillips E, Schork MA, Tilley B, *et al.* A randomized trial of sodium fluoride as a treatment for postmenopausal osteoporosis. *Osteoporos Int* 1991;**1**:155–61.

169. Meunier PJ, Sebert JL, Reginster JY, Briancon D, Appelboom T, Netter P, *et al.* Fluoride salts are no better at preventing new vertebral fractures than calcium-vitamin D in postmenopausal osteoporosis: the FAVO study. *Osteoporos Int* 1998;**8**:4–12.

170. Pak CY, Sakhaee K, Adams-Huet B, Piziak V, Peterson RD, Poindexter JR. Treatment of postmenopausal osteoporosis with slow-release sodium fluoride. Final report of a randomized controlled trial. *Ann Intern Med* 1995;**123**:401–8.

171. Reginster JY, Meurmans L, Zegels B, Rovati LC, Minne HW, Giacovelli G, *et al.* The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis. A randomized, controlled trial. *Ann Intern Med* 1998;**129**:1–8.

172. Riggs BL, Hodgson SF, O'Fallon WM, Chao EW, Wahner HW, Muhs JM, *et al.* Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990;**322**:802–9.

173. Ringe JD, Dorst A, Kipshoven C, Rovati LC, Setnikar I. Avoidance of vertebral fractures in men with idiopathic osteoporosis by a three year therapy with calcium and low-dose intermittent monofluorophosphate. *Osteoporos Int* 1998;**8**:47–52.

174. Ringe JD, Kipshoven C, Coster A, Umbach R. Therapy of established postmenopausal osteoporosis with monofluorophosphate plus calcium: dose-related effects on bone density and fracture rate. *Osteoporos Int* 1999;**9**:171–8.

175. Sebert JL, Richard P, Mennecier I, Bisset JP, Loeb G. Monofluorophosphate increases lumbar bone density in osteopenic patients: a double-masked randomized study. *Osteoporos Int* 1995;**5**:108–14.

176. Mamelle N, Meunier PJ, Dusan R, Guillaume M, Martin JL, Gaucher A, *et al.* Risk-benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. *Lancet* 1988;**2**:361–5.

177. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant H, *et al.* Reduction of vertebral fracture risk in post-menopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999;**282**:637–45.

178. Lufkin EG, Whitaker MD, Nickelsen T, Argueta R, Caplan RH, Knickerbocker RK, *et al.* Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res* 1998;**13**:1747–54.

179. Delmas PD, Mitlak BH, Christiansen C. Effects of raloxifene in postmenopausal women. *N Engl J Med* 1998;**338**:1313–14.

180. Walsh BW, Kuller LH, Wild RA, Paul S, Farmer M, Lawrence JB, *et al.* Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA* 1998;**279**:1445–51.

181. Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, *et al.* Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;**337**:1641–7.

182. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, *et al.* The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999;**281**:2189–97.

183. Khovidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. *Ann Intern Med* 1999;**130**:431–9.

184. Jordan VC, Glusman JE, Eckert S, Lippman M, Powles T, Costa A, *et al.* Incident primary breast cancers are reduced by raloxifene: integrated data from multicenter, double-blind, randomised trials in ~12,000 postmenopausal women. *Proc Am Soc Clin Oncol* 1998;**17**:122a.

185. Nickelsen T, Lufkin EG, Riggs BL, Cox DA, Crook TH. Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in postmenopausal women. *Psychoneuroendocrinology* 1999;**24**:115–28.

186. Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;**128**:801–9.

187. Ebrahim S, Thompson PW, Baskaran V, Evans K. Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. *Age Ageing* 1997;**26**:253–60.

188. Hardman AE, Hudson A, Jones PRM, Norgan NG. Brisk walking and plasma high density lipoprotein cholesterol concentration in previously sedentary women. *BMJ* 1989;**299**:1204–5.

189. Leon AS, Conrad J, Hunninghake DB, Serfass R. Effects of a vigorous walk programme on body composition and carbodydrate and lipid metabolism of obese young men. *Am J Clin Nutr* 1979;**32**:1776–87.

190. Arthur RS, Piraino B, Candib D, Cooperstein L, Chen T, West C, *et al.* Effect of low-dose calcitriol and calcium therapy on bone histomorphometry and urinary calcium excretion in osteopenic women. *Miner Electrolyte Metab* 1990;**16**:385–90.

191. Falch JA, Odegaard OR, Finnanger AM, Matheson I. Postmenopausal osteoporosis: no effect of three years treatment with 1,25-dihydroxycholecalciferol. *Acta Med Scand* 1987;**221**:199–204.

192. Lems WF, Jacobs JW, Bijlsma JW, van Veen GJ, Houben HH, Haanen HC, *et al.* Is the addition of sodium fluoride to cyclical etidronate beneficial in the treatment of corticosteroid induced osteoporosis? *Ann Rheum Dis* 1997;**56**:357–63.

193. Pak CY, Sakhaee K, Zerwekh JE, Parcel C, Peterson R, Johnson K. Safe and effective treatment of osteoporosis with intermittent slow release sodium fluoride: augmentation of vertebral bone mass and inhibition of fractures. *J Clin Endocrinol Metab* 1989;**68**:150–9.

194. Shiota E. Evaluation of the drug therapy for established osteoporosis by dual-energy x-ray absorptiometry. *Fukuoka Igaku Zasshi* 1998;**89**:172–8.

195. Shiraki M, Kushid K, Fukunaga M, Kishimoto H, Taga M, Nakamura T, *et al.* A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. *Osteoporos Int* 1999;**10**:183–92.

196. Black DM, Palermo L, Nevitt MC, Genant HK, Christensen L, Cummings SR. Defining incident vertebral deformity: a prospective comparison of several approaches. *J Bone Miner Res* 1999;**14**:90–101.

197. Michaelsson K, Baron JA, Farahmand BY, Johnell O, Magnusson C, Persson PG, *et al.* Hormone replacement therapy and risk of hip fracture: population based case–control study. *BMJ* 1998;**316**:1858–63.

198. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of withdrawal of calcium and vitamin D supplements on bone mass in elderly men and women. *Am J Clin Nutr* 2000;**72**:745–50.

199. Devine A, Dick IM, Heal SJ, Criddle RA, Prince RL. A 4-year follow-up study of the effects of calcium supplementation on bone density in elderly postmenopausal women. *Osteoporos Int* 1997;**7**:23–8.

200. Pouilles JM, Tremollieres F, Ribot C. Prevention of post-menopausal bone loss with 1-alpha-hydroxy vitamin D3. A three-year prospective study. *Clin Rheumatol* 1992;**11**:492–7.

201. Lindsay R, Hart DM, Maclean A, Clark AC, Kraszewski A, Garwood J. Bone response to termination of oestrogen treatment. *Lancet* 1978;**i**:1325–7.

202. Stevenson JC, Kanis JA, Christiansen C. Bone-density measurement. *Lancet* 1992;**339**:370–1.

203. Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. *N Engl J Med* 1980;**303**:1195–8.

204. Kristensen B, Ejlertsen B, Mouridsen HT, Andersen KW, Lauritzen JB. Femoral fractures in postmenopausal breast cancer patients treated with adjuvant tamoxifen. *Breast Cancer Res Treat* 1996;**39**:321–6.

205. Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PW, Anderson JJ. The effect of post-menopausal estrogen therapy on bone density in elderly women. *N Engl J Med* 1993;**329**:1141–6.

206. Keil DP, Felson DT, Anderson JJ. Hip fracture and the use of estrogens in postmenopausal women. *N Engl J Med* 1987;**317**:1169–74.

207. Haji-Fuleihan G, Luckery M, Bauer R, Wasnich R, Krupa D, Reda C, *et al.* Effects of discontinuation of alendronate in early postmenopausal women. *J Bone Miner Res* 1997;**12**:S143.

208. Khan SA, Kanis JA, Vasikaran S, Kline WF, Matuszewski BK, McCloskey EV, *et al.* Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. *J Bone Miner Res* 1997;**12**:1700–7.

209. Stock JL, Bell NH, Chesnut CH 3rd, Ensrud KE, Genant HK, Harris ST, *et al.* Increments in bone mineral density of the lumbar spine and hip and suppression of bone turnover are maintained after discontinuation of alendronate in postmenopausal women. *Am J Med* 1997;**103**:291–7.

210. Landman JO, Hamdy NA, Pauwels EK, Papapoulos SE. Skeletal metabolism in patients with osteoporosis after discontinuation of long-term treatment with oral pamidronate. *J Clin Endocrinol Metab* 1995;**80**:3465–8.

211. Wasnich R, Davis J, Workman P, *et al.* Effects of alendronate discontinuation on BMD in early postmenopausal women. *J Bone Miner Res* 1998;**23**:S402.

212. Delmas PD, Balena R, Confravreux E, Hardouin C, Hardy P, Bremond A. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. *J Clin Oncol* 1997;**15**:955–62.

213. Talbot JR, Fischer MM, Farley SM, Libanati C, Farley J, Tabuenca A, *et al.* The increase in spinal bone density that occurs in response to fluoride therapy for osteoporosis is not maintained after the therapy is discontinued. *Osteoporos Int* 1996;**6**:442–47.

214. Johnell O, Steinbeck M, Rosen M, Gullberg B, Kanis JA. Therapeutic strategies in the prevention of hip fracture with drugs affecting bone metabolism. *Bone* 1993;**14**:S85–7.

215. Johnell O, Oden A, Kanis JA, Caulin F. Prevention of osteoporotic fractures. *Calcif Tissue Int* 1997;**61**:500.

216. Torgerson DJ, Reid DM. The economics of osteoporosis and its prevention. A review. *PharmacoEconomics* 1997;**11**:126–38.

217. Daley E, Vessey MP, Barlow D, Gray A, McPherson K, Roche M. Hormone replacement therapy in a risk-benefit perspective. In: Berg G, Hammar M, editors. The modern management of the menopause: a perspective for the 21st century. Proceedings Second International Congress on the Menopause, Stockholm, June 20–24, 1994. London: Parthenon; 1994. p.473–97.

218. Roche M, Vessey M. Hormone replacement therapy in the menopause – risks, benefits and costs. In: Drife JO, Studd JWW, editors. HRT and osteoporosis. 1990. p.363–72.

219. Weinstein MC, Schiff I. Cost-effectiveness of hormone replacement therapy in the menopause. *Obstet Gynecol Surv* 1983;**38**:445–55.

220. Cheung AP, Wren BG. A cost-effectiveness analysis of hormone replacement therapy in the menopause. *Med J Aust* 1992;**156**:312–16.

221. McClung MR, Geusens P, Miller P, Zippel H, Bensen WG, Roux C, *et al.* Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001;**344**:333–40.

222. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, *et al.* Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;**327**:1637–42.

223. Heikinheimo RJ, Inkovaara JA, Harju EJ, Haavisto MV, Kaarela RH, Kataja JH, *et al.* Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int* 1992;**51**:105–10.

224. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996;**124**:400–6.

225. Koumulainen MH, Kroger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, *et al.* HRT and vit D in prevention of non-vertebral fractures in postmenopausal women: a 5 year randomized trial. *Maturitas* 1998;**31**:45–54.

226. Naessen T, Persson I, Adami HO, Bergstrom R, Bergkvist L. Hormone replacement therapy and the risk for first hip fracture. A prospective, population-based cohort study. *Ann Intern Med* 1990;**113**:95–103.

227. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. *Ann Intern Med* 1995;**122**:9–16.

228. Porter M, Penney GC, Russell D, Russell E, Templeton A. A population based survey of women's experience of the menopause. *Br J Obstet Gynaecol* 1996;**103**:1025–8.

229. Rymer J, Morris EP. Menopausal symptoms. *BMJ* 2000;**321**:1516–19.

230. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Annu Rev Public Health* 1998;**19**:55–72.

231. Posthuma WFM, Westendorp RGJ, Vandenbroucke JP. Cardioprotective effect of hormone replacement therapy in postmenopausal women: is the evidence biased? *BMJ* 1994;**308**:1268–9.

232. Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;**315**:149–53.

233. Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, *et al.* Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997;**336**:1769–75.

234. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, *et al.* Postmenopausal estrogen therapy and cardiovascular disease. *N Engl J Med* 1991;**325**:756–62.

235. Vessey MP. Exogenous oestrogens and the risk of breast cancer. *Proc R Coll Physicians Edinb* 1999;**29**:133–6.

236. Cauley JA, Seeley DG, Browner WS, Ensrud K, Kuller LH, Lipschutz RC, *et al.* Estrogen replacement therapy and mortality among older women. The study of osteoporotic fractures. *Arch Intern Med* 1997;**157**:2181–7.

237. Perez Gutthann S, Garcia Rodrigues LA, Castellsague J, Duque Oliart A. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997;**314**:796–800.

238. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;**348**:977–80.

239. Jick H, Derby LE, Wald Myers M, Vasilakis C, Newton KM. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996;**348**:981–3.

240. Kanis JA, Beneton MNC, Gennari C, *et al.* Effects of anabolic steroids on cortical bone and fracture. In: Christiansen C, Riis B, editors. Osteoporosis 1993. Proceedings 4th International Conference on Osteoporosis. Copenhagen, 1993. p.308–10.

241. Haguenauer D, Welch V, Shea B, Tugwell P, Adachi JD, Wells G. Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis. *Osteoporos Int* 2000;**11**:728–38.

242. Wasnich R, Davis J, Ross P, Vogel J. Effect of thiazide on rates of bone mineral loss: a longitudinal study. *BMJ* 1990;**301**:1303–5.

243. Ray WA, Griffin MR, Downey W, Melton LJ 3rd. Long-term use of thiazide diuretics and risk of hip fracture. *Lancet* 1989;**i**:687–90.

244. Felson DT, Sloutskis D, Anderson JJ, Anthony JM, Kiel DP. Thiazide diuretics and the risk of hip fracture. Results from the Framingham study. *JAMA* 1991;**265**:370–3.

245. LaCroix AZ, Wienpahl J, White LR, Wallace RB, Scherr PA, George LK, *et al.* Thiazide diuretic agents and the incidence of hip fracture. *N Engl J Med* 1990;**322**:286–90.

246. Jones G, Nguyen T, Sambrook PN, Eisman JA. Thiazide diuretics and fractures: can meta-analysis help? *J Bone Miner Res* 1995;**10**:106–11.

247. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;**308**:367–72.

248. Sanders KM, Pasco JA, Ugoni AM, Nicholson GC, Seeman E, Martin TJ, *et al.* The exclusion of high trauma fractures may underestimate the prevalence of bone fragility fractures in the community: the Geelong osteoporosis study. *J Bone Miner Res* 1998;**13**:1337–42.

249. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associated with low appendicular bone mass in elderly women? *Ann Intern Med* 1991;**115**:837–42.

250. Melton LJ, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL. Vertebral fractures predict subsequent fractures. *Osteoporos Int* 1999;**10**:214–21.

251. Kotowicz MA, Melton LJ 3rd, Cooper C, Atkinson EJ, O'Fallon WM, Riggs BL. Risk of hip fracture in women with vertebral fracture. *J Bone Miner Res* 1994;**9**:599–605.

252. Lippuner K, von Overbeck J, Perrelet R, Bosshard H, Jaeger P. Incidence and direct medical costs of hospitalizations due to osteoporotic fractures in Switzerland. *Osteoporos Int* 1997;**7**:414–25.

253. Phillips S, Fox N, Jacobs J, Wright W. The direct medical costs of osteoporosis for American women aged 45 and older, 1986. *Bone* 1988;**9**:271–9.

254. Melton LJ 3rd, Thamer M, Ray NF, Chan JK, Chesnut CH 3rd, Einhorn TA, *et al.* Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. *J Bone Miner Res* 1997;**12**:16–23.

255. Donaldson LJ, Cook A, Thomson R. Incidence of fractures in a geographically defined population. *J Epidemiol Community Health* 1990;**44**:241–5.

256. Johansen A, Evans RJ, Stone MD, Richmond PW, Lo SV, Woodhouse KW. Fracture incidence in England and Wales: a study based on the population of Cardiff. *Injury* 1997;**28**:655–60.

257. Falch J, Kaastad TS, Bohler G, Espeland J, Sundsvold OJ. Secular increase and geographic differences in hip fracture incidence in Norway. *Bone* 1993;**14**:643–5.

258. Kanis JA, McCloskey EV. Epidemiology of vertebral osteoporosis. *Bone* 1992;**13** Suppl 2:S1–10.

259. Donnelly S, Spector TD, Reaney L, Doyle DV, Kanis JA, McCloskey EV. Incidence of vertebral fracture in early postmenopausal women in the United Kingdom: the Chingford study. *Osteoporos Int*; in press.

260. Palvanen M, Kannus P, Niemi S, Parkkari J. Secular trends in the osteoporotic fractures of the distal humerus in elderly women. *Eur J Epidemiol* 1998;**14**:159–64.

261. Frost ML, Blake GM, Fogelman I. Quantitative ultrasound and bone mineral density are equally strongly associated with risk factors for osteoporosis. *J Bone Miner Res* 2001;**16**:406–14.

262. Kanis JA, Johnell O, Oden A, Jonsson B, de Laet C, Dawson A. Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. *Bone* 2000;**27**:585–90.

263. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000;**15**:721–7.

264. Zamet JS, Darbar UR, Griffiths GS, Bulman JS, Bragger U, Burgin W, *et al.* Particulate bioglass as a grafting material in the treatment of periodontal intrabony defects. *J Clin Periodontol* 1997;**24**:410–18.

265. Johnell O, Oden A, Caulin F, Kanis JA. Acute and long-term increase in fracture risk after hospitalisation for vertebral fracture. *Osteoporos Int* 2001;**12**:207–14.

266. Parker MJ, Anand JK. What is the true mortality of hip fracture? *Public Health* 1991;**105**:443–6.

267. Meyer HE, Tverdal A, Falch JA, Pedersen JI. Factors associated with mortality after hip fracture. *Osteoporos Int* 2000;**11**:228–32.

268. Poor G, Atkinson EJ, O'Fallon WM, Melton LJ. Determinants of reduced survival following hip fractures in men. *Clin Orthop* 1995;**319**:260–5.

269. Todd CJ, Freeman C, Camilleri-Ferrante C, Laxton C, Muriel P, Palmer C, *et al.* Anglian audit of hip fracture 2. Cambridge: Cambridge Health Services Research Group, University of Cambridge; 1999.

270. Forsen L, Sogaard AJ, Meyer HE, Edna T, Kopjar B. Survival after hip fracture: short and long-term excess mortality according to age and gender. *Osteoporos Int* 1999;**10**:73–8.

271. Laxton C, Freeman C, Todd C, Payne BV, Camilleri-Ferrante C. Morbidity at 3 months after hip fracture: data from the East Anglian audit. *Health Trends* 1997;**29**:55–60.

272. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. *Arch Intern Med* 1999;**159**:1215–20.

273. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 1999;**353**:878–82.

274. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ 3rd. Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* 1993;**137**:1001–5.

275. Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. *Lancet* 1991;**338**:355–8.

276. Johansson C, Black D, Johnell O, Oden A, Mellstrom D. Bone mineral density is a predictor of survival. *Calcif Tissue Int* 1998;**63**:190–6.

277. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. *Osteoporos Int* 2000;**11**:556–61.

278. Office of National Statistics. Mortality Series. DH2 no 25. London: Stationery Office; 1998.

279. Office of National Statistics. Cancer survival trends in England and Wales 1971–1995. Deprivation and NHS region. London: Stationery Office; 2001.

280. Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR. Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. *JAMA* 1996;**276**:1404–8.

281. Zhang Y, Kiel DP, Kreger BE, Cupples LA, Ellison RC, Dorgan JF, *et al.* Bone mass and the risk of breast cancer among postmenopausal women. *N Engl J Med* 1997;**336**:611–17.

282. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HAW. Coronary event and case fatality rates in an English population: results of the Oxford myocardial incidence study. *Heart* 1998;**80**:40–4.

283. Expectation of life: United Kingdom females – 1999. London: Government Actuary Office; 1999.

284. Sculpher M, Torgerson D, Goeree R, O'Brien B. A critical structured review of economic evaluations of interventions for the prevention and treatment of osteoporosis. Discussion Paper 169. York: University of York Centre for Health Economics; 1999.

285. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, *et al.* Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fracture. *J Bone Miner Res* 2000;**15**:1384–92.

286. Brazier JE, Kohler B, Walters S. A prospective study of the health related quality of life impact of hip fracture. Sheffield: SCHaRR, University of Sheffield; 2000.

287. Hutton J, Brown R, Borowitz M, Abrams K, Rothman M, Shakespeare A. A new decision model for cost–utility comparisons of chemotherapy in recurrent metastatic breast cancer. *PharmacoEconomics* 1996;**9**:8–22.

288. Gabriel SE, Kneeland TS, Melton LJ 3rd, Moncur MM, Ettinger B, Tosteson AN. Health-related quality of life in economic evaluations for osteoporosis: whose values should we use? *Med Decis Making* 1999;**19**:141–8.

289. Gold DT. The clinical impact of vertebral fractures: quality of life in women with osteoporosis. *Bone* 1996;**18**:185–9S.

290. Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrie SE, *et al.* Quality of life related to fear of falling and hip fracture in older women: a time trade-off study. *BMJ* 2000;**320**:341–6.

291. Dolan P. Modelling valuation for Euroqol health states. *Med Care* 1997;**35**:351–63.

292. Fitzpatrick R, Zeibland S, Jenkinson C, Mowat A. A comparison of the sensitivity to change of several health status measures in rheumatoid arthritis. *J Rheumatol* 1993;**20**:429–36.

293. Brazier J, Deverill M, Green C. A review of the use of health status measures in economic evaluation. *J Health Serv Res Policy* 1999;**4**:174–84.

294. Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, *et al.* The Beaver Dam health outcomes study: initial catalog of health-state quality factors. *Med Decis Making* 1993;**13**:89–102.

295. Roberge R, Berthelot J, Cranswick K. Adjusting life expectancy to account for disability in the population: a comparison of three techniques. *Soc Indicators Res* 1999;**48**:217–43.

296. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a UK national questionnaire survey. *BMJ* 1998;**316**:736–41.

297. Dolan P, Torgerson D, Kakarlapudi TK. Health-related quality of life of Colles' fracture patients. *Osteoporos Int* 1999;**9**:196–9.

298. Gold MR, Siegel JE, Russell LB. Cost-effectiveness in health and medicine. Oxford: Oxford University Press; 1996.

299. Tengs TO, Wallace A. One thousand health related quality of life estimates. *Med Care* 2000;**38**:583–637.

300. NHS Centre for Reviews and Dissemination. Available from: http://agatha.york.ac.uk/nf2.htm

301. Beech R, Withey C, Morris R. Understanding variations in lengths of stay between hospitals for fractured neck of femur patients and the potential consequences of reduced stay targets. *J Public Health Med* 1995;**17**:77–84.

302. Best L, Milne R. Bisphosphonates (alendronate and etidronate) in the management of osteoporosis. DEC report no. 79. Southampton: Wessex Institute for Health Research and Development; 1998.

303. Drummond MF, Heyse J, Cook J, McGuire A. Selection of end points in economic evaluations of coronary-heart-disease interventions. *Med Decis Making* 1993;**13**:184–90.

304. Fox HJ, Hughes SJ, Pooler J, Prothero D, Bannister GC. Length of hospital stay and outcome after femoral neck fracture: a prospective study comparing the performance of two hospitals. *Injury* 1993;**24**:464–6.

305. Francis RM, Anderson FH, Torgerson DJ. A comparison of the effectiveness and cost of treatment for vertebral fractures in women. *Br J Rheumatol* 1995;**34**:1167–71.

306. French FH, Torgerson DJ, Porter RW. Cost analysis of fracture of the neck of femur. *Age Ageing* 1995;**24**:185–9.

307. Hollingworth W, Todd CJ, Parker MJ. The cost of treating hip fractures in the twenty-first century. *J Public Health Med* 1995;**17**:269–76.

308. Hollingworth W, Todd C, Parker M, Roberts JA, Williams R. Cost-analysis of early discharge after hip fracture. *BMJ* 1993;**307**:903–6.

309. Morris S, McGuire A, McPherson K. The cost-effectiveness of raloxifene therapy for postmenopausal women in the UK. London: City University, 1999.

310. O'Cathain A. Evaluation of a hospital at home scheme for the early discharge of patients with fractured neck of femur. *J Public Health Med* 1994;**16**:205–10.

311. Parker MJ, Todd CJ, Palmer CR, Camilleri-Ferrante C, Freeman C, Laxton C, *et al.* Inter-hospital variations in length of hospital stay following hip fracture. *Age Ageing* 1998;**27**:333–7.

312. Reid DM, Torgerson DJ. Pharmacoeconomic aspects of intermittent cyclical etidronate therapy in the treatment of postmenopausal and corticosteroid-induced osteoporosis. *Rev Contemp Pharmacother* 1998;**9**:287–92.

313. Taylor R, Kirby B. Cost implications of cardiac rehabilitation in older patients. *Coron Artery Dis* 1999;**10**:53–6.

314. Torgerson DJ, Dolan P. Prescribing by general practitioners after an osteoporotic fracture. *Ann Rheum Dis* 1998;**57**:378–9.

315. Torgerson DJ, Reid DM. The pharmacoeconomics of hormone replacement therapy. *PharmacoEconomics* 1999;**16**:9–16.

316. Torgerson DJ, Reid DM. Osteoporosis prevention through screening: will it be cost-effective? *Baillieres Clin Rheumatol* 1993;**7**:603–22.

317. Torgerson DJ, Donaldson C, Reid DM. Using economics to prioritise research: a case study of randomized trials for the prevention of hip fractures due to osteoporosis. *J Health Serv Res Policy* 1996;**1**:141–6.

318. Torgerson DJ, Donaldson C, Reid DM. Bone mineral density measurements: are they worthwhile? *J R Soc Med* 1996;**89**:457–61.

319. Torgerson DJ, Gosden T, Reid DM. The economics of osteoporosis prevention. *Trends Endocrinol Metab* 1997;**8**:236–9.

320. Townsend J. Hormone replacement therapy: assessment of present use, costs, and trends. *Br J Gen Pract* 1998;**48**:955–8.

321. Townsend J, Buxton M. Cost-effectiveness scenario analysis for a proposed trial of hormone replacement therapy. *Health Policy* 1997;**39**:181–94.

322. Withey C, Morris R, Beach R, Backhouse A. Outcome following fractured neck of femur – variation in acute hospital care or case mix? *J Public Health Med* 1995;**17**:429–37.

323. Netten A, Denett J, Knight J. Unit costs of health and social care 1998. Canterbury: Personal Social Services Research Unit, University of Kent; 1998.

324. GDP and GDP deflators at market prices. 2000. URL: www.hmtreasury.gov.uk/deflators/figures.html (July 2000).

325. Pathways Through Care Study Group. Pathways through care: the processes and outcomes of hospital care for elderly people. Newcastle-upon-Tyne: University of Newcastle, Centre for Health Services Research; 1996.

326. Netten A, Denett J. Unit costs of health and social care. Canterbury: Personal Social Services Research Unit, University of Kent; 1996.

327. Yuen P. OHE compendium of health statistics. 11th edition. London: Office of Health Economics; 1999.

328. de Laet CEDH, van Hout BA, Burger H, Weel AEAM, Hofman A, Pols HAP. Incremental cost of medical care after hip fracture and first vertebral fracture: the Rotterdam study. *Osteoporos Int* 1999;**10**:66–72.

329. Chrischilles E, Shireman T, Wallace R. Costs and health effects of osteoporotic fractures. *Bone* 1994;**15**:377–86.

330. Wolstenholme JL, Smith SJ, Whynes DK. The costs of treating breast cancer in the United Kingdom: implications for screening. *Int J Technol Assess Health Care* 1998;**14**:277–89.

331. Dolan P, Torgerson DJ, Wolstenholme J. Costs of breast cancer treatment in the United Kingdom. *Breast* 1999;**8**:205–7.

332. Pickin DM, Payne JN, Haq IU, McCabe CJ, Ward SE, Jackson PR, *et al.* Statin therapy/ Co-A reductase inhibitor treatment in the prevention of coronary heart disease. Guidance note for purchasers. Report no. 96/04. Sheffield: Trent Institute for Health Services Research; 1996.

333. Piercy J, Pledger G. Estimating the resource implications of coronary heart disease in Newcastle. (Cost-effective purchasing occasional paper 2). York: University of York Health Economics Consortium; 1991.

334. England and Wales mid-1996 population estimates. 2000. URL:www.statistics.gov.uk/statsbase/xsdataset.asp [July 2000].

335. Netten A, Curtis L. Unit costs of health and social care 2000. Canterbury: University of Kent; 2000.

336. Garton MJ, Torgerson DJ, Donaldson C, Russell IT, Reid DM. Recruitment methods for screening programmes: trial of a new method within a regional osteoporosis study. *BMJ* 1992;**305**:82–4.

337. Sonnenberg FA, Beck JR. Markov models in medical decision making. *Med Decis Making* 1993;**13**:322–38.

338. Sox HC, Blatt MA, Higgins MC, Marton KI. Medical decision making. Boston: Butterworth-Heinemann; 1998.

339. O'Hagan A. Curve fitting and optimal design for prediction [with discussion]. *J Roy Statist Soc B* 1978;**40**:1–42.

340. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. London: Oxford University Press; 1996.

341. National Institute for Clinical Excellence 2000. http://www.nice.org.uk/nice-web/

342. Raftery J. NICE: a faster access to modern treatments? Analysis of guidance on health technologies. *BMJ* 2001;**232**:1300–3.

343. Nevitt MC, Thompson DE, Black DM, Rubin SR, Ensrud K, Yates AJ, *et al.* Effect of alendronate on limited-activity days and bed-disability days caused by back pain in post-menopausal women with existing vertebral fractures. *Arch Intern Med* 2000;**160**:77–85.

344. Johnell O, Kanis JA, de Laet C, Jonsson B, Zethraeus N, Oden A. Sequential changes in quality of life after osteoporotic fractures. *Osteoporos Int* 2002;**13** Suppl 1: S70.

345. Kanis JA, Delmas P, Burckhardt P, Cooper C, Togerson D. Guidelines for diagnosis and management of osteoporosis. *Osteoporos Int* 1997;**7**:390–406.

Trials meeting the inclusion criteria

Trials are listed alphabetically by their identifying 'name'; the reference number relates to the principal publication(s) for each trial, indicated by an asterisk (*). Note that most of the subsidiary references do not appear in the main reference list.

Abellan Perez, 1995[139]

* Abellan Perez M, Bayina Garcia FJ, Calabozo M, Carpintero Benitez P, Figueroa Pedrosa M, Fernandez Crisostoma C, *et al.* [Multicenter comparative study of synthetic salmon calcitonin administered nasally in the treatment of established postmenopausal osteoporosis. In Spanish.] *An Med Interna* 1995;**12**:12–16.

Adami, 1995[93]

Adami S, Baroni MC, Broggini M, Carratelli L, Caruso I, Gnessi L, *et al.* Treatment of postmenopausal osteoporosis with continuous daily oral alendronate in comparison with either placebo or intranasal salmon calcitonin. *Osteoporos Int* 1993;**3** Suppl 3:S21–7.

* Adami S, Passeri M, Ortolani S, Broggini M, Carratelli L, Caruso I, *et al.* Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *Bone* 1995;**17**:383–90.

Agrawal, 1981[61]

*Agrawal R, Wallach S, Cohn S, Tessier M, Verch R, Hussain M, *et al.* Calcitonin treatment of osteoporosis. In: Calcitonin 1980: proceedings of an international symposium; Milan, October 1980. Amsterdam: Excerpta Medica; 1981 p.237–46.

Aloia, 1988[117]

* Aloia JF, Vaswani A, Yeh JK, Ellis K, Yasumura S, Cohn SH. Calcitriol in the treatment of postmenopausal osteoporosis. *Am J Med* 1988;**84**:401–8.

Arthur, 1990[190]

* Arthur RS, Piraino B, Candib D, Cooperstein L, Chen T, West C, *et al.* Effect of low-dose calcitriol and calcium therapy on bone histomorphometry and urinary calcium excretion in osteopenic women. *Miner Electrolyte Metab* 1990;**16**:385–90.

Birkenhager, 1992[164]

Birkenhager JC, Birkenhager-Frenkel DH, Erdtsieck RJ, Kooy PPM, Pols HAP. Hormonal replacement therapy with and without nandrolone in postmenopausal osteoporosis. *J Bone Miner Res* 1991;**6** Suppl 1:S278.

* Birkenhager JC, Erdtsieck RJ, Zeelenberg J, van Kuik C, van Veen LC, Birkenhager-Frenkel DH, *et al.* Can nandrolone add to the effect of hormonal replacement therapy in postmenopausal osteoporosis? *Bone Miner* 1992;**18**:251–65.

Bone, 1997[94]

* Bone HG, Downs RW Jr, Tucci JR, Harris ST, Weinstein R, Licata AA, *et al.* Dose–response relationships for alendronate treatment in osteoporotic elderly women. *J Clin Endocrinol Metab* 1997;**82**:265–74.

Weinstein RS, Bone H, Tucci J, *et al.* Alendronate treatment of osteoporosis in elderly women. *J Bone Miner Res* 1994;**9** Suppl 1:S144, 1994.

Brockstedt, 1996[73]

* Brockstedt H, Melsen F, Mosekilde L. Double-blind, randomized study comparing the therapeutic effects of continuous and pulse dosing sodium monofluorophosphate (NaMFPh) in spinal crush fracture osteoporosis [abstract]. *Osteoporos Int* 1996; **6** Suppl 1:254.

Carfora, 1998[95]

* Carfora E, Sergio F, Bellini P, Sergio C, Falco D, Zarcone, R. Effect of treatment of postmenopausal osteoporosis with continuous daily oral alendronate and the incidence of fractures. *Gazzetta Med Ital Arch Sci Med* 1998;**157**(4):105–9.

Chesnut, 1983[96]

* Chesnut CH 3rd, Ivey JL, Gruber HE, Matthews M, Nelp WB, Sisom K, *et al.* Stanozolol in postmenopausal osteoporosis: therapeutic efficacy and possible mechanisms of action. *Metab Clin Exp* 1983;**32**:571–80.

Chesnut, 1995[96]

* Chesnut CH 3rd, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST, *et al.* Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995;**99**:144–52.

Clemmesen, 1997[97]

* Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. *Osteoporos Int* 1997;**7**:488–95.

Cristallini, 1993[128]

* Cristallini S, Pedetti M, Donatelli C, Gregorio F, Filipponi P. [The effect of different "coherent"-type therapeutic plans on bone mineral density and on the incidence of vertebral fractures in advanced osteoporosis. In Italian.] *Recent Prog Med* 1993;**84**:336–45.

Dykman, 1984[63]

* Dykman TR, 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. *Arthr Rheum* 1984;**27**:1336–43.

Ebeling, 1998[70]

* Ebeling PR, Wark JD, Yeung S, Poon C, Salehi N, Nicholson GC, *et al.* Effects of calcitriol or calcium on bone mineral density and fractures in men with idiopathic osteoporosis. *Osteoporos Int* 1998; **8** Suppl 3:114, 1998.

Ebrahim, 1997[187]

* Ebrahim S, Thompson PW, Baskaran V, Evans K. Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. *Age Ageing* 1997;**26**:253–60.

Ellerington, 1996[129]

* Ellerington MC, Hillard TC, Whitcroft SI, Marsh MS, Lees B, Banks LM, *et al.* Intranasal salmon calcitonin for the prevention and treatment of postmenopausal osteoporosis. *Calcif Tissue Int* 1996;**59**:6–11.

Ettinger, 1999[182]

Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, *et al.* The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999;**281**:2189–97.

*Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant H, *et al.* Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999;**282**:637–45.

Falch, 1987[191]

Falch JA, Odegaard OR, Finnanger AM. 3 years' treatment with 1.25$(OH)_2$ vitamin D_3 does not reduce bone loss or fracture rate in postmenopausal women with fracture of the distal forearm. In: Norman AW, Schaefer K, Grigoleit H, Herrath D, editors. Vitamin D. Chemical, biochemical and clinical update. Berlin: Walter de Gruyter; 1985. p.1004–5.

* Falch JA, Odegaard OR, Finnanger AM, Matheson I. Postmenopausal osteoporosis: no effect of three years treatment with 1,25-dihydroxycholecalciferol. *Acta Med Scand* 1987;**221**:199–204.

FIT[98,99]

* Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, *et al.* Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;**348**:1535–41.

Black DM, Reiss TF, Nevitt MC, Cauley J, Karpf D, Cummings SR. Design of the Fracture Intervention Trial. *Osteoporos Int* 1993;**3** Suppl 3:S29–39.

Cummings SR, Black DM, Thompson DE. Alendronate reduces the risk of vertebral fractures in women without pre-existing vertebral fractures: results of the Fracture Intervention Trial. *J Bone Miner Res* 1996;**12** Suppl 1:S149.

* Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, *et al.* Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;**280**:2077–82.

Cummings SR, Black DM, Vogt TM. Changes in BMD substantially underestimate the anti-fracture effects of alendronate and other antiresorptive agents. *J Bone Miner Res* 1996;**11** Suppl 1:S102.

Ensrud KE, Black DM, Palermo L, Bauer DC, Barrett-Connor E, Quandt SA, *et al.* Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. *Arch Intern Med* 1997;**157**:2617–24.

Hochberg MC, Ross PD, Black D, Cummings SR, Genant HK, Nevitt MC, *et al.* Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. *Arthr Rheum* 1999;**42**:1246–54.

Hochberg MC, Ross PD, Cummings SR, Black D, Musliner T, Nevitt MC, *et al.* Larger increases in bone mineral density with alendronate therapy are associated with lower risk of new vertebral fractures. *Osteoporos Int* 1998;**8** Suppl 3:13.

Nevitt MC, Thompson DE, Black DM, Rubin SM, Ensrud K, Yates J, *et al.* The effect of osteoporosis treatment on limitation of activity due to back pain. *J Bone Miner Res* 1997;**12** Suppl 1:S144.

Nevitt MC, Thompson DE, Black DM, Rubin SR, Ensrud K, Yates AJ, *et al.* Effect of alendronate on limited-activity days and bed-disability days caused by back pain in postmenopausal women with existing vertebral fractures. *Arch Intern Med* 2000;**160**:77–85.

Fujita, 1992[64]

* Fujita T, Fukase M, Shimada T, Yamamoto H. Treatment of established osteoporosis with 1-alpha (OH) vitamin D_3 and low dose intermittent elcatonin (eel calcitonin derivative). *J Bone Miner Metab* 1992;**10**:37–40.

Fujita, 1993[58]

* Fujita T, Orimo H, Inoue T, Kaneda K, Sakurai M, Morita R, *et al.* [Double-blind multicenter comparative study with alfacalcidol of etidronate disodium (EHDP) in involutional osteoporosis. In Japanese.] *Rinsho Hyoka* **21**:261–302.

Gallagher, 1989[118]

* Gallagher JC, Riggs BL, Recker RR, Goldgar D. The effect of calcitriol on patients with postmenopausal osteoporosis with special reference to fracture frequency. *Proc Soc Exp Biol Med* 1989;**3**:287–92.

Gallagher, 1990a[119]

*Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol. A randomized controlled study. *Ann Intern Med* 1990;**113**:649–55.

Gallagher, 1990b[74]

*Gallagher JC. Effect of fluoride in osteoporosis [abstract]. *J Bone Miner Res* 1990;**5** Suppl 1:S230.

Gennari, 1985[65]

*Gennari C, Chierichetti SM, Bigazzi S, Fusi L, Gonnelli S, Ferrara R, *et al.* Comparative effects on bone mineral content of calcium and calcium plus salmon calcitonin given in two different regimes in post-menopausal osteoporosis. *Curr Ther Res* 1985;**38**:455–64.

Geusens, 1986[163]

*Geusens P, Dequeker J. Long-term effect of nandrolone decanoate, 1 alpha-hydroxyvitamin D3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: a double-blind controlled study. *Bone Miner* 1986;**1**:347–57.

Geusens P, Dequeker J, Verstraeten A, Nijs J, van Holsbeeck M. Bone mineral content, cortical thickness and fracture rate in osteoporotic women after withdrawal of treatment with nandrolone decanoate, 1-alpha hydroxyvitamin D3, or intermittent calcium infusions. *Maturitas* 1986;**8**:281–9.

Guañabens, 1996[75]

*Guañabens N, Farrerons J, Perez-Edo L, Monegal A, Renau A, Roca M, *et al.* Comparison of the efficiency and safety of cyclic etidronate versus sodium fluoride in postmenopausal osteoporosis [abstract]. *Osteoporos Int* 1996;**6** Suppl 1:255.

Gutteridge, 1993[80]

*Gutteridge DH, Kent GN, Prince RL, Nicholson GC, Stewart GO, Jones CE, *et al.* Fluoride treatment of osteoporosis: cyclical non-blinded or continuous blinded studies? *Osteoporos Int* 1993;**3** Suppl 1:215–17.

Gutteridge, 1996[79]

Gutteridge DH, Kent GN, Prince RL, Nicholson GC, Stewart GO, Jones CE, *et al.* Fluoride treatment of osteoporosis: cyclical non-blinded or continuous blinded studies? *Osteoporos Int* 1993a;**3** Suppl 1:215–17.

Gutteridge DH, Price RI, Prince RL, Jones CE, Stewart GO, Nicholson GC, *et al.* Fluoride ± estrogen in osteoporosis – spinal bone gain, lower limb bone loss and stress fractures. *J Bone Miner Res* 1993b;**3** Suppl 1:S341.

*Gutteridge DH, Drury PH, Stewart GO, Prince RL, Price RI, Retallack RW, *et al.* Cyclic Na fluoride + HRT in postmenopausal osteoporosis – more vertebral fractures with NaF: less with HRT and NaF [abstract]. *Osteoporos Int* 1996;**6** Suppl 1:263.

Hansson, 1987[167]

*Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. *Calcif Tissue Int* 1987;**40**:315–17.

Harris, 1999[100]

*Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, *et al.* Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999;**282**:1344–52.

Hizmetli, 1998[130]

*Hizmetli S, Elden H, Kaptanoglu E, Nacitarhan V, Kocagil S. The effect of different doses of calcitonin on bone mineral density and fracture risk in post-menopausal osteoporosis. *Int J Clin Pract* 1998;**52**:453–5.

Hodsman, 1997[131]

*Hodsman AB, Fraher LJ, Watson PH, Ostbye T, Stitt LW, Adachi JD, *et al.* A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 1997;**82**:620–8.

Kleerekoper, 1991[168]

*Kleerekoper M, Peterson EL, Nelson DA, Phillips E, Schork MA, Tilley B, *et al.* A randomized trial of sodium fluoride as a treatment for postmenopausal osteoporosis. *Osteoporos Int* 1991;**1**:155–61.

Leidig-Bruckner, 1997[76]

*Leidig-Bruckner G, Eberwein S, Bruckner T, Wolf S, Ziegler R. Long term follow-up of lumbar and femoral bone mineral density and vertebral fractures in patients with manifest postmenopausal osteoporosis after fluoride therapy alone or combined with estrogens or anabolica. *Exp Clin Endocrinol Diabetes* 1997;**105**:A58.

Lems, 1997[192]

*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.

Liberman, 1995[101]

Devogelaer JP, Broll H, Correa-Rotter R, Cumming DC, de Deuxchaisnes CN, Geusens P, *et al.* Oral alendronate induces progressive increases in bone mass of the spine, hip, and total body over 3 years in postmenopausal women with osteoporosis. *Bone* 1996;**18**:141–50.

Harris ST, Watts NB, Hosking D, Adami S, Quan H, Shapiro DE, *et al.* Treatment with alendronate prevents fractures in women with postmenopausal osteoporosis. *Osteoporos Int* 1996;**6** Suppl 1:261.

Liberman UI, Hirsch LJ. Esophagitis and alendronate. *N Engl J Med* 1996;**335**:1069–70.

*Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, *et al.* Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;**333**:1437–43.

Meunier PJ. Oral alendronate increases bone-mineral density and reduces vertebral fracture incidence in postmenopausal osteoporosis. *Br J Rheumatol* 1997; **36** Suppl 1:15–19.

Recker RR, Karpf DB, Quan H, Devogelaer C, Leite MO, Farus MJ, *et al.* Three-year treatment of osteoporosis with alendronate: effect on vertebral fracture incidence. In: Proceedings 77th Annual Meeting, Endocrine Society, 1995.

Seeman E, de Deuxchaisnes CN, Meunier P, Santora AC. Treatment of postmenopausal osteoporosis with oral alendronate. *Bone* 1995;**16** Suppl 1:S120.

Tucci JR, Tonino RP, Emkey RD, Peverly CA, Kher U, Santora AC 2nd. Effect of three years of oral alendronate treatment in postmenopausal women with osteoporosis. *Am J Med* 1996;**101**:488–501.

Lindsay, 1999[102]

*Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE, *et al.* Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab* 1999;**84**:3076–81.

Lufkin, 1992[143]

*Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, *et al.* Treatment of post-menopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;**117**:1–9.

Lufkin, 1998[178]

Nickelsen T, Lufkin EG, Riggs BL, Cox DA, Crook TH. Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in postmenopausal women. *Psychoneuroendocrinology* 1999;**24**:115–28.

*Lufkin EG, Whitaker MD, Nickelsen T, Argueta R, Caplan RH, Knickerbocker RK, *et al.* Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res* 1998;**13**:1747–54.

Lyritis, 1994[166]

*Lyritis GP, Androulakis C, Magiasis B, Charalambaki Z, Tsakalakos N. Effect of nandrolone decanoate and 1-alpha-hydroxy-calciferol on patients with vertebral osteoporotic collapse. A double-blind clinical trial. *Bone Miner* 1994;**27**:209–17.

Mamelle, 1988[176]

*Mamelle N, Meunier PJ, Dusan R, Guillaume M, Martin JL, Gaucher A, *et al.* Risk–benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. *Lancet* 1988;**ii**:361–5.

Mamelle N, Meunier PJ, Netter P. Fluoride and vertebral fractures. *Lancet* 1990;**336**:243.

Maugeri, 1994[157]

*Maugeri D, Panebianco P, Russo MS, Motta M, Tropea S, Motta L, *et al.* Ipriflavone-treatment of senile osteoporosis: results of a multicenter, double-blind clinical trial of 2 years. *Arch Gerontol Geriatr* 1994;**19**:253–63.

McClung, 1998[77]

McClung M, Bensen W, Bolognese M, Bonnick S, Ettinger M, Harris S, *et al.* Risedronate treatment of postmenopausal women with low bone mass: preliminary data [abstract]. *Osteoporos Int* 1996;**6** Suppl 1:257.

*McClung M, Bensen W, Bolognese M, Bonnick S, Ettinger M, Harris S, *et al.* Risedronate increases bone mineral density at the hip, spine and radius in postmenopausal women with low bone mass. *Osteoporos Int* 1998;**8** Suppl 3:111.

Meunier, 1998[169]

*Meunier PJ, Sebert JL, Reginster JY, Briancon D, Appelboom T, Netter P, *et al.* Fluoride salts are no better at preventing new vertebral fractures than calcium-vitamin D in postmenopausal osteoporosis: the FAVO study. *Osteoporos Int* 1998;**8**:4–12.

Montessori, 1997[103]

*Montessori ML, Scheele WH, Netelenbos JC, Kerkhoff JF, Bakker, K. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. *Osteoporos Int* 1997;**7**:52–8.

Orimo, 1987[120]

*Orimo H, Shiraki M, Hayashi T, Nakamura, T. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D3. *Bone Miner* 1987;**3**:47–52.

Orimo, 1994[121]

*Orimo H, Shiraki M, Hayashi Y, Hoshino T, Onaya T, Miyazaki S, *et al.* Effects of 1 alpha-hydroxyvitamin D3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. *Calcif Tissue Int* 1994;**54**:370–6.

Ott, 1989[122]

*Ott SM, Chesnut CH 3rd. Calcitriol treatment is not effective in postmenopausal osteoporosis [see comments]. *Ann Intern Med* 1989;**110**:267–74.

Ott SM, Chesnut CH 3rd. Tolerance to doses of calcitriol is associated with improved bone density in women with postmenopausal osteoporosis. *J Bone Miner Res* 1990;**5**:S186.

Overgaard, 1992[60]

Overgaard K, Christiansen C. A new biochemical marker of bone resorption for follow-up on treatment with nasal salmon calcitonin. *Calcif Tissue Int* 1996;**59**:12–16.

*Overgaard K, Hansen MA, Jensen SB, Christiansen C. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. *BMJ* 1992;**305**:556–61.

Pacifici, 1988[104]

*Pacifici R, McMurtry C, Vered I, Rupich R, Avioli LV. Coherence therapy does not prevent axial bone loss in osteoporotic women: a preliminary comparative study. *J Clin Endocrinol Metab* 1988;**66**:747–53.

Pak, 1989[193]

*Pak CY, Sakhaee K, Zerwekh JE, Parcel C, Peterson R, Johnson K. Safe and effective treatment of osteoporosis with intermittent slow release sodium fluoride: augmentation of vertebral bone mass and inhibition of fractures. *J Clin Endocrinol Metab* 1989;**68**:150–9.

Pak, 1995[170]

*Pak CY, Sakhaee K, Adams-Huet B, Piziak V, Peterson RD, Poindexter JR. Treatment of post-menopausal osteoporosis with slow-release sodium fluoride. Final report of a randomized controlled trial. *Ann Intern Med* 1995;123:401–8.

Pak CY, Sakhaee K, Piziak V, Peterson RD, Breslau NA, Boyd P, *et al.* Slow-release sodium fluoride in the management of postmenopausal osteoporosis. A randomized controlled trial [see comments]. *Ann Intern Med* 1994;**120**:625–32.

Passeri, 1992[158]

*Passeri M, Biondi M, Costi D, Bufalino L, Castiglione GN, Di Peppe C, *et al.* Effect of ipriflavone on bone mass in elderly osteoporotic women. *Bone Miner* 1992;**19** Suppl 1:S57–62.

Passeri, 1995[159]

*Passeri M, Biondi M, Costi D, Dall'Aglio E, Pedrazzoni M, Bufalino L, *et al.* Effects of 2-year therapy with ipriflavone in elderly women with established osteoporosis. *Ital J Miner Electrolyte Metab* 1995;**9**:137–44.

Pols, 1999[105]

*Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Wilkin TJ, *et al.* Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. *Osteoporos Int* 1999;**9**:461–8.

Pontiroli, 1991[132]

*Pontiroli AE, Pajetta E, Calderara A, Alberetto M, Pozza G, Manganelli V, *et al.* Intranasal and intramuscular human calcitonin in female osteoporosis and in Paget's disease of bones: a pilot study. *J Endocrinol Invest* 1991;**14**:47–51.

'PROOF' study[78]

Chesnut CH III. Salmon calcitonin in the treatment of osteoporosis. *Osteoporos Int* 1998;**8** Suppl 3:147.

*Chesnut C, Baylink DJ, Doyle D, Genant H, Harris S, Kiel DP, *et al.* Salmon calcitonin nasal spray prevents vertebral fractures in established osteoporosis: further interim results of the 'PROOF' study. *Osteoporos Int* 1998;**8** Suppl 3:13.

Gimona A. The PROOF study: methodology. *Osteoporos Int* 1998;**8** Suppl 3:146.

Kanis JA, McCloskey EV. Effect of calcitonin on vertebral and other fractures. *QJM* 1999;**92**:143–9.

Stock JL, Avioli LV, Baylink DJ, Chesnut C, Genant HK, Maricic MJ, *et al.* Calcitonin–salmon nasal spray reduces the incidence of new vertebral fractures in post-menopausal women: three year interim results of the PROOF study. *J Bone Miner Res* 1997;**12**:S149.

Recker, 1996[142]

*Recker RR, Hinders S, Davies KM, Heaney RP, Stegman MR, Lappe JM, *et al.* Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* 1996;**11**:1961–6.

Recker R, Kimmel DB, Hinders S, Davies KM. Antifracture efficacy of calcium in elderly women. *J Bone Miner Res* 1994;**9** Suppl 1:135.

Reginster, 1998[171]

*Reginster JY, Meurmans L, Zegels B, Rovati LC, Minne HW, Giacovelli G, *et al.* The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis. A randomized, controlled trial. *Ann Intern Med* 1998;**129**:1–8.

Reginster JY, Zegels B, Meurmans L, Rovati LC, Taquet AN, Setnikar I, *et al.* Monofluorophosphate decreases vertebral fracture rate in postmenopausal osteoporosis: a randomised, placebo-controlled, double blind study. *Osteoporos Int* 1996;**6** Suppl 1:239.

Reginster, 2000[106]

*Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, *et al.* Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000;**11**:83–91.

Reid, 1994[107]

*Reid IR, Wattie DJ, Evans MC, Gamble GD, Stapleton JP, Cornish J. Continuous therapy with pamidronate, a potent bisphosphonate, in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 1994;**79**:1595–9.

Rico, 1992[134]

*Rico H, Hernandez ER, Revilla M, Gomez-Castresana F. Salmon calcitonin reduces vertebral fracture rate in postmenopausal crush fracture syndrome. *Bone Miner* 1992;**16**:131–8.

Rico, 1995[135]

*Rico H, Revilla M, Hernandez ER, Villa LF, Alvarez de Buergo M. Total and regional bone mineral content and fracture rate in postmenopausal osteoporosis treated with salmon calcitonin: a prospective study. *Calcif Tissue Int* 1995;**56**:181–5.

Riggs, 1990[172]

Melton LJ 3rd, Egan KS, O'Fallon WM, Riggs BL. Influence of fracture criteria on the outcome of a randomized trial of therapy. *Osteoporos Int* 1998;**8**:184–91.

*Riggs BL, Hodgson SF, O'Fallon WM, Chao EY, Wahner HW, Muhs JM, *et al.* Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990;**322**:802–9.

Ringe, 1987[136]

*Ringe JD, Welzel D. Salmon calcitonin in the therapy of corticoid-induced osteoporosis. *Eur J Clin Pharmacol* 1987;**33**:35–9.

Ringe, 1990[137]

*Ringe JD. [Treatment of primary osteoporosis with calcium and salmon calcitonin. In German]. *Dtsch Med Wochenschr* 1990;**115**:1176–82.

Ringe, 1998[173]

*Ringe JD, Dorst A, Kipshoven C, Rovati LC, Setnikar I. Avoidance of vertebral fractures in men with idiopathic osteoporosis by a three year therapy with calcium and low-dose intermittent monofluorophosphate. *Osteoporos Int* 1998;**8**:47–52.

Ringe JD, Kipshoven C, Rovati L, Setnikar I. Therapy of idiopathic male osteoporosis: a three year study with calcium and low dose intermittent monofluorophosphate [abstract]. *Osteoporos Int* 1996;**6** Suppl 1:96.

Ringe, 1999[174]

*Ringe JD, Kipshoven C, Coster A, Umbach R. Therapy of established postmenopausal osteoporosis with monofluorophosphate plus calcium: dose-related effects on bone density and fracture rate. *Osteoporos Int* 1999;**9**:171–8.

Rozhinskaya, 1999[72]

*Rozhinskaya L, Marova E, Sazonova N. Effectiveness of monofluorophosphate in established steroid osteoporosis. *Osteoporos Int* 1999;**9**(4 suppl 1):S11–12.

Schurch, 1998[186]

Schurch MA, Rizzoli R, Slosman D, Bonjour JP. Protein supplements increase serum IGF-1 and prevent proximal femur bone loss in elderly with a recent hip fracture. *Osteoporos Int* 1996;**6** Suppl 1:94.

*Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;**128**:801–9.

Sebert, 1995[175]

Sebert JL, Richard P, Mennecier I, Bisset JP, Loeb G. A double-blind study with a combined therapy (monofluorophosphate and calcium) in marked osteopenia without vertebral fracture. *J Bone Miner Res* 1993; **8** Suppl 1:S255.

*Sebert JL, Richard P, Mennecier I, Bisset JP, Loeb G. Monofluorophosphate increases lumbar bone density in osteopenic patients: a double-masked randomized study. *Osteoporos Int* 1995;**5**:108–14.

Shiota, 1998[194]

*Shiota E. Evaluation of the drug therapy for established osteoporosis by dual-energy x-ray absorptiometry. *Fukuoka Igaku Zasshi* 1998;**89**:172–8.

Shiraki, 1996[123]

*Shiraki M, Kushida K, Yamazaki K, Nagai T, Inoue T, Orimo H. Effects of 2 years' treatment of osteoporosis with 1 alpha-hydroxy vitamin D3 on bone mineral density and incidence of fracture: a placebo-controlled, double-blind prospective study. *Endocr J* 1996;**43**:211–20.

Shiraki, 1999[195]

*Shiraki M, Kushid K, Fukunaga M, Kishimoto H, Taga M, Nakamura T, *et al.* A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. *Osteoporos Int* 1999;**10**:183–92.

Shiraki, 2000[68]

*Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. *J Bone Miner Res* 2000;**15**:515–21.

Storm, 1990[108]

*Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990a;**322**:1265–71.

Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Etidronate for postmenopausal osteoporosis [letter]. *N Engl J Med* 1990b;**323**:1210.

Thiébaud, 1994[115]

*Thiébaud D, Burckhardt P, Melchior J, Eckert P, Jacquet A, Schnyder P, *et al.* Two years' effectiveness of intravenous pamidronate (APD) versus oral fluoride for osteoporosis occurring in the postmenopause. *Osteoporos Int* 1994;**4**:76–83.

Tilyard, 1992[124]

Tilyard M. Low-dose calcitriol versus calcium in established postmenopausal osteoporosis. *Metabolism* 1990a;**39**(4 suppl 1):50–2.

Tilyard MW. 1,25 dihydroxyvitamin-d3 vs calcium in the treatment of established postmenopausal osteoporosis. *J Bone Miner Res* 1990b;**5** Suppl 2:S275.

Tilyard MW. 1,25 dihydroxyvitamin-d3 (calcitriol) in the treatment of postmenopausal osteoporosis. In: Cohn DV, Gennari C, Tashjian AH Jr, editors. Calcium regulating hormones and bone metabolism: basic and clinical aspects. volume II. Amsterdam: Elsevier Science; 1992. p.395–9.

*Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992;326:357–62.

Tilyard MW. Treatment of postmenopausal osteoporosis with 1,25-dihydroxyvitamin D3. *Osteoporos Int* 1993;**3** Suppl 1:194–5.

Watts, 1990[109]

Harris ST, Watts NB, Jackson RD, Genant HK, Wasnich RD, Ross P, *et al.* Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. *Am J Med* 1993;**95**:557–67.

Harris ST. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis [letter]. *Am J Med* 1995;**99**:225.

Miller PD, Watts NB, Licata AA, Harris ST, Genant HK, Wasnich RD, *et al.* Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment. *Am J Med* 1997;**103**:468–76.

*Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, *et al.* Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;**323**:73–9.

Wimalawansa, 1998[110]

*Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with post-menopausal osteoporosis. *Am J Med* 1998;**104**:219–26.

Zarcone, 1997[144]

*Zarcone R, Carfora E, Sergio F, Bellini P, Longo M, Tartaglia E, *et al.* [Oestrogen therapy in women with postmenopausal osteoporosis. In Italian]. Minerva Ginecol 1997;49:355–9.

Trials excluded from the systematic review

These are listed in alphabetical order, with any reference number appearing at the end of the reference in parentheses [ ]. The reason for exclusion is given after each reference.

Buckle RM. 3 year study of sodium fluoride treatment on vertebral fracture incidence in osteoporosis. *J Bone Miner Res* 1989;**4**:S186. [62]

(Described as double-blind but does not specify that patients were randomised to treatment groups.)

Caniggia A, Delling G, Nuti R, Lore F, Vattimo A. Clinical, biochemical and histological results of a double-blind trial with 1,25-dihydroxyvitamin D3, estradiol and placebo in post-menopausal osteoporosis. *Acta Vitaminol Enzymol* 1984;**6**:117–28.

(Described as double-blind but does not specify that patients were randomised to treatment groups.)

Chevalley T, Rizzoli R, Nydegger V, Slosman D, Rapin CH, Michel JP, *et al.* Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int* 1994;**4**:245–52.

(Compared two different calcium preparations but comparative data on their effects on fracture rates not provided.)

Devogelaer JP, Boutsen Y, Malghem J, Depresseux G, Nagant de Deuxchaisnes C. Efficacy of therapy of involutional osteoporosis with disodium monofluorophosphate and calcium. *Osteoporos Int* 1996; **6** Suppl 1:252.

(Described as double-blind but does not specify that patients were randomised to treatment groups.)

Diamond T, McGuigan L, Schone M, Levy S, Rae D. A 2 year open randomized controlled trial comparing calcitriol to cyclical etidronate for the treatment of glucocorticoid- induced osteoporosis. *J Bone Miner Res* 1997;**12**:S634.

(Unavailable within the study timescale.)

Dilsen G, Gülbaba G, Sindel D. Calcitriol in the treatment of osteoporosis. *Osteoporos Int* 1998; **8** Suppl 3:101. [69]

(Results in the intervention and control arms not compared.)

Gallagher JC. Treatment of postmenopausal osteoporosis with fluoride plus either calcium or calcitriol. *J Bone Miner Res* 1992;**7** Suppl 1:S318. [71]

(Results in the intervention and control arms not compared.)

Hayashi Y. Investigation of fracture frequency of Japanese osteoporosis patients: effects of drug therapy. *J Bone Miner Metab* 1988;**6**:120. [66]

(Unavailable within the study timescale.)

Hayashi Y, Fujita T, Inoue T. Decrease of vertebral fracture in osteoporotics by administration of 1 alpha hydroxy-vitamin D_3. *J Bone Miner Metab* 1992;**10**:184–8. [67]

(Both men and women were quasi-randomised, by alternate allocation, but only results for women presented.)

Hedlund LR, Gallagher JC. Increased incidence of hip fracture in osteoporotic women treated with sodium fluoride. *J Bone Miner Res* 1989;**4**:223–5.

(Patients not randomised to two groups as reported: results of two separate randomised trials are combined – one comparing sodium fluoride plus calcium with sodium fluoride plus calcitriol, the other comparing calcitriol with placebo – in order to compare effects of fluoride with those of calcitriol/placebo.)

Itami Y, Fujita T, Inoue T, *et al.* Effect of alphacalcidol on osteoporosis – multicenter double-blind study. *J Clin Exp Med* 1982;**123**:958–73.

(Unavailable within study timescale.)

Lyritis GP, Tsakalakos N, Paspati I, Skarantavos G, Galanos A, Androulakis C. The effect of a modified etidronate cyclical regimen on postmenopausal osteoporosis: a four-year study. *Clin Rheum* 1997;**16**:354–60.

(Although specified that patients were enrolled at random, it was not clearly specified that they were randomised to treatment groups.)

Meunier PJ. Calcium, vitamin D and vitamin K in the prevention of fractures due to osteoporosis. *Osteoporos Int* 1999;**9** (Suppl 2):48–52.

(Unavailable within study timescale.)

Nakatsuka K, Inaba M, Aratani H, Iba K, Sato T, Koike T, *et al.* [Effects of long-term administration of alfacalcidol on bone mass and bone metabolism in patients with primary osteoporosis – comparison with calcium preparations. In Japanese]. *Nippon Ronen Igakkai Zasshi* 1997;**34**:569–76. [57]

(Unable to obtain translation.)

Ringe JD, Coster A, Meng T, Schacht E, Umbach R. Treatment of glucocorticoid-induced osteoporosis with alfacalcidol/calcium versus vitamin D/calcium. *Calcif Tissue Int* 1999;**65**:337–40.

(Not specified that patients randomised into study groups.)

Shiraki M [Vitamin K2. In Japanese]. *Nippon Rinsho* 1998;**56**:1525–30. [56]

(Unable to obtain translation.)

Vose GP, Keele DK, Milner AM, Rawley R, Roach TL, Sprinkle EE 3rd. Effect of sodium fluoride, inorganic phosphate, and oxymetholone therapies in osteoporosis: a six-year progress report. *J Gerontol* 1978;**33**:204–12.

(Some patients had normal BMD.)

Appendix 1

MEDLINE search strategy for RCTs

1 exp osteoporosis/
2 bone diseases, metabolic/
3 osteoporo$.tw.
4 1 or 2 or 3
5 (bone adj6 densit$).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$.tw.
26 lumbar vertebrae/
27 20 or 21 or 22 or 23 or 24 or 25 or 26
28 19 and 27
29 fractur$.tw.
30 20 or 21 or 22 or 23 or 24 or 25
31 (fractur$ adj6 (colles$ or (hip or hips) or (femur adj6 neck) or (femoral adj6 neck) or (spine or spinal) or vertebra$)).tw.
32 18 or 28 or 31
33 estrogen replacement therapy/
34 estrogen replacement therapy.tw.
35 oestrogen replacement therapy.tw.
36 hormone replacement therapy.tw.
37 ert.tw.
38 ort.tw.
39 hrt.tw.
40 33 or 34 or 35 or 36 or 37 or 38 or 39
41 exp menopause/
42 climacteric/
43 menopaus$.tw.
44 postmenopaus$.tw.
45 climacteric.tw.
46 41 or 42 or 43 or 44 or 45
47 40 or 46
48 32 and 47
49 4 or 14 or 48
50 randomized controlled trial.pt.
51 controlled clinical trial.pt.
52 randomized controlled trials/
53 random allocation/
54 double-blind method/
55 single-blind method/
56 50 or 51 or 52 or 53 or 54 or 55
57 (animal not human).sh.
58 56 not 57
59 clinical trial.pt.
60 exp clinical trials/
61 (clin$ adj25 trial$).tw.
62 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
63 placebos/
64 placebo$.tw.
65 random$.tw.
66 research design/
67 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66
68 67 not 57
69 68 not 58
70 comparative study.sh.
71 evaluation studies/
72 follow-up studies/
73 prospective studies/
74 (control$ or prospectiv$ or volunteer$).tw.
75 70 or 71 or 72 or 73 or 74
76 75 not 57
77 76 not (58 or 69)
78 58 or 69 or 77
79 49 and 78

Appendix 2

Details of handsearching

The five journals identified for handsearching were as follows:

- *Osteoporosis International*
- *Journal of Bone and Mineral Research*
- *Annals of Internal Medicine*
- *New England Journal of Medicine*
- *American Journal of Medicine.*

It was not possible to handsearch the entire runs of these journals from January 1990 onwards as had been intended, because volumes were either missing from local libraries or could not be supplied by the British Library. Thus, only the issues listed below were searched.

- *Osteoporosis International*: 1990, **1**(1); 1994, **5**(1–6); 1995, **6**(1–6 plus suppl 1 & 2); 1996, **7**(1–6 plus suppl 1, 2 & 3); 1997, **8**(1–6 plus suppl 1 & 3); 1998, **9**(1–2, 4–5); 1999, **10**(1).
- *Journal of Bone and Mineral Research*: 1990, **5**; 1991, **6** (incl suppl 1); 1992, **7**(3–4,7,9–10,12 plus suppl 1); 1993, **8**(1–4,7–12, plus suppl 1 & 2); 1998, **13**; 1999, **14**(1–5,8).
- *Annals of Internal Medicine*: 1990–99, **112–130**; 2000, **132**(1–9).
- *New England Journal of Medicine*: 1990–97, **322–337**; 1998–2000, **339–341**, **342**(1–19).
- *American Journal of Medicine*: 1990–97, **88–103**; 1998, **104**(1–4,6 plus suppl 2A,3A,4A,5A), **105**; 1999, **106**(1–4,6, plus suppl 1A,5A,5B), **107**.

Appendix 3

Quality assessment tool*

	Score
Was randomisation to study groups blinded?	
Not randomised	**0**
States randomised but no description or quasi-randomised (i.e. allocation by date of birth, hospital record number, 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 outcomes of patients who withdrew described and included in analysis?	
Not mentioned or states number of withdrawals only	**1**
Stated 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	**2**
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 percentage of possible score)	

* After: Gillespie WJ, Henry DA, O'Connell DL, Robertson J. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis [Cochrane review]. The Cochrane Library, Issue 1; Oxford: Update Software; 1999

Appendix 4

Details of RCTs (by study)*

Bisphosphonates 142
Vitamin D derivatives 158
Calcitonin 164
Calcium 176
Oestrogen 178
Oestrogen-like molecules 182
Anabolic steroids 185
Fluoride 186
SERMs 196
Exercise 198
Protein supplements 199
Vitamin K_2 200
Comparisons with active treatments 201

* NB. The reference numbers quoted are the principal ones for each particular trial. For details of other relevant references, see 'Trials meeting the inclusion criteria' (page 125). This applies also to the references cited as sources of 'Additional information'.

Bisphosphonates

Study	Adami, 1995[93]
Setting	Italy
Date of intervention	Not specified
Source of funding	Not specified
Design	RCT, double-blind between alendronate and placebo, with open-label calcitonin arm
Study population	Postmenopausal women with osteoporosis (lumbar T-score > –2), 5% of whom had vertebral fracture at entry
Recruitment procedure used	Not specified
Number of patients	286
Length of study	2 years
Main intervention/s	Alendronate Intranasal salmon calcitonin
Primary outcome measures	BMD (spine)
Secondary outcome measures	BMD (hip) Biochemical indices of bone turnover
Definition of incident vertebral fracture	Not applicable: only clinically apparent fractures were recorded
Results: all fractures	No significant trends noted between treatment groups in relation to number of fractures
Quality score	9/15
Comments	• Alendronate arm placebo-controlled but calcitonin arm not because no intranasal placebo available • Blinding not possible in relation to calcitonin arm and although assessors of BMD scans were blinded to treatment allocation, no such assurance is given in relation to fracture outcomes • All patients received elemental calcium, 500 mg daily • 41 women (14.3%) withdrew from treatment, 15 (5.2%) because of adverse events • Analysis was on ITT basis • All treatment groups were similar to placebo with regard to both the overall safety profile and upper gastrointestinal adverse events • Quality score low partly because of lack of information about method of randomisation, but more because of lack of information about methods used to identify and confirm fractures. However, study not designed to detect significant differences in fracture rates, and fracture data only collected as part of adverse event reporting. Perhaps, therefore, unreasonable to expect such detail to be provided

Study	Bone, 1997[94]
Setting	USA
Date of intervention	Not specified
Source of funding	Merck Research Laboratories
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Healthy elderly women with osteopaenia or osteoporosis (T-score < –2 but no more than one lumbar crush fracture): 37% had vertebral fracture at entry
Recruitment procedure used	'At 15 clinical sites throughout the United States'
Number of patients	359
Length of study	2 years
Main intervention/s	Alendronate
Primary outcome measures	Lumbar BMD
Secondary outcome measures	Biochemical indices of bone and mineral metabolism Bone histomorphometry Vertebral and non-vertebral fractures
Definition of incident vertebral fracture	20% or more decrease in vertebral height*
Results: vertebral fracture	Alendronate did not have a statistically significant effect on vertebral fracture
Results: non-vertebral fracture	At doses of 2.5 and 5.0 mg, alendronate significantly reduced incidence of non-vertebral fracture
Quality score	14/18
Comments	• All patients received elemental calcium, 500 mg daily • 131 women (36.5%) withdrew, 38 (10.6%) because of adverse events • No significant difference between treatment and placebo groups in terms of adverse effects which were suspected to be drug-related: 19.8% of women on alendronate, 1.0 mg, 25.8% on 2.5 mg, 17.2% on 5.0 mg, and 23.1% in placebo group suffered such adverse effects • Alendronate as well-tolerated by women aged over 70 years as by those aged 60–69 years

* *Method described in Genant HK,* et al. J Bone Miner Res *1993;**8**:1137–48.*

Bisphosphonates *contd*

Study	Carfora, 1998[95]
Setting	Italy
Date of intervention	December 1993–May 1996
Source of funding	Not specified
Design	Randomised, placebo-controlled
Study population	Postmenopausal women with osteoporosis (lumbar spine T-score < –2.5)
Recruitment procedure used	Not specified
Number of patients	136
Length of study	30 months
Main intervention/s	Alendronate
Outcome measures	BMD Vertebral fractures Biochemical markers
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	RR = 0.55 for new fracture in women treated with alendronate, compared with those receiving placebo
Results: non-vertebral fracture	–
Quality score	7/15
Comments	• All patients received elemental calcium, 500 mg daily • No information provided regarding withdrawals • Tolerance said to be excellent, the only adverse events being intolerance 'at superior tract of the gastroenteric apparatus' and cutaneous rash. Episodes of nausea, dyspepsia, mild gastro-oesophagitis and abdominal pain appeared during first 15 months of treatment with alendronate, 20 mg

Study	Chesnut, 1995[96]
Setting	USA
Date of intervention	Not specified
Source of funding	Merck Research Laboratories
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Healthy postmenopausal white or Asian women with spinal osteopenia (lumbar spine BMD 0.88 g/cm^2 or less) but no vertebral or hip fractures attributable to osteoporosis
Recruitment procedure used	Advertisements and medical announcements
Number of patients	188
Length of study	2 years
Main intervention/s	Alendronate
Primary outcome measures	Lumbar BMD
Secondary outcome measures	Vertebral fracture Non-vertebral fracture
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	No vertebral fractures in any patient
Results: non-vertebral fracture	13 non-vertebral fractures occurred in 12 patients, evenly distributed across treatment groups and not considered related to therapy
Quality score	9/18
Comments	• All patients received elemental calcium, 500 mg daily • 34 women (18.1%) withdrew during course of study. No information given as to how many withdrew from treatment and control arms • 18 women withdrew because of adverse clinical experiences, of whom nine were women in alendronate arm who withdrew because of adverse upper gastrointestinal events (seven receiving 40 mg and only one < 20 mg daily); another withdrew because of a rash which was considered to be alendronate-related • Generally, alendronate was associated with few side-effects • Study not designed to identify effect of alendronate on skeletal fractures • Presence of vertebral fractures attributable to osteoporosis was exclusion criterion and may explain total absence of incident vertebral fractures

Bisphosphonates *contd*

Study	Clemmesen, 1997[97]
Setting	Belgium and Denmark
Date of intervention	December 1990–
Source of funding	Not specified
Design	Two-centre, double-masked, placebo-controlled randomised
Study population	Healthy postmenopausal women with established osteoporosis (at least one but no more than four vertebral fractures)
Recruitment procedure used	Mainly from outpatients attending two osteoporosis clinics
Number of patients	132
Length of study	2 years + 1 additional year of follow-up
Main intervention/s	Oral risedronate, taken either continuously or cyclically for 2 weeks of 12-week cycle
Primary outcome measures	BMD at spine
Secondary outcome measures	BMD at femoral neck, trochanter and Ward's triangle Biochemical markers of bone turnover Incident vertebral fractures
Definition of incident vertebral fracture	A reduction of at least 15% (Belgium) or 25% (Denmark) in anterior-to-posterior wall ratio, or in anterior or posterior wall compared with adjacent vertebrae
Results: vertebral fracture	Tendency towards lower incidence and rate of new vertebral fractures in group taking daily continuous risedronate but not statistically significant
Results: non-vertebral fracture	Nine women in group treated with cyclical risedronate suffered non-vertebral fracture, compared with four in each of other two groups
Quality score	13/18
Comments	• All patients took calcium, 1 g daily • 39 women (30%) withdrew from study: 15 (34%) from continuous risedronate group, 11 (25%) from cyclic risedronate group and 13 (30%) from placebo group • Of women not completing study, 19 (14.4%) dropped out because of adverse events and 20 (15.2%) because of lack of interest. Not stated from which groups they came • All women completing study had taken at least 80% of dispensed medication • Three patients in each group reported moderate to severe upper gastrointestinal adverse events • No serious adverse events were considered causally related to risedronate • Study not prospectively powered statistically to assess efficacy of risedronate on vertebral fracture incidence • Different vertebral fracture thresholds used at two centres, so valid global fracture analysis could not be performed • All non-vertebral fractures related to falls • Bioavailabity of risedronate may have been impaired by giving it as gelatin capsules, allowing non-dairy fluids in period 1–2 hours before and after capsule intake, and allowing it to be taken 2 hours after meal

Bisphosphonates *contd*

Study	FIT, 1996[98] (women with pre-existing vertebral fractures)
Setting	USA
Date of intervention	May 1992–February 1996[a,b]
Source of funding	Merck Research Laboratories
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Healthy postmenopausal women with established osteoporosis (at least one existing vertebral fracture)
Recruitment procedure used	Population-based: each of 11 clinical centres involved developed local plan using methods such as direct mailings, media advertising, telephone solicitation, group meetings[a]
Number of patients	2027
Length of study	Mean of 2.9 years
Main intervention/s	Alendronate sodium
Primary outcome measures	Incidence of new vertebral fractures
Secondary outcome measures	Incidence of non-pathological clinical fractures (including both non-vertebral and symptomatic vertebral fractures)[a] Change in height[a] Changes in BMD of hip, spine, radius and total body[a] Changes in biochemical markers of bone metabolism[a]
Definition of incident vertebral fracture	20% or greater decrease in anterior, middle or posterior height between baseline and end of study. Additionally, for any vertebra deformed at baseline, minimum absolute change of 4 mm[a]
Results: vertebral fracture	RR of radiographic fracture in treatment group compared with control group was 0.53 (95% CI, 0.41 to 0.68). This consistent regardless of age, BMD, number of pre-existing fractures or history of postmenopausal fracture[b] Relative hazard of clinically apparent vertebral fractures was 0.45 (0.27–0.72)
Results: non-vertebral fracture	Relative hazard of any clinical fracture in treatment group compared with control group 0.72 (95% CI, 0.58 to 0.90). RR of any non-vertebral fracture 0.80 (0.63 to 1.01); hip 0.49 (0.23 to 0.99); wrist 0.52 (0.31 to 0.87); other 0.99 (0.75 to 1.31)
Quality score	18/18
Comments	• 97% of participants identified themselves as Caucasian, 1% Asian, 1% African–American • All patients with estimated calcium intake at baseline of less than 1000 mg daily (81.2% of treatment and 83.4% of placebo group) were given elemental calcium, 500 mg, + vitamin D, 250 IU, daily • Non-steroidal anti-inflammatory drugs taken for month or longer during study by about 75% of women in both groups • Analysis undertaken on ITT basis; total number of withdrawals not given • Follow-up radiographs obtained for 1946 patients, 98% of those surviving at study close-out, of which 1916 were obtained as part of close-out visit; for other 30 participants radiographs taken at 24 months used • Compliance considered good – by final visit, 89% of surviving treatment group and 87% of surviving placebo group still taking medication and, of these, 96% in each group had taken at least 75% of pills since last clinic visit; however, this may be due in part to recruitment methods used • 7.6% of women in treatment group and 9.6% in placebo group permanently discontinued study medication because of adverse experiences • Adverse experiences resulting in hospital admission significantly less common in treatment than placebo group (24.5% versus 29.9%, $p = 0.009$). However, difference reduced when admission for fractures excluded (18.2% versus 20.7%, $p = 0.17$) • Upper gastrointestinal problems experienced by 41.3% of women in treatment group and 40.0% in control group ($p = 0.67$). Rate of events did not increase after dose increased to 10 mg • Women in treatment group had significantly fewer days in bed due to back pain than in placebo group (mean 1.9 versus 5.1 days over 3-year period, $p = 0.001$), and fewer days of limited activity because of such pain (mean 61.8 versus 73.2 days, $p = 0.04$)[c] • Subgroup analysis indicated that treatment with alendronate effective even in those women at highest risk of fracture because of advanced age or severe osteoporosis[b] • Authors noted that results may not be applicable to women living in institutions or in poor health

Additional information from: [a] *Black*, et al. *1993;* [b] *Ensrud*, et al. *1997*; [c] *Nevitt*, et al. *2000*

Bisphosphonates *contd*

Study	FIT, 1998[99] (women without pre-existing vertebral fractures)
Setting	USA
Date of intervention	May 1992–May 1997[a]
Source of funding	Merck Research Laboratories
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Healthy postmenopausal women with osteopaenia (femoral neck BMD 0.68 g/cm^2) but no vertebral fractures
Recruitment procedure used	Population-based.[a] Each of 11 clinical centres involved developed local plan using methods such as direct mailings, media advertising, telephone solicitation, group meetings
Number of patients	4432
Length of study	Mean of 4.2 years
Main intervention/s	Alendronate sodium
Primary outcome measures	Incidence of non-pathological non-traumatic clinical fractures (including both non-vertebral and symptomatic vertebral fractures)
Secondary outcome measures	Incidence of new vertebral fractures[a] Change in height[a] Changes in BMD of hip, spine, radius and total body[a] Changes in biochemical markers of bone metabolism[a]
Definition of incident vertebral fracture	20% or greater decrease in anterior, middle or posterior height between baseline and end of study.[a] Additionally, for any vertebra that was deformed at baseline, a minimum absolute change of 4 mm
Results: vertebral fracture	RR of radiographic fracture in treatment group compared with control group 0.56 (95% CI, 0.39 to 0.80); reduction significant in women whose initial T-score was –2.5 or less (RR = 0.50, 95% CI, 0.31 to 0.82) but not in those with initial T scores greater than –2.5
Results: non-vertebral fracture	Relative hazard of any clinical fracture in treatment compared with control group 0.86, but reduction not significant (95% CI, 0.73 to 1.01). Relative hazard of any non-vertebral fracture 0.88 (0.74 to 1.04); hip 0.79 (0.43 to 1.44); wrist 1.19 (0.87 to 1.64); other 0.79 (0.65 to 0.96). Alendronate significantly reduced risk of clinical fractures in women with initial T-score of –2.5 or less (relative hazard 0.64; 95% CI, 0.50 to 0.82) but not in those with T-score greater than –2.5 (relative hazard 1.08; 95% CI, 0.87 to 1.35)
Quality score	18/18
Comments	• 97% of participants were white • BMD cut-off chosen because considered to correspond to 2 SDs below mean for normal young adult white women but subsequently found to correspond to 1.6 SD below mean; consequently, about one-third of women in trial actually had higher BMD than intended • All patients with estimated calcium intake at baseline of less than 1000 mg/day (82% in each group) given elemental calcium, 500 mg, + vitamin D, 250 IU daily • Although women taking oestrogen in preceding 6 months excluded from study, 9.2% of women in treatment group and 11.1% in placebo group took oestrogen at some time during study • Analysis undertaken on ITT basis; number of withdrawals not given • By final visit, 81.3% of surviving treatment group and 82.5% of surviving placebo group were still taking medication and, of these, 96% from each group had taken at least 75% of pills since last clinic visit; however, this may be due in part to recruitment methods used • 34 participants (12 in treatment and 22 in placebo group) stopped taking study medication because their rate of bone loss exceeded predetermined limits • Adverse events not significantly different between groups: 9.9% of women in treatment and 10.2% in placebo group permanently discontinued study medication because of adverse experiences; 29.1% of women in treatment and 26.9% in placebo group suffered adverse experiences resulting in hospital admission. Upper gastrointestinal problems experienced by 47.5% of women in treatment group and 47.2% in control group • Follow-up radiographs obtained for 4134 women, 95% of those surviving at study close-out.

[a] *Additional information from Black DM*, et al. *1993*

Bisphosphonates *contd*

Study	Harris, 1999[100]
Setting	USA
Date of intervention	December 1993–January 1998
Source of funding	Procter & Gamble Pharmaceuticals Hoechst Marion Roussel
Design	Multicentre, double-masked, placebo-controlled, randomised
Study population	Ambulatory postmenopausal women with established osteoporosis
Recruitment procedure used	Variety of study centres
Number of patients	2458
Length of study	3 years
Main intervention/s	Oral risedronate
Primary outcome measures	Incidence of new vertebral fractures Incidence of radiographically confirmed non-vertebral fractures Changes from baseline BMD
Definition of incident vertebral fracture	New fracture defined as loss of height of at least 15% in anterior, posterior or middle height in vertebra that was normal at baseline, or semi-quantitatively as increase in grade from 0 to 1, 2 or 3. Worsening fracture defined as change of 4 mm or more in vertebral height since previous radiograph, or change of grade in previously fractured vertebra
Results: vertebral fracture	Cumulative incidence of vertebral fracture reduced by 41% in group taking risedronate, 5 mg, compared with placebo (95% CI, 18 to 58%; p = 0.003)
Results: non-vertebral fracture	Cumulative incidence of non-vertebral fracture reduced by 39% in group taking risedronate, 5 mg, compared with placebo (95% CI, 6 to 61%; p = 0.02)
Quality score	18/18
Comments	• All patients took oral calcium, 1000 mg daily • 1500 women (61%) withdrew from study; however, this figure is inflated because one arm, that taking risedronate, 2.5 mg daily, discontinued after 1 year. Risedronate, 5 mg daily, group: 324 women (39.5%) withdrew; placebo group: 365 (344.5%) withdrew; risedronate, 2.5 mg daily, group: 163 (20.0%) withdrew before discontinued • 86% of those who experienced vertebral fracture had at least one 'new' fracture (i.e. fracture of previously normal vertebra) • Overall incidence of adverse events similar across treatment groups, as was incidence of both serious and drug-related adverse events • Most common adverse events associated with withdrawal related to digestive system: placebo group, 56 withdrawals (42%); risedronate, 5 mg daily, group, 49 (36%) • Most upper gastrointestinal adverse events were mild to moderate in severity;incidence similar in placebo and risedronate, 5 mg daily, groups • Patients not excluded from study on basis of history of, or ongoing, gastrointestinal disorders • No significant biochemical changes in renal, hepatic or haematological parameters were observed in any group • Among those who withdrew, incident vertebral fractures occurred in a higher percentage of placebo group than in risedronate, 5 mg daily, group; this may have reduced apparent treatment effect

Bisphosphonates *contd*

Study	Liberman, 1995[101]
Setting	Multinational (North America, Europe, South America, Mexico, Israel, Australia, New Zealand)
Date of intervention	Not specified
Source of funding	Merck Research Laboratories
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Healthy postmenopausal women with osteoporosis lumbar T-score < –2.5) but no vertebral fractures
Recruitment procedure used	Not specified
Number of patients	994
Length of study	3 years
Main intervention/s	Alendronate sodium
Primary outcome measures	Effect on BMD at lumbar spine Effect on calcium-regulating hormones[a,b] Effect on biochemical indices of bone turnover[a,b] Safety and tolerability of daily oral alendronate
Secondary outcome measures	Effect on BMD at other sites[a,b] Incidence of vertebral fractures Progression of vertebral deformities Height loss Symptomatic non-vertebral fractures
Definition of incident vertebral fracture	Reduction of at least 20%, with absolute decrease of at least 4 mm, in height of any vertebral body between baseline and follow-up
Results: vertebral fracture	Treatment associated with reductions in incidence of vertebral fractures (RR 0.52; 95% CI, 0.28 to 0.95). Decreased risk still seen when stratified by age (under 65 years or 65 years and older) or the presence or absence of previous vertebral fracture
Results: non-vertebral fracture	Treatment associated with trend towards reduction in incidence of fractures at non-vertebral sites (estimated risk 0.79; 95% CI, 0.52 to 1.22)
Quality score	12/18
Comments	• 87.4% of patients were white, 0.4% black, 12.2% other races • Both contributory trials excluded women with history of osteoporotic fracture of proximal femur and/or of more than one fracture of lumbar spine (this latter being to ensure that at least three vertebrae from L1–L4 were evaluable) • Both contributory trials had three treatment groups (oral alendronate, 5 mg, 10 mg, and 20 mg reduced to 5 mg for last year, daily). Intended from outset that fracture data would be pooled as it was anticipated that numbers would otherwise not be large enough to allow detection of significant effect • As continuous therapy with oral alendronate, 10 mg daily, produced greater decrease in incidence of vertebral fractures than other doses, pooling may have underestimated its efficacy in preventing fractures • All patients received elemental calcium, 500 mg daily • Baseline characteristics only given for 881 women included in analysis of vertebral fractures; no information given regarding comparability of all groups at entry • Analysis undertaken on ITT basis • Of 162 women (16.3%) who withdrew from trial, 97 (16.2%) were from treatment groups and 65 (16.4%) from placebo group. Of those in placebo group, 6.0% withdrew owing to clinical adverse events, compared with 5.4% of those taking oral alendronate, 5 mg daily, 4.1% taking 10 mg daily, and 8.0% taking 20/5 mg daily • All four groups had similar rates of adverse upper gastrointestinal events, leading to withdrawal in placebo group of 2.0%, 3.5% in oral alendronate, 5 mg daily, 1.0% in 10 mg daily and 2.0% in 20/5 mg daily groups • No evidence of an increased incidence of serious or severe adverse oesophageal effects seen in treatment compared with placebo groups. As severe oesophagitis has been associated with alendronate use, authors suggested results due primarily to fact that participants had regular follow-up visits with frequent reinforcement of dosing instructions, but also recognised that trial participants in general have fewer coexisting conditions than normal patients[c]

Additional information obtained from: [a] *Devogelaer*, et al., *1996*; [b] *Tucci*, et al., *1996*; [c] *Liberman & Hirsch, 1996*

Bisphosphonates *contd*

Study	Lindsay, 1999[102]
Setting	USA
Date of intervention	Not specified
Source of funding	Merck and Company
Design	Multicentre, randomised, placebo-controlled
Study population	Postmenopausal women with osteoporosis and receiving HRT (T-score at lumbar spine or femoral neck < –2 and at other site < 1.5); 57% had previous fracture
Recruitment procedure used	Through 38 sites
Number of patients	428
Length of study	1 year
Main intervention/s	Alendronate
Primary outcome measures	BMD at lumbar spine
Secondary outcome measures	BMD at hip trochanter and femoral neck
Biochemical markers	Adverse events including clinically apparent fractures
Definition of incident vertebral fracture	Symptomatic fractures only
Results: vertebral fracture	No symptomatic vertebral fractures identified in either group
Results: non-vertebral fracture	Non-vertebral fractures more common in intervention than in control group but not statistically significant (p = 0.293)
Quality score	10/18
Comments	• All patients received vitamin D, 400 IU daily • All patients were receiving ongoing HRT for at least 1 year prior to study entry. Oestrogen component of HRT was at least lowest dose recommended by manufacturer for management of osteoporosis, or approximately equivalent to at least 0.625 mg/day conjugated equine oestrogen • All those with intact uterus received medroxyrogesterone acetate in either cyclical or continuous low-dose regimens. Other progestin preparations not permitted • Patients whose baseline calcium intake less than 1000 mg daily provided with supplemental calcium carbonate to bring them up to this level • Patients stratified according to duration of previous HRT to ensure equal distribution between groups of women who received HRT for less or more than 2 years. Mean duration of HRT use approximately 10 years • Of 34 women (7.9%) who withdrew from study, 11 (5.1%) were from intervention group and 23 (10.7%) from control group • Five women (2.3%) withdrew from intervention group and 11 (5.1%) from control group because of adverse effects. Remainder withdrew for other reasons, primarily their own request • Adverse effects evenly distributed between two groups. Back pain was only adverse effect that was significantly more common in intervention group • Over 90% of women in each group were at least 90% compliant with both study drug and HRT

Bisphosphonates *contd*

Study	McClung, et *al*., 1998[77]
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Postmenopausal women with osteopaenia (T-score at lumbar spine < –2)
Recruitment procedure used	Not specified
Number of patients	648
Length of study	18 months
Main intervention/s	Oral risedronate
Primary outcome measures	BMD at lumbar spine
Secondary outcome measures	BMD at femoral neck and trochanter Non-vertebral fracture
Definition of incident vertebral fracture	Not applicable
Results: vertebral fracture	Not applicable
Results: non-vertebral fracture	Few in number and comparable between groups
Quality score	7/15
Comments	• Only published in abstract form • All participants received elemental calcium, 1 g daily • Two risedronate groups, 2.5 mg and 5 mg daily, and placebo group • 38% of women withdrew from study. While this not broken down between treatment arms, it was stated that 8% of those taking risedronate and 11% of those taking placebo withdrew because of adverse events • Incidence of mild-to-moderate upper gastrointestinal adverse events comparable between groups

Study	Montessori, 1997[103]
Setting	The Netherlands
Date of intervention	February 1991–
Source of funding	Procter & Gamble Pharmaceuticals
Design	Open-label, RCT
Study population	Postmenopausal women with osteopaenia (lumbar Z-score < –1); 36% had vertebral fracture on entry
Recruitment procedure used	65 participants recruited through screening programme conducted in two general practices; remainder from hospital files or incidental referrals
Number of patients	80
Length of study	3 years
Main intervention/s	Intermittent cyclical oral etidronate
Primary outcome measures	BMD
Secondary outcome measures	Vertebral fractures
Definition of incident vertebral fracture	Reduction of 20% or more in anterior, middle or posterior height, plus reduction of 10% or more in area in previously unfractured vertebra
Results: vertebral fracture	Although trend towards lower rate of fracture in women in etidronate group, low number of incident fractures did not allow testing for statistically significant differences
Results: non-vertebral fracture	No non-vertebral fractures in either group
Quality score	15/18
Comments	• Both groups received calcium, 500 mg daily, etidronate group for days 15–90 of 90-day cycle, control group throughout • Of 16 women (20%) who withdrew from study, 5 (12.5%) were from etidronate group and 11 (27.5%) from control group • Adverse events mostly mild and evenly distributed over both groups. Two cases of cancer in control group considered unrelated to study medication • Only one patient withdrew because of an adverse event (severe diarrhoea) almost immediately after enrolment. Patient's group was not given • Although an open trial, radiologists who assessed spinal radiographs were blinded to treatment status • Lumbar BMD comparable in both groups at baseline. Higher proportion of women with prevalent vertebral fractures seen in control than in etidronate group (43.6% versus 28.2%) but not statistically significant

Bisphosphonates *contd*

Study	Pacifici, 1988[104]
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, RCT
Study population	White women with osteoporosis or osteopenia (at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation)
Recruitment procedure used	Women attending hospital for osteoporosis screening
Number of patients	128
Length of study	2 years
Main intervention/s	Cyclical potassium phosphate followed by etidronate Conjugated oestrogens and medroxyprogesterone acetate
Primary outcome measures	Bone mineral content
Secondary outcome measures	Incident vertebral fractures Total vertebral height loss Biochemical measures
Definition of incident vertebral fracture	Compression fractures: loss of posterior height greater than 15% compared with mean of posterior height of nearest (above and below) intact vertebrae. Wedging and biconcave fractures: loss of anterior and central height greater than 20% compared with posterior height of same vertebra
Results: vertebral fracture	Incidence of vertebral fractures almost identical in three groups. However, total vertebral height loss in hormone-treated group significantly lower (7.5 ± 4.4%, $p < 0.05$) than in etidronate (13.6 ± 10.6%) and control (20.8 ± 20.2%) groups, which were not significantly different from each other
Results: non-vertebral fracture	–
Quality score	8/15
Comments	• All participants received calcium, 1000 mg daily • In all, 58 women (45%) withdrew from study: numbers said to be evenly distributed between three groups. Reasons: financial problems, geographical relocation, loss of interest, dissatisfaction with results of treatment; numbers citing each reason not given • Baseline characteristics not presented in relation to 35 women who dropped out during first year of study; no information regarding comparability of all groups at entry • Significant side-effects reported only in hormone group, consisting primarily of pelvic congestion and cyclic bleeding; number of women affected not specified

Bisphosphonates *contd*

Study	Pols, 1999[105]
Setting	Europe, North America, Latin America, South Africa and China
Date of intervention	Not specified
Source of funding	Merck Research Laboratories
Design	Multinational, randomised, double-blind, placebo-controlled
Study population	Healthy postmenopausal women with osteopaenia (lumbar T-score < –2)
Recruitment procedure used	153 centres in 34 countries
Number of patients	1908
Length of study	1 year
Main intervention/s	Alendronate
Primary outcome measures	Lumbar BMD
Secondary outcome measures	Biochemical markers of bone turnover Clinical non-vertebral fracture
Results: vertebral fracture	–
Results: non-vertebral fracture	Treatment associated with significant decrease in incidence of non-vertebral fractures (relative hazard 0.53; 95% CI, 0.30 to 0.90)
Quality score	11/15
Comments	• All patients received elemental calcium, 500 mg daily • Of 211 women (11.1%) who withdrew, 118 (12.4%) were from treatment and 93 (9.7%) from placebo group • No statistically significant differences found in overall incidence of adverse effects (alendronate 67.1%, placebo 69.7%), adverse events considered by investigator to be possibly, probably or definitely drug-related (19.1% versus 18.0%) or adverse events resulting in permanent discontinuation of study medication (6.4% versus 5.6%). Serious adverse events also equally common between groups (alendronate 6.5%, placebo 6.3%) • No significant differences between groups in overall incidence of upper gastrointestinal adverse events (alendronate 21.3%, placebo 19.3%), or specific upper gastrointestinal adverse events such as abdominal pain, dyspepsia, nausea • Not possible to evaluate effect of treatment on vertebral fractures as baseline spinal radiographs not obtained for comparison

Bisphosphonates *contd*

Study	Reginster, 2000[106]
Setting	Europe and Australia
Date of intervention	Not specified
Source of funding	Procter & Gamble Pharmaceuticals Hoechst Marion Roussel
Design	Multinational, multicentre, double-masked, placebo-controlled, randomised
Study population	Postmenopausal women with established osteoporosis (at least two vertebral fractures)
Recruitment procedure used	Not specified
Number of patients	1226
Length of study	3 years
Main intervention/s	Risedronate
Primary outcome measures	Proportion of participants with at least one incident vertebral fracture
Secondary outcome measures	Non-vertebral osteoporosis-related fractures (fractures of clavicle, humerus, wrist, pelvis, hip or leg regardless of trauma) Standing height BMD at lumbar spine, femoral neck, femoral trochanter and mid-shaft radius Markers of bone turnover
Definition of incident vertebral fracture	Loss of height of at least 15% in anterior, posterior or middle height in vertebra that was normal at baseline, or semi-quantitatively an increase in grade from 0 to 1, 2 or 3
Results: vertebral fracture	Risedronate, 2.5 mg, reduced RR of vertebral fracture to 0.50 (95% CI, 0.30 to 0.84) at 12 months. Risedronate, 5 mg, reduced RR to 0.39 (95% CI, 0.22 to 0.68) at 12 months and 0.51 (95% CI, 0.36 to 0.75) at 3 years
Results: non-vertebral fracture	Risedronate, 5 mg, reduced RR to 0.67 (95% CI, 0.44 to 1.04)
Quality score	14/18
Comments	• All participants received calcium, 1000 mg daily • Those with baseline 25-hydroxyvitamin D below 40 nmol/l received vitamin D, up to 500 IU daily; 35% required this supplementation, proportion being similar across all groups • Women were not excluded from study because of previous or current gastrointestinal illness or use of medications associated with gastrointestinal intolerance (e.g. non-steroidal anti-inflammatory drugs) • Although all women had two or more baseline vertebral fractures based on initial screening radiographic assessment, 2% had none and 6% only one, based on post-study serial quantitative and qualitative assessment • There were two risedronate groups, 2.5 mg and 5 mg daily, and a placebo group. Risedronate, 2.5 mg, group discontinued after 2 years because other data showed 5 mg dose produced more consistent effect in increasing BMD, while having safety profile similar to 2.5 mg dose • Of 684 women (60.7%) who withdrew from study, 338 (82.4%) were from 2.5 mg arm, 156 (38.2%) from 5 mg arm and 186 (45.6%) from placebo arm. Includes those who were discontinued by protocol amendment noted above • In 2.5 mg group, 53 women (12.9%) withdrew because of adverse events, compared with 65 (15.9%) in 5 mg group and 83 (20.3%) in placebo group. No clinically meaningful differences seen between groups in incidence of adverse events • Tablet counts indicated that 86% of women were compliant with medication (compliance defined as taking at least 80% of medication)

Bisphosphonates *contd*

Study	Reid, 1994[107]
Setting	New Zealand
Date of intervention	Not specified
Source of funding	Not specified
Design	Small, randomised, double-blind, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (at least one vertebral fracture)
Recruitment procedure used	Not specified
Number of patients	61
Length of study	2 years
Main intervention/s	Pamidronate
Primary outcome measures	BMD
Secondary outcome measures	Incidence of vertebral fractures
Definition of incident vertebral fracture	Reduction of more than 20% in anterior, middle or posterior height (with, in previously fractured vertebrae, loss of height of at least 4 mm)
Results: vertebral fracture	Trend towards reduction in fracture rate in treatment group (13/100 patient years versus 24/100 patient years in placebo group) but not statistically significant (p = 0.07)
Results: non-vertebral fracture	–
Quality score	8/15
Comments	• Authors recognise that size of study not intended to allow statistically significant result in relation to vertebral fracture • All patients took elemental calcium, 1 g daily • Of 13 women (21.3%) who withdrew from trial, five (16.1%) were from treatment group and eight (26.7%) from placebo group • Baseline characteristics only given for 48 women who completed study; there is no information regarding comparability of all groups at entry • There was 82% compliance in each group, as assessed by tablet counts • Only common side-effects were gastrointestinal, minor in most cases, and no less common in placebo group

Bisphosphonates *contd*

Study	Storm, 1990[108]
Setting	Denmark
Date of intervention	Patients enrolled from October 1983 to April 1986
Source of funding	Norwich Eaton Pharmaceuticals
Design	Small, double-blind, placebo-controlled, randomised
Study population	Postmenopausal women with established osteoporosis (at least one but no more than four atraumatic vertebral crush fractures)
Recruitment procedure used	Not specified
Number of patients	66
Length of study	150 weeks
Main intervention/s	Intermittent cyclical etidronate
Primary outcome measures	Bone mineral content at lumbar spine and distal non-dominant forearm Spinal deformity index Loss of height Rate of new vertebral fractures
Secondary outcome measures	Clinically overt non-vertebral fractures Biochemical markers Bone histomorphometry
Definition of incident vertebral fracture	Reduction of at least 20% in anterior, middle or posterior height (or all three), plus reduction in area of at least 10%
Results: vertebral fracture	Although no significant difference between overall rate of fracture in treatment and control groups from baseline to end of study, after approximately 1 year of treatment etidronate was associated with significant decrease in rate of new vertebral fractures and stabilisation in progression of vertebral deformity
Results: non-vertebral fracture	Groups did not differ in terms of numbers of patients sustaining all (spontaneous and traumatic) non-vertebral fractures. All such fractures in etidronate group occurred before week 60; in placebo group, seven occurred before/during week 60 and three after week 60
Quality score	14/18
Comments	• All patients received elemental calcium, 500 mg, and vitamin D, 400 IU, daily • Dietary calcium intake not recorded; no dietary restrictions or changes implemented during study • In all, 26 women (39.4%) withdrew, 13 from each group, none because of adverse events; of five deaths in each group, none were related to either study drugs or patient's osteoporosis • No significant side-effects related to etidronate observed • Subgroup analysis (in terms of numbers of fractures in weeks 1–60 and weeks 60–150) not pre-planned

Bisphosphonates *contd*

Study	Watts, 1990[109]
Setting	USA
Date of intervention	Not specified
Source of funding	Norwich Eaton Pharmaceuticals
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Healthy postmenopausal white or Asian women with established osteoporosis (at least one but no more than four vertebral crush fractures)
Recruitment procedure used	Media announcements and letters to physicians
Number of patients	429
Length of study	2 years
Main intervention/s	Intermittent cyclical oral etidronate, with or without phosphate
Primary outcome measures	Spinal BMD Incidence of new vertebral fractures
Secondary outcome measures	Incidence of non-vertebral fractures
Definition of incident vertebral fracture	Reduction of 20% or more in anterior, middle or posterior height, plus reduction of 10% or more in area in previously unfractured vertebra
Results: vertebral fracture	Five patients (5.1%) in etidronate-only group and three (3.1%) in etidronate–phosphate group suffered new vertebral fractures compared with seven (7.6%) in phosphate-only group and ten (11.0%) in placebo-only group. Difference between etidronate–phosphate group and placebo-only group statistically significant (p = 0.034). Effect greatest in subgroup of patients whose baseline BMD was below 50th percentile of baseline values for total study population. Of these, three patients (5.8%) in etidronate-only group and three (6.1%) in etidronate–phosphate group suffered new vertebral fractures compared with seven (17.5%) in phosphate-only group and ten (21.3%) in placebo-only group.
Results: non-vertebral fracture	No apparent differences seen between treatment groups in numbers of non-vertebral fractures that could be attributed to osteoporosis
Quality score	14/18
Comments	• All patients given elemental calcium, 500 mg, for days 18–91 of 91-day cycle • All patients counselled in ways to achieve dietary calcium intake of at least 700 mg daily • Exceptions to stated entry criteria were granted to nine women whose weight exceeded 80 kg and five women whose age exceeded 75 years • 66 women (15.4%) withdrew from study. Of these, six withdrew after randomisation but before beginning of regimen. Of remaining 60, 27 (12.8%) received etidronate and 33 (15.6%) received placebo • Baseline characteristics not given for six women who withdrew immediately after randomisation • Only seven women (1.6%) withdrew because of adverse events, one (0.9%) in phosphate-only, three (2.9%) in etidronate-only, one (0.9%) in etidronate–phosphate and two (1.9%) in placebo-only group • Adverse effects were mild, generally infrequent and comparably distributed between treatment groups: 5–6% in all groups suffered nausea during days 1–17 (phosphate/placebo and etidronate/placebo phases of cycle); however, during days 1–3 (phosphate/placebo phase), 39% of those receiving phosphate suffered diarrhoea compared with 9% receiving placebo • Pooling of results from etidronate-treated groups and those not receiving etidronate indicated significantly fewer etidronate-treated patients with new vertebral fractures (8 versus 17, p = 0.044) • Pooling of results for subgroup with low BMD indicated significantly fewer etidronate-treated patients with new vertebral fractures (6 versus 17, p = 0.006) • Pooling of treatment groups and subgroup analysis in terms of BMD not pre-planned • Combination of etidronate and phosphate resulted in no apparent additional benefit beyond that offered by etidronate alone • After first 2 years, patients could choose to continue the original blinded treatment or take calcium alone.[a] Patients who completed full 3 years, whether on blinded therapy or calcium, were eligible for inclusion in 2-year, open-label follow-up study in which all patients took intermittent cyclical etidronate. They were then re-randomised to receive intermittent cyclical therapy with either etidronate or placebo.[b] However, only results of original 2-year double-blinded RCT are included in this review

Additional information from: [a] *Harris*, et al., *1993;* [b] *Miller*, et al., *1997*

Bisphosphonates *contd*

Study	Wimalawansa, 1998[110]
Setting	UK
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, RCT
Study population	Postmenopausal women with established osteoporosis (spinal T-score –2 and at least one but no more than four atraumatic thoracic vertebral crush fractures)
Recruitment procedure used	Not specified
Number of patients	72
Length of study	4 years
Main intervention/s	HRT plus etidronate, given separately and in combination
Primary outcome measures	BMD
Secondary outcome measures	Biochemical markers Non-vertebral fractures New vertebral fractures Height loss
Definition of incident vertebral fracture	Reduction of 20% or more in anterior, middle or posterior vertebral height plus reduction of 15% or more in area in previously unaffected vertebra. Further deterioration in height or area of previously affected vertebra not considered a new fracture
Results: vertebral fracture	Trend to fewer vertebral fractures in treatment groups than in control group (two in patients taking HRT alone, three in patients taking etidronate alone, one in patients taking combined therapy, and five in control group). However, numbers too small for results to be statistically significant even when expressed as fractures/1000 patient years
Results: non-vertebral fracture	No statistically significant difference between groups in terms of non-vertebral fractures
Quality score	14/18
Comments	• All participants given elemental calcium, 1 g, and vitamin D_2, 400 units (10 µg) daily • All participants given advice on lifestyle, dietetic modifications, and encouraged to walk about 2 miles daily • Of 14 participants (19.4%) who withdrew, three were from the HRT group, three from etidronate group, four from combined therapy group and four from control group. Five withdrew as result of oestrogen-related adverse effects, two from inability to tolerate medications, five from other medical problems, one died and one was lost to follow-up. Withdrawals due to toxicity were distributed as follows: HRT, three; etidronate, one; combined therapy, two; control group, one • In all, 23 women distributed through all groups complained of minor side-effects attributable to calcium but continued supplementation • Six women (35%) taking etidronate alone complained of nausea; no women in any other group complained of this • Although quality of trial was relatively good, numbers were too small to produce significant results in relation to fractures as opposed to BMD

Vitamin D derivatives

Study	Aloia, 1988[117]
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	Double-blind, placebo-controlled, randomised
Study population	Healthy postmenopausal women with established osteoporosis (at least one non-traumatic vertebral compression fracture)
Recruitment procedure used	Media releases and letters to physicians
Number of patients	34
Length of study	2 years
Main intervention/s	Oral calcitriol
Outcome measures	BMD Incidence of vertebral fracture Biochemical measures Bone biopsy
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	Although trend towards lower incidence in treatment group, this not statistically significant
Results: non-vertebral fracture	–
Quality score	8/15
Comments	• All patients received vitamin D, 400 IU daily • All patients had daily calcium intake assessed at entry and were instructed in 1000 mg intake. Dietary calcium subsequently reduced to 500 mg daily in treatment group because of persistent hypercalciuria • Baseline characteristics only given for 27 women who completed study; no information regarding comparability of all groups at entry • Seven women (20.6%) withdrew from study, five (29.4%) from treatment and two (11.8%) from placebo group • None of withdrawals seemed attributable to treatment; one withdrawal in placebo group due to dizziness and nausea was considered by patient to be caused by 'drug' • Hypercalciuria occurred in all patients treated with calcitriol; authors considered that this could have been avoided by parenteral administration of drug • More fractures in placebo than intervention group at baseline but not statistically significant

Vitamin D derivatives *contd*

Study	Dykman, 1984[63]
Setting	USA
Date of intervention	Not specified
Source of funding	Not known – probably not pharmaceutical company
Design	Double-blind, placebo-controlled, randomised
Study population	Ambulatory rheumatic disease patients (white and black) with glucocorticoid-induced osteopenia
Recruitment procedure used	Not specified
Number of patients	30
Length of study	18 months
Main intervention/s	Oral calcitriol
Primary outcome measures	Forearm bone mass
Secondary outcome measures	Vertebral and non-vertebral fractures
Definition of incident vertebral fracture	Definition not given
Results: all fractures	Three patients (23%) in calcitriol group and four (40%) in control group sustained fractures; not statistically significant
Quality score	9/18
Comments	• All patients received calcium, 500 mg, and vitamin D, 400 IU, daily • Calcitriol dose increased from 0.25 µg daily by 0.25 µg daily every 1 or 2 months as long as urinary calcium levels remained < 350 mg/24 hours up to maximum of 1.0 µg daily; mean dose by end of study, 0.4 µg daily • Baseline characteristics only given for 23 men who completed study; no information regarding comparability of all groups at entry • Seven patients (23.3%) withdrew from study, three (10%) because of non-compliance but none because of adverse events; not specified from which groups they withdrew • Toxicity frequent – 12/13 patients in calcitriol group who completed study had at least one episode of hypercalciuria or hypercalcaemia, compared with three in calcium group – but no evidence that any patients with normal renal function sustained any long-lasting complications

Study	Fuji, 1992[64]
Setting	Japan
Date of intervention	1984–90
Source of funding	Not specified
Design	Randomised, open-label, controlled
Study population	Women with established osteoporosis (at least one non-traumatic vertebral fracture)
Recruitment procedure used	Patients with established osteoporosis consulting medical outpatient clinic of Knob Memorial Hospital
Number of patients	32
Length of study	Not specified
Main intervention/s	Alfacalcidol, with and without low-dose, intermittent, elcatonin (eel calcitonin derivative)
Primary outcome measures	Vertebral fractures
Secondary outcome measures	–
Definition of incident vertebral fracture	20% decrease in ratio of anterior or middle height of vertebral body (whichever is larger) and posterior height of same or adjacent vertebra (whichever is larger)
Results: vertebral fracture	Low-dose intermittent elcatonin failed to reduce rate of vertebral fractures. Alfacalcidol seemed to be effective and effect seemed augmented by simultaneous administration of elcatonin, but too few patients to reach definite conclusion
Results: non-vertebral fracture	–
Quality score	11/15
Comments	• Patients not given calcium supplements; their calcium intake averaged 400–500 mg daily • Starting dose of alfacalcidol was 0.75 µg daily, increased stepwise to 1.5 µg daily as long as urinary Ca/Cr stayed below 0.4. When exceeded 0.4, alfacalcidol was temporarily discontinued and then restarted at lower dose • No specific physical therapy prescribed but adequate exercise recommended in all patients • Two patients (6.3%) withdrew, both from alfacalcidol group (25% of that group) • Quasi-randomised – patients being allocated to groups on basis of date of first visit • Groups only approximately homogeneous in relation to age and number of vertebral deformities at baseline • Conducted 1984–90; mean duration of interventions not specified

Vitamin D derivatives *contd*

Study	Gallagher, 1989[118]
Setting	USA
Date of intervention	Not specified
Source of funding	Hoffman La Roche (US) National Institutes of Health
Design	Two comparable small, double-blind, randomised, placebo-controlled trials
Study population	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral fracture)
Recruitment procedure used	Not specified
Number of patients	71
Length of study	1 year as placebo-controlled trial
Main intervention/s	Synthetic calcitriol
Primary outcome measures	Vertebral fracture rates
Secondary outcome measures	–
Definition of incident vertebral fracture	Decrease of 15% in anterior height from baseline
Results: vertebral fracture	Combined data from two trials show lower incidence of fracture in treatment group (15 fractures) compared with placebo group (32 fractures). Authors found this statistically significant when expressed in terms of fracture rates/1000 patient years (450 compared with 823, $p = 0.023$)
Results: non-vertebral fracture	–
Quality score	9/15
Comments	• Data from two similar double-blind, randomised, placebo-controlled trials reported and combined. At end of first year, all patients from placebo arm crossed over to treatment; thus only results of first, placebo-controlled year reported here • Baseline characteristics only given for 62 women with results that could be included in analysis of fracture outcomes; no information regarding comparability of all groups at entry • All patients allowed free calcium intake • Nine patients (12.7%) withdrew from study during first year, five (13.2%) from combined placebo arm, four (12.1%) from combined treatment arm • One withdrawal was due to patient's death, three because patients did not satisfy initial criteria for definition of osteoporotic fracture; no reasons given for remaining five patients dropping out

Vitamin D derivatives *contd*

Study	Gallagher, 1990a[119]
Setting	USA
Date of intervention	Not specified
Source of funding	Hoffman La Roche
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral fracture)
Recruitment procedure used	Direct referral to bone clinic
Number of patients	50
Length of study	2 years
Main intervention/s	Calcitriol
Primary outcome measures	Safety BMD
Secondary outcome measures	Incidence of vertebral fracture
Definition of incident vertebral fracture	15% reduction in anterior or posterior vertebral height
Results: vertebral fracture	No statistically significant difference between treatment and control groups
Results: non-vertebral fracture	–
Quality score	9/15
Comments	• Dose of calcitriol increased from 0.25 µg twice daily to maximum of 1.0 µg twice daily, dose being adjusted to maintain serum calcium < 2.74 mmol/l or urine calcium < 9.96 mmol/day; mean dose after 2 years, 0.62 µg daily • All patients took vitamin D_2, 400 IU daily (incorporated in multivitamin tablet) • Dietary calcium intake estimated on entry to study and all patients instructed to adjust intake to 1000 mg daily, using calcium supplements if necessary. During course of study, calcium intake was reduced to 600 mg daily to prevent hypercalcaemia • Baseline characteristics only given for 40 women who completed study; no information regarding comparability of all groups at entry • Although double-blind, study nurse became unblinded as serum and urine calcium levels rose in first few weeks. However, she was not involved in any technical analysis; it seems to be implied, but not stated, that outcome assessors were blinded to treatment allocation • Ten women (20%) withdrew, seven (28%) from treatment group and three (12%) from control group; in one case (treatment group), withdrawal was due to nausea

Study	Orimo, 1987[120]
Setting	Japan
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, randomised
Study population	Women with established senile osteoporosis (decreased vertebral density and at least one crush fracture)
Recruitment procedure used	Not specified
Number of patients	86
Length of study	Mean length of treatment 1.7–2.1 years
Main intervention/s	Alfacalcidol, with and without calcium, compared with calcium alone and no treatment
Primary outcome measures	Vertebral crush fractures
Secondary outcome measures	–
Definition of incident vertebral fracture	Reduction of 20% or more in anterior, middle or posterior vertebral height compared with baseline
Results: vertebral fracture	Occurrence of new fractures reduced in patients treated with alfacalcidol + calcium compared with control group (p = < 0.01). Calcium alone not effective but enhanced effect of alfacalcidol
Results: non-vertebral fracture	–
Quality score	10/15
Comments	• Although open-label, outcome assessors were blinded to treatment status • Control group received no treatment other than analgesic agents when they complained of occasional low back pain • No information given on planned length of study or number of withdrawals. Instead, mean length of treatment in each group given • Significant difference between calcium and control groups in number of fractures at baseline. This may have made calcium alone appear less effective than it actually was • Although all patients described as having decreased bone mass, no definition of decreased bone mass provided • Results statistically significant only when expressed in terms of fractures/1000 patient years. However, these data only provided graphically; precise figures not given

Vitamin D derivatives *contd*

Study	Orimo, 1994[121]
Setting	Japan
Date of intervention	Not specified
Source of funding	Not specified
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (decreased bone mass; 65% had fracture of spine, femur neck or radius at entry)
Recruitment procedure used	Five medical institutions
Number of patients	80
Length of study	1 year
Main intervention/s	Alfacalcidol
Outcome measures	BMD Incidence of new vertebral fractures Incidence of non-vertebral fractures
Definition of incident vertebral fracture	Either anterior or central height 20% less than posterior height
Results: vertebral fracture	Two patients (5.3%) in treatment group and seven (16.7%) in control group suffered vertebral fractures. There was 73% reduction in vertebral fracture rate/1000 patient years (from 277 in control group to 75 in treatment group, $p = 0.029$)
Results: non-vertebral fracture	No non-vertebral fractures in either group
Quality score	12/18
Comments	• All patients took elemental calcium, 300 mg daily. No specific instructions given regarding dietary calcium intake • Baseline characteristics only given for 74 women who completed study; no information regarding comparability of all groups at entry • Six women (7.5%) withdrew from study, four (10.5%) from treatment group and two (4.8%) from control group. All seemed to be for personal reasons with exception of one in treatment group, due to side-effects • Compliance among those who completed study satisfactory (97.3% of treatment group and 97.5% of control group followed regimen) • No patients with overt vitamin D deficiency were included in study • Although decreased bone mass specified as inclusion criterion, cut-off level not stated • Although presence of fractures specified as inclusion criterion, 30 patients (24/53 who had adequate X-rays for inclusion in fracture analysis) had no fractures at baseline • Women with causes of secondary osteoporosis such as bilateral oophorectomy excluded

Vitamin D derivatives *contd*

Study	Ott, 1989[122]
Setting	USA
Date of intervention	Not specified
Source of funding	Hoffman La Roche (US) National Institutes of Health
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (at least two non-traumatic vertebral compression fractures)
Recruitment procedure used	Media advertisements
Number of patients	86
Length of study	2 years
Main intervention/s	Calcitriol
Primary outcome measures	Change in bone mass
Secondary outcome measures	Side-effects Effect on bone remodelling Fracture incidence
Definition of incident vertebral fracture	Loss of anterior height of more than 15% resulting in anterior/posterior ratio of less than 85%
Results: vertebral fracture	Treatment not associated with improvement in fracture rates
Results: non-vertebral fracture	Treatment not associated with improvement in fracture rates
Quality score	12/18
Comments	• Calcium intake of all patients initially 1000 mg daily, using supplements if necessary • Dose of calcitriol increased from 0.25 µg twice daily to maximum of 1.0 µg twice daily; mean dose at 96 weeks 0.43 ± 0.03 µg/day • During study, to prevent hypercalcaemia, calcium intake and dose of calcitriol adjusted to maintain serum calcium < 2.54 mmol/l or urine calcium < 8.75 mmol/day • Of 14 women (16.3%) who withdrew from study, eight (9.3%) were from treatment group and six (14.0%) from control group. Majority withdrew for personal reasons • Treatment group had significantly higher serum and urine calcium values but renal function not worse than in placebo group • No major side-effects of calcitriol identified during study • Minor symptoms (e.g. upper respiratory or urinary tract infections, back pain and indigestion) similar in both groups

Study	Shiraki, 1996[68]
Setting	Japan
Date of intervention	October 1989–March 1993
Source of funding	Not specified
Design	Randomised, double-blind, placebo-controlled
Study population	Women aged 60 years or more with diagnosis of definite or probable osteoporosis, 49% of whom had at least one vertebral fracture at entry
Recruitment procedure used	Not specified
Number of patients	113
Length of study	2 years
Main intervention/s	Alfacalcidol
Primary outcome measures	BMD Vertebral and non-vertebral fractures
Definition of incident vertebral fracture	Either anterior or central vertebral height 20% less than posterior height
Results: vertebral and non-vertebral fracture	Combined rate of vertebral and non-vertebral fracture in treatment group was one-third that in placebo group; not statistically significant
Quality score	13/18
Comments	• All patients took elemental calcium, 300 mg daily • Analgesics permitted for severe pain • In all, 34 women (30.1%) were excluded from fracture analysis, 20 (35.1%) from treatment and 14 (25%) from control group, because of absence of X-ray films. No reasons given for this, so not clear how many excluded because of withdrawal, for whatever reason, and how many for technical reasons relating to X-rays

Calcitonin

Study	Adami, 1995[93]
Setting	Italy
Date of intervention	Not specified
Source of funding	Not specified
Design	RCT, double-blind between alendronate and placebo, with open-label calcitonin arm
Study population	Postmenopausal women with osteoporosis (lumbar T-score > –2), 5% of whom had vertebral fracture at entry
Recruitment procedure used	Not specified
Number of patients	286
Length of study	2 years
Main intervention/s	Alendronate Intranasal salmon calcitonin
Primary outcome measures	BMD (spine)
Secondary outcome measures	BMD (hip) Biochemical indices of bone turnover
Definition of incident vertebral fracture	Not applicable: only clinically apparent fractures recorded
Results: all fractures	No significant trends noted between treatment groups in relation to number of fractures
Quality score	9/15
Comments	• Alendronate arm placebo-controlled but calcitonin arm was not because no intranasal placebo available • Blinding not possible in relation to calcitonin arm and although assessors of BMD scans blinded to treatment allocation, no such assurance was given in relation to fracture outcomes • All patients received elemental calcium, 500 mg daily • Of 41 withdrawals (14.3%) from treatment, 15 (5.2%) were due to adverse events • Analysis on ITT basis • All treatment groups similar to placebo group with regard to both overall safety profile and upper gastrointestinal adverse events • Quality score is low partly because of lack of information about method of randomisation but more because of lack of information about methods used to identify and confirm fractures. However, study not designed to detect significant differences in fracture rates, and fracture data only collected as part of adverse event reporting. It is therefore perhaps unreasonable to expect such detail to be provided

Calcitonin *contd*

Study	Agrawal, 1981[61]
Setting	USA
Date of intervention	Not specified
Source of funding	Medical Research Service of the Veterans Administration US Energy Research and Development Administration Armour Pharmaceutical Company Marion Laboratories
Design	Open-label, RCT
Study population	Male veterans aged 50 years and over with established osteoporosis (at least one non-traumatic vertebral compression fracture)
Recruitment procedure used	Veterans Administration medical centres
Number of patients	39
Length of study	2 years
Main intervention/s	Subcutaneous salmon calcitonin
Outcome measures	Total body calcium Bone mineral content New vertebral events Biochemical indices Peripheral fractures
Definition of incident vertebral fracture	Development of compression or collapse in vertebra previously of normal height, or further compression or collapse in previously involved vertebra
Results: vertebral fracture	Eight new vertebral events in eight patients in calcitonin treatment group who had X-rays suitable for analysis, compared with 21 in seven patients in vitamin D_2 + calcium group and 21 in ten patients in vitamin D_2 alone group
Results: non-vertebral fracture	Although fewer fractures in calcitonin treatment group than in other groups, this not subject to statistical analysis because of instances of multiple fractures in both other groups, and it was not possible to quantitate degree of trauma involved
Quality score	9/15
Comments	• Calcitonin group and control group both received vitamin D_2, 1300 IU, + calcium, 100 mg, daily. Third group only received vitamin D_2, 800 IU daily • Baseline characteristics only given for 26 men who completed 1–2 years of study; no information regarding comparability of all groups at entry • Baseline characteristics of 26 patients indicate that calcitonin group had more affected vertebrae than other groups at study entry • Of 13 (33.3%) participants who died or withdrew, five died from causes unrelated to study; initial bone biopsy found that one had osteomalacia and another normal trabecular bone volume. Remaining six (15.4%) apparently withdrew voluntarily. No information given as to which groups they withdrew from • In all, 22 patients completed 2 full years of observation • Only one side-effect was noted, of moderately severe nausea in calcitonin group • Authors reported mean of one new vertebral event per patient in calcitonin group compared with 2.0 in vitamin D_2 + calcium group and 2.4 in group receiving vitamin D_2 alone. These means seem inconsistent with other figures given

Calcitonin *contd*

Study	Cristallini, 1993[128]
Setting	Italy
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, RCT
Study population	Postmenopausal women with established osteoporosis (at least two non-traumatic vertebral fractures)
Recruitment procedure used	Not specified
Number of patients	125
Length of study	2 years
Main intervention/s	Intermittent cyclical intramuscular salmon calcitonin with either potassium phosphate or sodium fluoride
Primary outcome measures	BMD Vertebral fractures
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	No significant difference between two intervention groups and control group. Rate of fracture in intervention groups approximately same in second as in first year of treatment
Results: non-vertebral fracture	–
Quality score	6/15
Comments	• All patients received vitamin D_3, 0.25 µg, + elemental calcium, 1 g: control group received this daily and calcitriol groups on days 31–75 of 90-day cycle • Dietary calcium intake: 800–1800 mg daily • Of 48 women (38.4%) who withdrew from study, 12 (30%) were from calcitonin/potassium phosphate group, 12 (30%) from calcitonin/sodium fluoride group and 24 (53.3%) from control group • Five women (12.5%) withdrew from calcitonin/potassium phosphate group and four (10%) from calcitonin/sodium fluoride group because of flushing/gastrointestinal complaints. Two more (5%) withdrew from calcitonin/sodium fluoride group because of occult faecal blood and pain. Remainder withdrew due to 'dissatisfaction' • Because of extent of their bone loss, after 1 year patients in control group were assigned to different treatments not investigated in this study • Potential for confounding not clear as baseline data only provided for some patients in each group and their initial comparability therefore cannot be determined

Calcitonin *contd*

Study	Ellerington, 1996[129]
Setting	England
Date of intervention	Not specified
Source of funding	Sandoz Ltd Heart Disease and Diabetes Research Trust Cecil Rosen Foundation
Design	Double-blind, placebo-controlled, RCT
Study population	Healthy postmenopausal women with osteopenia (T-score in spine or hip < –1.2)
Recruitment procedure used	Not specified
Number of patients	117
Length of study	2 years
Main intervention/s	Intranasal salmon calcitonin
Primary outcome measures	BMD of lumbar spine and hip
Secondary outcome measures	Biochemical markers of bone metabolism Incident vertebral fracture
Definition of incident vertebral fracture	Authors used Kleerekoper's, Melton's and height-reduction-from-baseline methods
Results: vertebral fracture	Authors stated that 'too few events occurred in any group during the study to permit analyses of fracture data', and hence did not provide any data relating to fractures
Results: non-vertebral fracture	–
Quality score	10/15
Comments	• Dietary calcium intake assessed at baseline and at 12 and 24 months by detailed self-completion questionnaire. No patients received any calcium supplement during course of study • Twenty women (17%) withdrew or were excluded from study • An 11% drop-out rate seen in women who received calcitonin compared with 13% in those who received placebo • Four women withdrew because of adverse reactions (rhinitis, taste perversion or epistaxis); it was not stated which groups they were in • 34% of women who received calcitonin suffered minor local nasal or respiratory disorders compared with 24% of those who received placebo. Only 7% in placebo group suffered rhinitis, compared with 23% in calcitonin group

Calcitonin *contd*

Study	Fujita, 1992[64]
Setting	Japan
Date of intervention	1984–90
Source of funding	Not specified
Design	Randomised, open-label, controlled
Study population	Women with established osteoporosis (at least one non-traumatic vertebral fracture)
Recruitment procedure used	Patients with established osteoporosis consulting medical outpatient clinic of Kanebo Memorial Hospital
Number of patients	32
Length of study	Not specified
Main intervention/s	Alfacalcidol, with and without low-dose, intermittent, elcatonin (eel calcitonin derivative)
Primary outcome measures	Vertebral fractures
Secondary outcome measures	–
Definition of incident vertebral fracture	A 20% decrease in ratio of anterior or middle height of vertebral body (whichever is larger) and posterior height of same or adjacent vertebra (whichever is larger)
Results: vertebral fracture	Low-dose intermittent elcatonin failed to reduce rate of vertebral fractures. Alfacalcidol seemed effective and its effect appeared augmented by simultaneous administration of elcatonin but too few patients to reach definite conclusion
Results: non-vertebral fracture	–
Quality score	11/15
Comments	• Patients not given calcium supplements; calcium intake averaged 400–500 mg daily • Starting dose of alfacalcidol, 0.75 µg daily, increased stepwise to 1.5 µg as long as urinary Ca/Cr stayed below 0.4. When exceeded 0.4, alfacalcidol temporarily discontinued and then restarted at lower dose • No specific physical therapy prescribed but adequate exercise recommended in all patients • Two patients (6.3%) withdrew, both from alfacalcidol group (25% of group) • Quasi-randomised – patients allocated to groups on basis of date of first visit • Groups only approximately homogeneous in relation to age and number of vertebral deformities at baseline • Study conducted 1984–90; mean duration of interventions not specified

Calcitonin *contd*

Study	Gennari, 1985[65]
Setting	Italy
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, RCT
Study population	Postmenopausal women with established osteoporosis (at least two non-traumatic vertebral compression fractures)
Recruitment procedure used	Not specified
Number of patients	82
Length of study	1 year
Main intervention/s	Injected (intramuscular or subcutaneous) salmon calcitonin
Outcome measures	Bone mineral content of lumbar spine and femoral diaphysis Vertebral fractures Serum and urinary parameters
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	Fewer new vertebral fractures in two calcitonin groups than in control group but authors admit number of cases too small for any statistically significant conclusions to be drawn
Results: non-vertebral fracture	–
Quality score	6/15
Comments	• All participants received calcium, 1 g daily • While in hospital, patients started on regular diet with calcium content of about 600 mg daily with foods low in gelatine and cartilage, and were strongly recommended to continue this at home • Six participants (7.3%) withdrew because of adverse effects (three from daily calcitonin group, two from group receiving calcitonin on alternate days, and one from control group) • Further 12 (14.6%) were excluded from analysis because of poor compliance, and 19 because they had not yet completed full 12 months of treatment. Not clear to which groups these patients belonged • As analysed, each group consisted of 15 participants but not clear how many had originally been randomised to each group • Not clear whether groups were comparable at randomisation, as only characteristics of those who completed full year are given • No major adverse effects reported. Adverse effects leading to withdrawal were gastrointestinal discomfort (one patient in control group), nausea and vomiting (three in calcitonin groups) and flushing and fatigue (two in calcitonin groups). Also, some calcitonin-treated patients experienced mild and transient facial flushing, and mild inflammatory reaction at injection site • Study was not apparently placebo-controlled, and not clear to what extent participants, healthcare providers and outcome assessors blinded to treatment status

Calcitonin *contd*

Study	Hizmetli, 1998[130]
Setting	Turkey
Date of intervention	Recruitment, October 1994–August 1995
Source of funding	Not specified
Design	Open-label, RCT
Study population	Postmenopausal women with newly-diagnosed osteoporosis (T-score < –2.5)
Recruitment procedure used	Consecutive recruitment from women referred to Physical Therapy and Rehabilitation Department, Cumhuriyet University Faculty of Medicine
Number of patients	107
Length of study	2 years
Main intervention/s	Intranasal salmon calcitonin
Primary outcome measures	Lumbar and femoral neck BMD Vertebral fracture
Secondary outcome measures	–
Definition of incident vertebral fracture	Decrease in anterior vertebral height of more than 25% of posterior height
Results: vertebral fracture	Although more fractures seen in control group than in both calcitonin groups, this was not statistically significant
Results: non-vertebral fracture	–
Quality score	9/15
Comments	• All patients received elemental calcium, 1000 mg daily • Patients also received vitamin D, 50,000 IU weekly, if their 24-hour urinary calcium excretion less than 120 mg, and 400 IU daily if more than 120 mg • Twenty women (18.7%) withdrew from study: six (17.1%) from group receiving calcitonin, 50 IU; six (14.6%) from group receiving calcitonin, 100 IU; eight (25.8%) from control group. Five women (6.6%) withdrew from calcitonin groups because of side-effects; all other withdrawals due to failure to attend

Calcitonin *contd*

Study	Hodsman, 1997[131]
Setting	Canada
Date of intervention	Not specified
Source of funding	Medical Research Council of Canada Rhône-Poulenc-Rorer
Design	Randomised, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (at least one vertebral compression fracture)
Recruitment procedure used	Not specified
Number of patients	39
Length of study	2 years
Main intervention/s	Cyclical subcutaneous salmon calcitonin
Primary outcome measures	Change in BMD at lumbar spine
Secondary outcome measures	Change in BMD at femoral neck Incident vertebral fracture rates Biochemical markers of bone formation and resorption Non-vertebral fracture
Definition of incident vertebral fracture	20% or greater reduction in posterior, middle or anterior vertebral height compared with baseline
Results: vertebral fracture	More vertebral fractures identified in calcitonin group than in control group. However, because of small numbers, this not statistically significant
Results: non-vertebral fracture	No non-vertebral fractures occurred in either group
Quality score	11/15
Comments	• Baseline characteristics only provided for 30 patients who completed study. However, characteristics of other nine said to be not significantly different • All patients received 800 IU equivalent of human parathyroid hormone by subcutaneous injection on days 1–28 and elemental calcium, 500 mg orally, on days 71–90 of 90-day cycle • Nine patients (23%) withdrew from study, three because of inability to learn self-injection technique, three because of localised inflammatory reactions to injections and three because underlying cancer identified • Inflammatory reactions were considered due to formulation vehicle used in human parathyroid hormone injections rather than the peptide itself • None of the cancer cases of appeared to be related to treatment protocol • Unspecified number of patients receiving calcitonin suffered mild nausea and skin flushing • Authors argued that vertebral fracture rates are low given that patients had average T-score of –3 or less and at least one vertebral fracture on entry. However, as both groups received human parathyroid hormone, they cannot demonstrate that these rates are lower than those in an untreated population

Calcitonin *contd*

Study	Overgaard, 1992[60]
Setting	Denmark
Date of intervention	Not specified
Source of funding	Danish Medical Research Council (drugs from Sandoz)
Design	Double-blind, randomised, placebo-controlled
Study population	Elderly women with moderate osteoporosis (T-score at distal forearm < –2), 6% of whom had vertebral fractures at entry
Recruitment procedure used	Questionnaire sent to all women aged 68–72 years in six municipalities near Glostrup Hospital
Number of patients	208
Length of study	2 years
Main intervention/s	Salcatonin nasal spray
Primary outcome measures	Bone mineral content of distal forearm and lumbar spine Rates of vertebral and peripheral fractures
Secondary outcome measures	Measures of bone turnover
Definition of incident vertebral fracture	Two definitions used: • Wedge deformities defined as reduction of at least 25% in anterior vertebral height compared with posterior height, and compression fractures as reduction of at least 25% in posterior height compared with adjacent vertebrae • Essentially same except that reduction has to be at least 20% and criteria applied following correction of height of each vertebra by adjustment factor
Results: vertebral fracture	Number of patients with incident vertebral fractures in the pooled salcatonin group significantly lower than in control group (four compared with six, $p < 0.01$)[a]
Results: non-vertebral fracture	Numbers too low to be statistically significant
Quality score	15/18
Comments	• Three salcatonin groups, receiving 50, 100 and 200 IU daily • All participants received calcium, 500 mg daily • In all, 32 participants (15.4%) withdrew – 24 (15.4%) from pooled intervention groups and eight (15.4%) from control group • A further 12 participants completed 2 years' treatment but for various reasons, including non-compliance, were not 'valid completers', and thus not included when results calculated • Side-effects not substantially more common in treatment groups (25–33%) than in control group (23%). General adverse events: headache, dizziness, nausea, constipation; local adverse effects: primarily nasal secretion and sneezing, nasal dryness, nasal crusts, irritation of nasal mucosa • Although study intended as dose–response study, with rates of vertebral and peripheral fractures as primary outcome measure, number of fractures was too small to support more than comparison of all fracture types between control and pooled calcitonin groups. Pooling was not pre-planned

Additional information from: [a] *Overgaard & Christiansen, 1996*

Calcitonin *contd*

Study	**Pontiroli, 1991**[132]
Setting	Italy
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, RCT
Study population	Women with postmenopausal or senile osteoporosis (at least one vertebral fracture)
Recruitment procedure used	Not specified
Number of patients	15
Length of study	6 months
Main intervention/s	Human calcitonin, either intranasally or intramuscularly
Primary outcome measures	Pain Metabolic indices Bone mineral content
Secondary outcome measures	New fractures
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	None in either group
Results: non-vertebral fracture	None in either group
Quality score	6/15
Comments	• Pilot study with very small numbers • Three women (20%) withdrew, one (14%) from intranasal and two (25%) from intramuscular group; six in each group treated for 2 months but only four in each group for additional 4 months • Side-effects, mainly nausea and flushing, more intense and prolonged with intramuscular than with intranasal calcitonin • Intranasal but not intramuscular calcitonin associated with significant decrease in pain score

Study	**PROOF study**[78] **(Stock, 1997)**
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	Multinational, multicentre, double-blind, randomised, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (at least one but not more than five non-traumatic vertebral fractures and T-score at lumbar spine < –2)[a]
Recruitment procedure used	Not specified
Number of patients	1255[b]
Length of study	5 years
Main intervention/s	Salmon calcitonin nasal spray (100, 200 or 400 IU daily)
Primary outcome measure	Time to first new vertebral fracture
Secondary outcome measure	Lumbar spine BMD Non-vertebral fracture
Definition of incident vertebral fracture	Greater than 20% and greater than 4 mm reduction in anterior, middle or posterior height of vertebral body[a]
Results: vertebral fracture	In 100 IU group, 46 fractures; in 200 IU group, 37; in 400 IU group, 46; in placebo group, 55.[c] RR reduction in new vertebral fractures compared with placebo was 18%, 36% and 23% for 100, 200 and 400 IU treatment groups, respectively.[b] At 200 IU, reduction in calcitonin group compared with placebo group statistically significant (p = 0.020)
Results: non-vertebral fracture	[c] No non-vertebral fractures in any group
Quality score	11/15
Comments	• All patients received calcium, 1000 mg, + vitamin D, 400 IU, daily. • Of 123 patients (9.8%) said to have withdrawn from study, 44 were from 100 IU group, 30 from 200 IU group, 34 from 400 IU group and 15 from placebo group.[c] Reasons for withdrawal not given • All analyses were ITT • Adverse effects, including those resulting in discontinuation of study drug, no more frequent in treatment groups than in placebo group • As yet only published in abstract form. Consequently, relatively little information provided and, as result, quality score is low and may rise when published in full • As yet, only interim results available

Additional information from: [a] *Ginola, 1998;* [b] *Chesnut, 1998*[78]*;* [c] *Kanis & McCloskey*, 1999

Calcitonin *contd*

Study	Rico, 1992[134]
Setting	Spain
Date of intervention	Not specified
Source of funding	Ministry of Education and Science
Design	Open-label, RCT
Study population	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral crush fracture)
Recruitment procedure used	Not specified
Number of patients	60
Length of study	2 years
Main intervention/s	Intermittent intramuscular salmon calcitonin
Primary outcome measure	Vertebral fracture rate
Secondary outcome measures	Spinal deformity index Height Non-vertebral fracture
Definition of incident vertebral fracture	Reduction of at least 20% in anterior, middle or posterior vertebral height (or all three) plus approximate reduction in area of at least 10%
Results: vertebral fracture	A 60% reduction in new fractures in intervention group compared with 35% increase in control group ($p < 0.025$). Spinal deformity index increased by 0.07 in intervention group compared with 0.12 in control group ($p < 0.05$), and mean height reduced by 1.0 and 1.4 cm, respectively ($p < 0.05$)
Results: non-vertebral fracture	Two patients in treatment group suffered fractures (in one case accompanied by significant trauma) versus four in control group (one accompanied by minor trauma due to fall)
Quality score	13/18
Comments	• All women received elemental calcium, 500 mg, for 10 days/month • Three patients (5%) withdrew from study, two (6.3%) from treatment and one (3.6%) from control group; one withdrawal from treatment group due to side-effects • Vertebral fracture results presented in graphic form only • Abstract describes study as 'retrospective randomised study' but full text does not indicate that it is anything other than normal RCT • Although outcome assessors blinded to treatment status, not clear that either patients or healthcare providers blinded; there is no mention of placebo

Study	Rico, 1995[135]
Setting	Spain
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, RCT
Study population	Postmenopausal women with established osteoporosis (more than one non-traumatic vertebral crush fracture)
Recruitment procedure used	Not specified
Number of patients	72
Length of study	2 years
Main intervention/s	Intermittent intramuscular salmon calcitonin
Primary outcome measures	Spinal deformity Vertebral fracture
Secondary outcome measures	Cortical bone mass Biochemical markers Height
Definition of incident vertebral fracture	Reduction of at least 20% in anterior, middle or posterior vertebral height (or all three) plus approximate reduction in area of at least 10% in previously unfractured vertebra
Results: vertebral fracture	Over 2 years, rate of vertebral fracture was 0.07/patient-year in intervention group and 0.45/patient-year in control group ($p = < 0.001$). Spinal deformity index increased by 0.04 in intervention group and by 0.13 in control group ($p = < 0.001$)
Results: non-vertebral fracture	One patient in each group sustained non-vertebral fracture or fractures
Quality score	13/18
Comments	• All participants received elemental calcium, 500 mg daily, for 10 days/month • Only four participants (5.6%) withdrew, three (8.3%) from intervention group and one (2.8%) from control group. Only one from each group withdrew because of unspecified side-effects • Although outcome assessors blinded to treatment status, not clear that either patients or healthcare providers blinded; there is no mention of placebo

Calcitonin *contd*

Study	Ringe, 1987[136]
Setting	Germany
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, RCT
Study population	Patients with 'incipient to severe signs' of steroid-induced osteoporosis
Recruitment procedure used	Not specified
Number of patients	38
Length of study	6 months
Main intervention/s	Subcutaneous salmon calcitonin
Primary outcome measure	Bone mineral content
Secondary outcome measures	Vertebral fractures/deformities Pain Adverse effects Non-vertebral fracture
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	No patients in treatment group suffered vertebral fracture, compared with three in control group. One in treatment group had worse back score (an index of deformity) at end of study compared with four in control group
Results: non-vertebral fracture	One patient in treatment group suffered non-vertebral fracture, compared with two in control group
Quality score	9/18
Comments	• Both groups received analgesic treatment on demand and physiotherapy • Baseline characteristics only given for 36 patients who completed study; no information regarding comparability of both groups at entry • Two patients (5.3%) withdrew from study: one dropped out of calcitonin group because of severe nausea; one from control group died in asthmatic crisis • Adverse effects seem to have occurred in treatment group only (perhaps not surprisingly, as this seems to have been an open trial). Three patients suffered hot flushes and three nausea; in one case, nausea was severe enough for treatment to be discontinued

Study	Ringe, 1990[137]
Setting	Germany
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, RCT
Study population	Men and women with primary osteoporosis (undefined)
Recruitment procedure used	Not specified
Number of patients	67
Length of study	1 year
Main intervention/s	Subcutaneous salmon calcitonin, daily or on alternate days
Outcome measures	Pain Vertebral and non-vertebral fractures BMD Bone biopsy
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	Fewer fractures in intervention groups than in control group but because of small numbers involved, difference not statistically significant
Results: non-vertebral fracture	Fewer fractures in intervention groups than in control group but because of small numbers involved, difference not statistically significant
Quality score	7/18
Comments	• All patients received calcium, 1 g daily • Patients continued to use analgesics (mostly non-steroidal anti-inflammatory drugs) and physiotherapy according to individual need • Baseline characteristics only given for 59 patients who completed study; no information regarding comparability of all groups at entry • Of patients who completed study, 32% were men • Eight patients (11.9%) withdrew from study, four because of insufficient cooperation and four because of side-effects (nausea or flushing after injection). Not specified which groups they withdrew from • Adverse events generally mild, commonest in all three groups being nausea • Calcitonin groups enjoyed significant reduction in pain

Calcium

Study	Gutteridge, 1993[80]
Setting	Australia
Date of intervention	Not specified
Source of funding	Australian National Health and Medical Research Council Medical Research Fund of Western Australia Orthopaedic Research and Education Committee of the University of Western Australia Sir Charles Gairdner Hospital Research Fund
Design	Open-label RCT
Study population	Postmenopausal women with established osteoporosis (at least one vertebral fracture following minor trauma)
Recruitment procedure used	Not specified
Number of patients	23
Length of study	36 months maximum
Main intervention/s	Intermittent cyclic enteric-coated sodium fluoride
Outcome measures	BMD Vertebral fractures
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	No statistically significant difference between treatment and control groups. Although authors claimed that results, excluding first year of treatment, suggest RR = 0.23 for fluoride group compared with calcium + vitamin D_2 group, this was not statistically significant; moreover, the untreated group were not included in this comparison
Results: non-vertebral fracture	–
Quality score	5/15
Comments	• Patients in fluoride group and calcium + vitamin D_2 group all received calcium, 1 g daily, + vitamin D_2, 0.5 mg (20,000 IU) weekly. There was also untreated control group • Patients received treatment for three or four cycles (27 or 36 months) depending on vertebral radiographic and densitometric response • Results come from pilot study preceding larger trial (Gutteridge, 1996[79]), for which recruitment still ongoing when pilot study results published • No information given about comparability of treatment and control groups at entry • No information given about withdrawals

Calcium *contd*

Study	Recker, 1996[142]
Setting	USA
Date of intervention	Recruitment November 1987–January 1990
Source of funding	National Dairy Funding and Research Board National Institutes of Health Lederle Laboratories
Design	Randomised, double-blind, placebo-controlled
Study population	Healthy elderly women with low self-chosen calcium intakes and prevalent vertebral fractures
Recruitment procedure used	Volunteers from 55 study sites (mostly government-sponsored meal sites for the elderly)
Number of patients	94
Length of study	Mean of 4.3 ± 1.1 years
Main intervention/s	Oral calcium
Primary outcome measures	Incidence of vertebral fractures Forearm bone mass changes
Definition of incident vertebral fracture	Greater than 20% reduction in anterior or posterior height relative to baseline. Positive and negative calls of incident fracture by algorithm judged against clinician's assessment, which was taken as standard
Results: vertebral fracture	Calcium supplementation significantly reduced rate of incident fractures in patients with pre-existing vertebral fractures (28.3% of patients in treatment group suffered fractures, compared with 51.2% in placebo group, $p = 0.023$)
Results: non-vertebral fracture	–
Quality score	12/15
Comments	• Results drawn from larger study of spine antifracture and bone-sparing efficacy of calcium in elderly women of European ancestry with low self-chosen calcium intakes, with and without pre-existing vertebral fractures. Although participants not selected on basis of low BMD, study was designed to evaluate vertebral fracture in two groups: women with and without prevalent vertebral fractures on entry • For logistical reasons, necessary to randomise patients to treatment without reference to their prevalent fracture status. Despite this, when broken down into fracture and non-fracture groups for analysis, subgroups were found to be similar in age and customary calcium intake, and prevalent fracture groups were also comparable in terms of baseline bone mineral content • Only data on those women with pre-existing vertebral fractures are examined here • Of 251 women who originally agreed to participate in both arms of study, 54 withdrew so early that they were regarded as having declined to participate; 18 withdrew later (12 deaths, six moved out of area). Withdrawal data not broken down by arm of study • Median compliance overall 64%

Oestrogen

Study	Lufkin, 1992[178]
Setting	USA
Date of intervention	Not specified
Source of funding	Ciba-Geigy Corporation
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (low BMD and at least one vertebral fracture)
Recruitment procedure used	Clinic attenders
Number of patients	75
Length of study	1 year
Main intervention/s	Cyclical transdermal oestradiol and oral medroxyprogesterone acetate
Outcome measures	Bone turnover assessed by biochemical markers and iliac bone histomorphometry BMD Incidence of vertebral fracture
Definition of incident vertebral fracture	Decrease of more than 15% in anterior, middle or posterior vertebral height relative to baseline
Results: vertebral fracture	12 women (35%) in placebo group suffered new fractures, compared with 7 (21%) in oestrogen group
Results: non-vertebral fracture	–
Quality score	11/15
Comments	• At recruitment, 38 women were receiving oestrogen, calcium supplements or vitamin D; these treatments discontinued 3 months before start of study in case of calcium, and 6 months before for oestrogen and vitamin D. Another 17 women had discontinued oestrogen use 4 or more years before study • Women whose calcium intake estimated at less than 800 mg daily were instructed to maintain a diet providing that amount • Eight women (10.7%) withdrew from study, 3 (8.3%) from treatment and 5 (12.8%) from placebo group • Two women withdrew from treatment group and one from placebo group because of skin reaction to patches • Subgroup analysis showed that effect of treatment was at least as marked in older as in younger women • Previous HRT did not affect results in relation to lumbar spine BMD and vertebral fracture rate • Study objective was to evaluate effectiveness of transdermal oestrogen; however, medroxyprogesterone acetate, used to prevent endometrial hyperplasia rather than for any effect in relation to osteoporosis, may have had additive effect to oestrogen in relation to osteoporosis

Oestrogen *contd*

Study	Pacifici, 1988[104]
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label RCT
Study population	White women with osteoporosis or osteopenia (at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation)
Recruitment procedure used	Women attending hospital for osteoporosis screening
Number of patients	128
Length of study	2 years
Main intervention/s	Cyclical potassium phosphate followed by etidronate Conjugated oestrogens and medroxyprogesterone acetate
Primary outcome measures	Bone mineral content
Secondary outcome measures	Incident vertebral fractures Total vertebral height loss Biochemical measures
Definition of incident vertebral fracture	Compression fractures: loss of posterior height greater than 15% compared with mean of posterior height of nearest (above and below) intact vertebrae. Wedging and biconcave fractures: a loss of anterior and central height greater than 20% compared with posterior height of same vertebra
Results: vertebral fracture	Incidence of vertebral fractures almost identical in all three groups. However, total vertebral height loss in hormone-treated group significantly lower (7.5 ± 4.4%, $p < 0.05$) than in etidronate (13.6 ± 10.6%) and control (20.8 ± 20.2%) groups, which not significantly different from each other
Results: non-vertebral fracture	–
Quality score	8/15
Comments	• All patients received calcium, 1000 mg daily • 58 women (45%) withdrew from study. Numbers of withdrawals said to be evenly distributed between three groups. Reasons given: financial problems, geographical relocation, loss of interest and dissatisfaction with results of treatment; however, numbers citing each reason not given • Baseline characteristics not presented in relation to 35 women who dropped out during first year of study; no information regarding comparability of groups at entry • Significant side-effects said to occur only in hormone group, consisting primarily of pelvic congestion and cyclic bleeding; number of women affected not specified

Oestrogen *contd*

Study	Wimalawansa, 1998[110]
Setting	UK
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label RCT
Study population	Postmenopausal women with established osteoporosis (spinal T-score –2 and at least one but no more than four atraumatic thoracic vertebral crush fractures)
Recruitment procedure used	Not specified
Number of patients	72
Length of study	4 years
Main intervention/s	HRT plus etidronate, given separately and in combination Primary outcome measures BMD
Secondary outcome measures	Biochemical markers Non-vertebral fractures New vertebral fractures Height loss
Definition of incident vertebral fracture	Reduction of 20% or more in anterior, middle or posterior vertebral height plus reduction of 15% or more in area in previously unaffected vertebra. Further deterioration in height or area of previously affected vertebra not considered new fracture
Results: vertebral fracture	Trend to fewer vertebral fractures in treatment groups compared with control group (two in patients taking HRT alone, three in those taking etidronate alone, one in patients taking combined therapy and five in control group). However, numbers too small for results to be statistically significant even when expressed as fractures/1000 patient years
Results: non-vertebral fracture	No statistically significant difference between groups in terms of non-vertebral fracture
Quality score	14/18
Comments	• All participants received elemental calcium, 1 g, and vitamin D_2, 400 units (10 µg), daily • All participants received advice on lifestyle and dietetic modifications, and encouraged to walk about 2 miles/day • Of 14 participants (19.4%) who withdrew, three were from HRT group, three from etidronate group, four from combined therapy group and four from control group. Five withdrew as result of oestrogen-related adverse effects, two from inability to tolerate medications, five from other medical problems, one died and one lost to follow-up. Withdrawals due to toxicity: HRT group 3, etidronate group 1, combined therapy group 2, control group 1 • In all, 23 women from all groups complained of minor side-effects attributable to calcium, but continued supplementation • Six women (35%) taking etidronate alone complained of nausea; no women from other groups complained of this • Although quality of trial relatively good, numbers too small to produce significant results in relation to fractures as opposed to BMD

Oestrogen *contd*

Study	Zarcone, 1997[144]
Setting	Italy
Date of intervention	January 1991–May 1996
Source of funding	Not specified
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal women with osteoporosis (maximum BMD at lumbar spine 0.88 g/cm^2)
Recruitment procedure used	Not specified
Number of patients	132
Length of study	64 months
Main intervention/s	Conjugated equine oestrogen in association with progestogen
Primary outcome measures	BMD – lumbar spine Vertebral fractures
Secondary outcome measures	Biochemical markers
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	16.7% of women in placebo group suffered new vertebral fractures during study compared with 10% of those on oestrogen, 0.15 or 0.3 mg daily, and 3.3% on 0.625 mg daily
Results: non-vertebral fracture	Brief reference made to treatment being associated with 'a notable reduction' in fractured neck of femur but no figures given
Quality score	7/18
Comments	• Calcium, 500 mg daily, given to women whose daily intake less than 1200–1500 mg • No demographic details given and comparability of groups not discussed • 12 women (9.1%) withdrew; not specified from which groups they came and only one reason given for all – 'the common prejudices which associate the use of oestrogen replacement therapy with health risks'

Oestrogen-like molecules

Study	Maugeri, 1994[157]
Setting	Italy
Date of intervention	June 1990–November 1993
Source of funding	Not specified
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Women over 65 with established osteoporosis (at least one vertebral fracture, and T-score at distal radius of < –2)
Recruitment procedure used	Not specified
Number of patients	100
Length of study	2 years
Main intervention/s	Oral ipriflavone Primary outcome measures BMD Bone metabolism marker parameters
Secondary outcome measures	Pain Incidence of vertebral fractures
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	Occurrence of new vertebral fractures described as minimal in treatment group and much more frequent in control group. However, actual figures not given
Results: non-vertebral fracture	–
Quality score	7/15
Comments	• All patients received calcium, 1 g daily • Not clear how many patients in each group initially • 16 women (16%) withdrew from study: three because of gastrointestinal side-effects (two in treatment and one in control group); remainder due to protocol violations or non-compliance (6) or failure to attend for examination at 6 months (7) • Nine women (9%) suffered side-effects: six in treatment group and three in control group. Most common side-effect was mild gastralgia during first 6 months of treatment, suffered by four women in treatment group and two in control group; it disappeared spontaneously without suspension of treatment or reduction of dose • No significant alterations in laboratory blood parameters, including serum lipids • Treatment group showed considerable improvement in pain scores and significant reduction in analgesic consumption • No evidence given that effect of treatment on either pain or vertebral fracture reached statistical significance

Oestrogen-like molecules *contd*

Study	Passeri, 1992[158]
Setting	Italy
Date of intervention	Not specified
Source of funding	Not specified
Design	Randomised, double-blind, placebo-controlled
Study population	Elderly women with established osteoporosis (at least one vertebral fracture, and T-score at distal radius of < –2)
Recruitment procedure used	Outpatient clinics
Number of patients	28
Length of study	1 year
Main intervention/s	Oral ipriflavone
Primary outcome measures	Bone mass Biomarkers
Secondary outcome measures	Incidence of vertebral fracture
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	No women in treatment group suffered vertebral fracture, whereas one woman in control group suffered two such fractures
Results: non-vertebral fracture	–
Quality score	11/15
Comments	• All patients received calcium, 1 g daily • Not clear whether any withdrawals other than one in placebo group who suffered vertebral fractures and withdrew because of associated back pain • Eight patients in intervention and five in control group suffered side-effects, most common being gastric discomfort or diarrhoea; one woman in each group suffered skin rashes. All symptoms disappeared spontaneously without interrupting treatment • Analysis appears to have been on ITT basis • Authors considered oral administration of drug to have played positive role in terms of compliance

Oestrogen-like molecules *contd*

Study	Passeri, 1995[159]
Setting	Italy
Date of intervention	Not specified
Source of funding	Chiese Farmaceutici SpA
Design	Two centre, randomised, double-blind, placebo-controlled
Study population	Elderly women with established osteoporosis (at least one vertebral fracture, and forearm Z-score of < –2)
Recruitment procedure used	Patients presenting at geriatric outpatient clinics at two university hospitals for evaluation of osteoporosis
Number of patients	49
Length of study	2 years
Main intervention/s	Oral ipriflavone
Primary outcome measures	BMD Safety
Secondary outcome measures	Incidence of new vertebral fractures Incidence of non-traumatic peripheral fractures, or peripheral fractures due to minimum trauma
Definition of incident vertebral fracture	20% or greater reduction in anterior compared with posterior vertebral height, or in posterior height compared with height of adjacent vertebrae
Results: vertebral fracture	Four women in treatment group (20% of those for whom X-rays available) suffered new vertebral fractures compared with eight in control group (40% of those for whom X-rays available)
Results: non-vertebral fracture	No women in treatment group suffered non-vertebral fractures compared with one from control group
Quality score	15/18
Comments	• All patients received elemental calcium, 1 g daily • 22 women (44.9%) withdrew from study: 11 (44.0%) from treatment and 11 (45.8%) from control group. Five dropped out because of adverse reactions (three in treatment and two in control group). Of rest, five withdrew due to of intercurrent illness, two because GPs changed therapy and ten for personal reasons or loss of interest • Most adverse reactions were gastrointestinal symptoms. As these equally distributed between groups, authors suggested at least some may be due to calcium supplement • Authors attributed high drop-out rate to age-related difficulty involved in these patients following study protocol for long period • All 27 completers used at least 75% dispensed medication during first year, and 93% continued to be good compliers (defined as using 75% or more of medication) for whole 2-year period (one woman in each group used 72%) • No serious adverse events; cardiac and pulmonary function, and blood pressure remained unchanged in both groups • Analysis of fracture outcomes undertaken on ITT basis

Anabolic steroids

Study	Chesnut, 1983[96]
Setting	USA
Date of intervention	Not specified
Source of funding	Sterling-Winthrop Research Institute Winthrop Laboratories National Institutes of Health
Design	Double-blind, randomised, placebo-controlled
Study population	Postmenopausal Caucasian women with vertebral osteopaenia or one or more atraumatic spinal compression fractures
Recruitment procedure used	Selected from patients self-referred or referred by their physicians to study
Number of patients	46
Length of study	29 months
Main intervention/s	Intermittent stanozolol
Primary outcome measures	Total body calcium Bone mass Biochemical markers
Secondary outcome measures	Incidence of vertebral fractures
Definition of incident vertebral fracture	Anterior vertebral height/posterior vertebral height x 100 = < 100%, or = 100% but with biconcavity of vertebral body
Results: vertebral fracture	Statistically nonsignificant trend towards reduction in vertebral fractures in treatment group
Results: non-vertebral fracture	–
Quality score	10/15
Comments	• All patients instructed by dietician on maintaining intake of elemental calcium, 1000 mg daily (by diet, supplements or both), throughout study period • Eight women (17.4%) withdrew from study, two (8.7%) from treatment and six (26.1%) from control group; reasons for withdrawals not reported • Authors noted that number of patients was too small and observation periods too short to produce statistically significant results in relation to vertebral fracture • Clinical side-effects noted by 57% of patients in treatment group and 30% in control group, but none severe enough to discontinue therapy • Increased facial hair noted by 30% of patients in treatment group (compared with 9% in control group); 22% in treatment group noted hoarseness and 9% acne compared with none in control group. Ankle oedema reported by 22% in each group • Elevated serum glutamate oxaloacetate transaminase level demonstrated on at least one occasion by 43% of patients in treatment group (compared with 0% in control group). However, mean level over 29-month period only slightly elevated and all returned to normal following discontinuation of treatment at end of study

Fluoride

Study	Brockstedt, 1996[73]
Setting	Denmark
Date of intervention	Not specified
Source of funding	Not specified
Design	Double-blind, randomised
Study population	Women with osteoporosis (undefined)
Recruitment procedure used	Not specified
Number of patients	92
Length of study	3 years
Main intervention/s	Sodium monofluorophosphate
Outcome measures	BMD Bone markers Vertebral fracture Adverse effects
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Mean number of new vertebral fractures increased equally in both groups
Results: non-vertebral fracture	–
Quality score	5/15
Comments	• Published in abstract form only • All women received calcium carbonate, 1000 mg daily • Full 3 years of study not completed by 38 women (41%). No reasons given for withdrawals, which were not broken down between treatment groups • No statistically significant difference between groups in terms of overall incidence of adverse effects. In continuous fluoride group, 50% and 45.7% of women suffered adverse gastrointestinal events and adverse musculoskeletal events, respectively, compared with 56.5% and 32.6%, respectively, in intermittent fluoride group

Study	Gutteridge, 1993[80]
Setting	Australia
Date of intervention	Not specified
Source of funding	Australian National Health and Medical Research Council Medical Research Fund of Western Australia Orthopaedic Research and Education Committee of the University of Western Australia Sir Charles Gairdner Hospital Research Fund
Design	Open-label RCT
Study population	Postmenopausal women with established osteoporosis (at least one vertebral fracture following minor trauma)
Recruitment procedure used	Not specified
Number of patients	23
Length of study	Maximum of 36 months
Main intervention/s	Intermittent cyclic enteric-coated sodium fluoride
Outcome measures	BMD Vertebral fractures
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	No statistically significant difference between treatment and control groups. Although authors claimed that results, excluding first year of treatment, suggested RR = 0.23 for fluoride group compared with calcium + vitamin D_2 group, this not statistically significant; moreover, untreated group not included in this comparison
Results: non-vertebral fracture	–
Quality score	5/15
Comments	• Patients in fluoride group and calcium + vitamin D_2 group all received calcium, 1 g daily, + vitamin D_2, 0.5 mg (20,000 IU) weekly. Untreated control group also • Patients received treatment for three or four cycles (27 or 36 months) depending on vertebral radiographic and densitometric response • Results from pilot study preceding larger trial (Gutteridge, 1996[79]) for which recruitment still ongoing when pilot study results published • No information given on comparability of treatment and control groups at entry • No information given about withdrawals

Fluoride *contd*

Study	Gutteridge, 1996[79]
Setting	Australia
Date of intervention	1989–[a]
Source of funding	Australian National Health and Medical Research Council Medical Research Fund of Western Australia
Design	Open-label, randomised, two-centre, controlled
Study population	Postmenopausal women aged under 80 years with established osteoporosis (at least one vertebral fracture but no hip fracture)
Recruitment procedure used	Not specified
Number of patients	100
Length of study	27 months
Main intervention/s	Intermittent cyclic enteric-coated sodium fluoride, with or without HRT
Outcome measures	BMD Vertebral fractures
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Interim results only available: in non-HRT groups, significantly more patients in fluoride than control groups suffered vertebral fractures (83% versus 36%, $p = 0.004$). Differences more marked in first 9-month cycle than in second (24% versus 0%). In HRT groups, fewer patients in fluoride than control groups suffered such fractures (29% versus 56%) but not statistically significant; difference most marked in first cycle (28% versus 0%)
Results: non-vertebral fracture	Stress fractures suffered by eight women (18%) in fluoride groups and none in control groups, mostly (6/8) below knee
Quality score	6/18
Comments	• All patients received calcium, 1 g daily, and vitamin D_2, 0.25–0.5 mg (10,000–20,000 IU) weekly • Initial dose of sodium fluoride, 60 mg, could be reduced or increased (to maximum 80 mg/day) depending on vertebral radiographic and densitometric responsea • Of 100 patients, 35 on HRT at entry continued; randomised separately from those not on HRT • Patients not on HRT received no previous treatment for osteoporosis (other than calcium) • Patients 'randomly adaptively assigned' to treatment • No information given about comparability of treatment and control groups at entry • Twelve women (12%) withdrew from trial, five (14%) from HRT groups, seven (11%) from non-HRT groups; no reasons given for withdrawals

[a] *Additional information from: Gutteridge, 1993*[80]

Study	Hansson, 1987[167]
Setting	Sweden
Date of intervention	Not specified
Source of funding	Swedish Medical Research Council Asker's Foundation
Design	Randomised, placebo-controlled
Study population	Postmenopausal women with established idiopathic osteoporosis (at least one, and maximum of three, vertebral compression fractures sustained during minor trauma)
Recruitment procedure used	Not specified
Number of patients	100
Length of study	3 years
Main intervention/s	Sodium fluoride
Primary outcome measures	Spinal bone mineral content
Secondary outcome measures	Vertebral fracture
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Number of fractures that occurred in each group too small to be statistically significant
Results: non-vertebral fracture	–
Quality score	5/15
Comments	• Three of four groups received calcium, 1 g daily. Fourth group received placebo in place of calcium • Groups comparable at entry in terms of age and BMD, but no information given regarding numbers of prevalent vertebral fractures at entry • Twelve women (12%) withdrew from study: one (4%) from fluoride, 30 mg, group, two (8%) from fluoride, 10 mg, group, three (12%) from calcium-only group, six (24%) from placebo-only group. Reasons for withdrawals not given

Fluoride *contd*

Study	Kleerekoper, 1991[168]
Setting	USA
Date of intervention	1981–
Source of funding	National Institutes of Health
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal white women with established osteoporosis (at least one vertebral compression fracture or two or more non-contiguous vertebral wedge deformities)
Recruitment procedure used	Not specified
Number of patients	84
Length of study	4 years
Main intervention/s	Sodium fluoride
Primary outcome measures	Vertebral fracture
Secondary outcome measures	Change in cortical bone mass Change in height Side-effects, including non-vertebral fractures
Definition of incident vertebral fracture	Reduction of one or more vertebral heights by 15% or more from previous value
Results: vertebral fracture	In fluoride group, 74% of women suffered vertebral fracture compared with 67% in placebo group: difference not statistically significant (p = 0.50)
Results: non-vertebral fracture	In the fluoride group, 13% of women suffered non-vertebral fracture compared with 3% in placebo group: difference not statistically significant (p = 0.29)
Quality score	9/18
Comments	• All patients also took calcium, 1500 mg daily • All patients instructed in active physical therapy/rehabilitation programme which continued throughout trial • In all, 40 women (47.6%) withdrew from study, 23 (50%) from intervention and 17 (44.7%) from control group; reasons not given. However, 22 of these women (13 fluoride, nine placebo) agreed to final follow-up visit • Analysis on ITT basis • Power of study reduced by low recruitment and high drop-out rate to 66% • Compliance defined as taking more than 75% of study medication. Of those taking medication, 62% of fluoride and 78% of placebo group compliant with calcium (p = 0.64), and 50% of fluoride and 72% of placebo group compliant with fluoride/placebo • Fluoride and placebo groups differed significantly in numbers who suffered osteomalacia (17% and 0%, respectively, p = 0.01) and bone lesions in lower extremities (rate/1000 person years, 936 and 302, respectively, p = 0.02) • In fluoride group, 109 non-vertebral bone lesions identified, with 30 in placebo group; 16 patients in fluoride and one in placebo group suffered non-vertebral bone lesions associated with pain sufficient to require dose change • Numbers of patients who suffered at least one gastrointestinal complaint (35% in fluoride, 16% in placebo group) just reached statistical significance (p = 0.05)

Fluoride *contd*

Study	Meunier, 1998[69]
Setting	France and Belgium
Date of intervention	Not specified
Source of funding	Not specified
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Ambulatory postmenopausal white women with established osteoporosis (at least one vertebral fracture)
Recruitment procedure used	Not specified
Number of patients	354
Length of study	2 years
Main intervention/s	Fluoride (as sodium fluoride or monofluorophosphate)
Primary outcome measures	Percentage of patients with at least one new vertebral fracture between T4 and L5 after 2 years
Secondary outcome measures	Percentage of patients who suffered at least one new non-vertebral fracture during 2 years Changes in BMD Biochemical measurements Safety and tolerance
Definition of incident vertebral fracture	Reduction of approximately 20% or more in any vertebral height
Results: vertebral fracture	Fluoride salts with calcium and vitamin D_2 supplementation no more successful in preventing new vertebral fractures than calcium and vitamin D_2 alone
Results: non-vertebral fracture	Fluoride salts with calcium and vitamin D_2 supplementation no more successful in preventing new non-vertebral fractures than calcium and vitamin D_2 alone
Quality score	14/18
Comments	• All patients took calcium, 1 g, and vitamin D_2, 800 IU, daily • Study treatment not given to 132 women (37.3%) for full 24 months. Treatment discontinuation rates said not to differ between groups but details not given • Lower limb pain syndrome noted more frequently in combined fluoride group than in control group (p = 0.001). In most cases (29/37), this occurred in first 12 months of treatment; it led to definitive discontinuation of treatment in 11.5% of combined fluoride group and 3.4% of control group, and in three patients (all receiving fluoride) led to short hospitalisation period • Authors suggested that, as proportion of patients with new vertebral fractures in control group was much lower than in previous French study, calcium and vitamin D_2 may have had anti-fracture effect in control group; as result, study may have had insufficient power to detect difference in fracture rates between treatment and control groups. Alternatively, they suggested duration of study may have been too short

Fluoride *contd*

Study	Pak, 1995[170]
Setting	USA
Date of intervention	1986
Source of funding	United States Public Health Service Institutional funds Mission Pharmaceutical Company (provision of drug only)[a]
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral fracture)
Recruitment procedure used	Patients referred for symptomatic osteoporosis by practising physicians because of inadequate response to conventional therapy or unwillingness of physicians to care for them[a]
Number of patients	110
Length of study	4 years
Main intervention/s	Intermittent slow-release sodium fluoride
Primary outcome measures	Incident vertebral fractures
Secondary outcome measures	BMD Safety
Definition of incident vertebral fracture	Reduction in any vertebral height of more than 20%, + decrease in vertebral area of more than 10%, from 1 year to next
Results: vertebral fracture	85.4% of patients in treatment group remained free of new fractures in previously unaffected vertebrae compared with 56.9% in placebo group (p = 0.001). No significant difference between groups in terms of recurrent fractures
Results: non-vertebral fracture	No significant difference between groups
Quality score	13/18
Comments	• All patients received calcium, 800 mg daily • Randomisation stratified to take account of 31 women taking oestrogen at recruitmenta • Of 34 women (30.9%) who withdrew from study, 17 (31.5%) were from treatment and 17 (30.4%) from placebo group. Majority of withdrawals due to lack of interest, travel problems and unrelated medical problems. One withdrawal from fluoride group due to pelvic fracture; one from control group due to nausea and vomiting • Groups did not differ significantly in frequency of side-effects • During treatment, fluoride group enjoyed significant reduction in severity and frequency of back pain compared with before treatment, whereas control group had only statistically non-significant reduction • Compliance, assessed by pill count, was 95.2 ± 7.9% in fluoride and 94.1 ± 6.4% in placebo group

[a] *Additional information from: Pak*, et al., *1994*

Fluoride *contd*

Study	Reginster, 1998[171]
Setting	Belgium
Date of intervention	Not specified
Source of funding	Rotta Research Group
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal white women with moderate osteoporosis (lumbar spine T-score of –2.5), 2% of whom had vertebral fractures at entry
Recruitment procedure used	Not specified
Number of patients	200
Length of study	4 years
Main intervention/s	Sodium monofluorophosphate
Primary outcome measures	Number of patients with new vertebral fractures during 4-year treatment period
Secondary outcome measures	BMD Biochemical markers of bone remodelling Peripheral fractures
Definition of incident vertebral fracture	Reduction of at least 20% and absolute decrease of at least 4 mm in any height of vertebral body since baseline
Results: vertebral fracture	In the treatment group, 2.4% of patients suffered new fractures compared with 10% in control group ($p = 0.05$)
Results: non-vertebral fracture	Incidence of peripheral fractures similar in both groups
Quality score	15/18
Comments	• All patients received elemental calcium, 1000 mg daily • Women prescribed HRT before enrolment for purposes other than bone therapy (about 10% in each group) continued to take it • Of 78 women (39%) who withdrew from study, 38 (38%) were from treatment and 40 (40%) from control group • Reasons for withdrawal similar in both groups in incidence, type and severity • Lower limb pain reported by 3% of treatment and 4.7% of control group • Only 36 patients not included in analysis of vertebral fracture rate, either because of early drop-out and no possibility of radiological follow-up (30 patients) or because their radiographs could not be evaluated (six patients) • Compliance with study medication good and identical in both groups: on average, evaluable patients in both groups took 87% of their tablets • If patients on HRT excluded from analysis, 2.8% of treatment group and 11.6% of control group suffered new vertebral fracture

Fluoride *contd*

Study	Riggs, 1990[172]
Setting	USA
Date of intervention	Not specified
Source of funding	National Institutes of Health
Design	Randomised, double-blind, placebo-controlled
Study population	Postmenopausal white women aged 50–75 years with established osteoporosis (low BMD at lumbar spine and at least one vertebral fracture)
Recruitment procedure used	Volunteers from patients at Mayo Clinic
Number of patients	202
Length of study	4 years
Main intervention/s	Sodium fluoride
Primary outcome measures	Vertebral fractures Side-effects, including non-vertebral fractures
Secondary outcome measures	Biochemical measurements BMD
Definition of incident vertebral fracture	Decrease of 15% in at least one of three heights within vertebra between any two examinations
Results: vertebral fracture	Using 15% fracture definition,[a] 55.8% of women in fluoride group suffered one or more vertebral fractures during course of study, compared with 62.8% in control group, but not statistically significant ($p = 0.579$). Re-analysis of results using 20% and 30% definitions of fracture resulted in even less difference between groups (20% definition – 50.0% versus 52.3%, $p = 0.919$; 30% definition – 32.7% versus 34.9%, $p = 0.737$)
Results: non-vertebral fracture	More women in fluoride than control group suffered non-vertebral fractures (61 versus 24; RR = 3.2; 95% CI, 1.8 to 5.6; $p < 0.01$). While no statistically significant difference between two groups in terms of complete fractures (35 versus 22; RR = 1.9; 95% CI, 1.1 to 3.4), significantly more women in fluoride than in control group suffered incomplete fractures (26 versus 2; RR = 16.8; 95% CI, 3.9 to 71.7; $p < 0.0005$)
Quality score	16/18
Comments	• When recruited, 153 women receiving treatment for osteoporosis (calcium, 29; calcium + vitamin D, 30; oestrogen, 22; calcium + oestrogen, 30; calcium + oestrogen + vitamin D, 31; vitamin D, 6; oestrogen + vitamin D, 5). Treatment with calcium and/or vitamin D discontinued for 3 months and with oestrogen for 6 months before start of study) • All patients received elemental calcium, 1500 mg daily • Patients encouraged to be active but no formal exercise or rehabilitation programme • Of 67 women (33.2%) who withdrew from trial, 35 (34.7%) were from treatment and 32 (31.7%) from placebo group. Ten said to have withdrawn because of side-effects, ten because of other developments, and 39 for personal reasons; six died and two were lost to follow-up. No information on how reasons for withdrawal related to treatment group • Tablet counts indicated median sodium fluoride dose = 71 mg/day and median calcium dose = 1329 mg/day in fluoride and 1305 mg/day in placebo group (not significant) • More women in fluoride group suffered one or more side-effects severe enough to require reduction in dosage (54 versus 25; RR = 3.0; 95% CI, 1.9 to 4.8; $p < 0.0001$) • Gastrointestinal pain, nausea and vomiting more common in fluoride group (17 versus 7; RR = 2.88; 95% CI, 1.2 to 7.1), although gastrointestinal bleeding and anaemia were not (9 versus 9; RR = 0.87; 95% CI, 0.3 to 2.3) • Lower extremity pain experienced by 37 women in fluoride and five in placebo group (RR = 9.85; 95% CI, 4.0 to 24.2). More severe symptoms occurred only in fluoride group and usually disappeared 4–8 weeks after treatment stopped; in eight women they recurred when drugs were resumed at lower level • Number of women in fluoride group suffering incomplete non-vertebral fractures likely to be underestimate as only women reporting persistent pain had X-ray of painful area • No significant difference between treatment groups in RR of vertebral fracture when broken down by year of treatment (fluoride versus control: year 1, RR = 1.47; 95% CI, 0.4 to 5.5; year 2, 0.58; 0.3 to 1.1; year 3, 0.53; 0.3 to 1.0; year 4, 0.94; 0.5 to 1.8) • However, data reanalysed[b] to show that, excluding year 1 data, and taking mean of patient numbers for years 2–4, RR = 0.57, in favour of fluoride (95% CI, 0.44 to 0.70; $p < 0.0001$) • Difference in vertebral fracture incidence between two groups even less apparent when women who previously received oestrogen treatment removed from analysis

Additional information from: [a] *Melton*, et al., *1998*; [b] *Gutteridge*, et al., *1993*[80]

Fluoride *contd*

Study	Ringe, 1998[173]
Setting	Germany
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label RCT
Study population	Men with early idiopathic osteoporosis (T-score < –2.5 but no significant deformity or signs of previous vertebral fractures)
Recruitment procedure used	Large cohort of men presenting at clinic with preliminary diagnosis of osteoporosis (no obvious risk factors for secondary osteoporosis) for definite diagnosis and treatment advice
Number of patients	64
Length of study	3 years
Main intervention/s	Intermittent oral monofluorophosphate with continuous calcium supplementation
Primary outcome measures	BMD of lumbar spine
Secondary outcome measures	BMD of five other sites Incidence of fractures (vertebral and non-vertebral) Combined pain-mobility score
Definition of incident vertebral fracture	Reduction of over 20% in anterior, median or posterior vertebral height in relation to baseline
Results: vertebral fracture	Risk of vertebral fracture significantly reduced in fluoride group (only 10% of patients in fluoride group suffered vertebral fracture compared with 40% in control group, $p = 0.015$)
Results: non-vertebral fracture	Risk of non-vertebral fracture also reduced in fluoride group (10% of patients suffered non-vertebral fracture compared with 27% in control group); reduction not statistically significant ($p = 0.0807$)
Quality score	13/18
Comments	• All patients took supplementary calcium. Fluoride group took 500 mg/day for 3 months of cycle during which they also took fluoride, and 1000 mg/day for remaining month, while control group took 1000 mg/day throughout • Fourteen men (21.9%) withdrew from study, seven (21.9%) from each group • Withdrawals due to poor compliance, change of therapy by GP, or for personal reasons not related to study medication. No withdrawals due to side-effects • Treatment produced significant improvement in relation to pain and mobility • All reported adverse events were mild to moderate, and transient in nature • Most common adverse event in treatment group, lower-limb pain syndrome, not experienced by control group. Disappeared after therapy interrupted for 4–5 weeks • Authors suggest that osteoporotic men may respond better to fluoride than osteoporotic women

Fluoride *contd*

Study	Ringe, 1999[174]
Setting	Germany
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label RCT
Study population	Postmenopausal women with established osteoporosis (T-score < –2.5 and at least one osteoporotic vertebral fracture)
Recruitment procedure used	Patients seen in outpatients clinic
Number of patients	145
Length of study	3 years
Main intervention/s	Intermittent or continuous monofluorophosphate with continuous calcium supplementation
Primary outcome measures	BMD Incidence of vertebral fractures
Secondary outcome measures	Incidence of non-vertebral fractures Combined pain-mobility score Height loss
Definition of incident vertebral fracture	Reduction of 20% or more in anterior, median or posterior vertebral height in relation to baseline
Results: vertebral fracture	By third year of treatment, risk of vertebral fracture significantly reduced in both fluoride groups compared with control group. Intermittent regimen showed clear trend to be more effective than continuous regimen, with significant reduction in fracture risk by year 2
Results: non-vertebral fracture	Risk of non-vertebral fracture also significantly reduced in both fluoride groups in comparison to control group; intermittent regimen showed clear trend to be more effective than continuous regimen
Quality score	13/18
Comments	• All patients also took calcium, 1000 mg daily • Forty women (27.6%) withdrew from study, 14 (28.6%) from intermittent monofluorophosphate group, 14 (29.2%) from continuous and 12 (25.0%) from control group • In first 6 months, 11 women (7.6%) withdrew for personal reasons or because of protocol violations. They were not included in either between-group comparison of initial characteristics or, because no outcome data available, in ITT analysis • Majority of remaining withdrawals due to non-compliance or to distance from treatment centre. However, four women withdrew from fluoride groups on their own physician's recommendation and two because of lower extremity pain syndrome; one woman withdrew from each of continuous fluoride groups because of diarrhoea possibly related to calcium intake and one from control group because of renal colic • Results reported here relate to new fractures only; although data also provided on worsening of existing fractured vertebrae, these not related to numbers of women who suffered them • Treatment produced significant improvement in relation to pain and mobility • Most commonly reported adverse events were lower-limb pain syndrome and gastrointestinal complaints; former not experienced by control group and disappeared 3–4 weeks after discontinuing therapy. Gastrointestinal symptoms occurred in all three groups; considered mainly attributable to calcium supplementation

Fluoride *contd*

Study	Sebert, 1995[175]
Setting	France
Date of intervention	Not specified
Source of funding	Not specified
Design	Randomised, double-blind, placebo-controlled
Study population	Men and women with severe osteopaenia (lumbar T-score < –2) but with no vertebral fractures
Recruitment procedure used	Recruited by two centres
Number of patients	94
Length of study	2 years
Main intervention/s	Sodium monofluorophosphate
Primary outcome measures	Variations in lumbar BMD
Secondary outcome measures	Incidence of vertebral fracture
Definition of incident vertebral fracture	A 25% reduction in anterior or middle height relative to posterior vertebral height, or in vertebral height relative to adjacent vertebrae
Results: vertebral fracture	Two vertebral fractures in fluoride group and one in control group; no statistically significant difference between groups
Results: non-vertebral fracture	None in either group
Quality score	14/18
Comments	• All patients received elemental calcium, 1000 mg daily • 35 patients (37.2%) withdrew or were considered non-eligible for trial, 19 (42.2%) from treatment and 16 (32.7%) from control group. Adequate reasons not given • Authors stated that duration of study was too short and sample size too small to draw any reasonable conclusions on effect of treatment on fracture incidence • In fluoride group, 22% of patients suffered minor gastrointestinal disorders compared with 18% in control group; not statistically significant ($p > 0.6$) • No statistically significant differences between groups in terms of numbers of patients suffering either pain in lower limbs (fluoride 11%, control group 4%, $p > 0.3$) or non-vertebral bone fissures (fluoride 4%, control group 0%, $p > 0.2$) • No statistically significant differences between groups in terms of tolerance of treatment; considered good/very good by over 80% patients in each group ($p = 0.9$)

SERMs

Study	Ettinger, 1999[182]
Setting	Multinational
Date of intervention	1994–
Source of funding	Eli Lilly
Design	Randomised, double-blind, placebo controlled
Study population	Postmenopausal women with osteoporosis (low BMD and/or vertebral fractures), 37% of whom had at least one vertebral fracture at entry
Recruitment procedure used	Approximately 50% of patients volunteers recruited by media advertising in USA and Canada; remainder enrolled by individual study sites which may have used own institutional or other databases to identify and contact potential patients
Number of patients	7705
Length of study	3 years
Main intervention/s	Raloxifene, 60 mg or 120 mg
Primary outcome measures	Proportion of women with one or more new non-traumatic vertebral fractures BMD
Secondary outcome measures	Proportion of women with non-traumatic non-vertebral fractures (excluding pathological fractures and those involving fingers, toes and skull) Breast cancer Other adverse events Biochemical markers of physiologic functions and bone turnover
Definition of incident vertebral fracture	Decrease in anterior, mid- or posterior vertebral height of at least 20% and at least 4 mm
Results: vertebral fracture	In pooled raloxifene groups, 272 women (6.0%) had at least one new vertebral fracture compared with 231 (10.1%) in pooled control groups; difference statistically significant
Results: non-vertebral fracture	Reported by 437 women (8.5%) in pooled raloxifene groups and 240 (9.3%) in pooled placebo groups; difference not statistically significant
Quality score	16/18
Comments	• Patients divided into two study groups, those with and without vertebral fractures at entry, and then randomised to receive either placebo or one of two doses of raloxifene • All women received calcium, 500 mg, + vitamin D_3, 400–600 IU, daily • Participants required to discontinue study if BMD decreased by at least 7% in lumbar spine or 10% in femoral neck at 1 year, or at least 11% and 14%, respectively, at 2 years, or if at any time during study they experienced more than two incident vertebral fractures. As women were at high risk of non-vertebral fracture, and more women removed from placebo than from intervention group for this reason, this may have decreased study's ability to detect statistically significant result in relation to non-vertebral fractures • By 36 months, 1804 women (23.4%) had withdrawn from study – 652 (25.3%) from placebo and 1152 (22.5%) from raloxifene groups. However, baseline and follow-up radiographs available for 6828 women (88.6%) • In all, 144 women (1.9%) discontinued study because of multiple fractures or excessive loss of BMD, 94 (3.6%) from pooled placebo and 50 (1.0%) from pooled raloxifene groups; 754 (9.8%) withdrew because of adverse events, 227 (8.8%) from pooled placebo and 527 (10.3%) from pooled raloxifene groups (p = 0.4) • Full baseline characteristics not provided separately for all 7705 participants as randomised to all six arms of study but only for those women with evaluable radiographs at 36 months, by study group subdivided into pooled raloxifene and placebo groups. Full baseline characteristics for all participants given but subdivided only into pooled placebo and pooled raloxifene groups[a] • Only incident fractures in vertebrae that were not fractured at baseline included in results • Venous thromboembolic events were only serious adverse effects considered to be causally related to raloxifene treatment. By 40 months, they were reported by eight (0.3%) patients in placebo, 25 (1.0%) in 60 mg and 24 (1%) in 120 mg raloxifene groups, RR = 3.1 (95% CI, 1.5 to 6.2) in combined treatment compared with placebo group • Breast cancer less common in combined treatment than in placebo group (RR = 0.3; 95% CI, 0.2 to 0.6) • Statistically non-significant trend towards reduced rate of non-traumatic non-vertebral fractures in pooled raloxifene compared with control group, led to study being continued for further year • 92% of women took more than 80% of study medication; no difference between groups in compliance terms

[a] *Additional information from: Cummings*, et al., *1999*

SERMs *contd*

Study	Lufkin, 1998[178]
Setting	USA
Date of intervention	Not specified
Source of funding	Eli Lilly
Design	Randomised, double-blind
Study population	Postmenopausal women, aged between 45 and 75 years, with established osteoporosis (low BMD and at least one non-traumatic vertebral fracture)
Recruitment procedure used	Not specified
Number of patients	143
Length of study	1 year
Main intervention/s	Raloxifene, 60 mg or 120 mg
Primary outcome measures	BMD Biochemical markers Adverse events
Secondary outcome measures	Proportion of women with one or more new non-traumatic vertebral fractures Number of new atraumatic non-vertebral fractures Effects on cognitive function and mood
Definition of incident vertebral fracture	At least 15% decrease in one or more of anterior, posterior, left lateral and right lateral vertebral heights compared with baseline
Results: vertebral fracture	Using fracture definition of decrease of at least 15% in vertical height, no significant difference seen between raloxifene and control groups in numbers of patients suffering incident vertebral fractures: 21 (44%), 20 (43%) and 18 (38%) in 60 mg, 120 mg and control groups, respectively. However, using definition of at least 30% decrease, significant dose-dependent reduction seen, with eight (17%), four (9%) and 13 (27%) patients suffering fractures in 60 mg, 120 mg and control groups, respectively ($p = 0.047$)
Results: non-vertebral fracture	No significant difference between the groups
Quality score	11/18
Comments	• Groups generally comparable at baseline except for minor but statistically significant differences in age and alcohol usage. Thus, control group, although falling between other two groups in age, had notably higher level of alcohol usage • All women received elemental calcium, 750 mg daily, plus vitamin D supplements to bring daily intake to 800 IU • Although 13 women (8.9%) withdrew from study, groups from which they withdrew not identified. Eight (5.4%) withdrew due to adverse events but none considered drug-related; no significant differences between groups in numbers of adverse events reported • Study not designed to have enough statistical power to detect differences in fracture rate • No major drug-related side-effects or adverse events reported. Of minor symptoms and signs, only arthralgia ($p = 0.027$) and dizziness ($p = 0.024$) significantly more frequent in raloxifene groups • Raloxifene significantly decreased serum low-density/high-density lipoprotein cholesterol ratio

Exercise

Study	Ebrahim, 1997[187]
Setting	England
Date of intervention	Not specified
Source of funding	Wolfson Family Trust
Design	Randomised, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (upper limb fracture in past 2 years)
Recruitment procedure used	Letters of invitation to consecutive suitable women identified from registers of Accident & Emergency departments and orthopaedic fracture clinics of two East London hospitals
Number of patients	165
Length of study	2 years
Main intervention/s	Brisk walking, building to 40 minutes three times weekly
Primary outcome measure	BMD
Secondary outcome measures	Fall frequency Radiographically-identified vertebral fractures Clinical fractures
Definition of incident vertebral fracture	Difference of 25% between anterior and posterior vertebral heights
Results: vertebral fracture	No significant difference between treatment and control groups
Results: non-vertebral fracture	–
Quality score	12/18
Comments	• All patients received advice about general health and balanced diet • Control group performed upper limb exercises • Acceptability of intervention low – only 165 of 508 women contacted (32.5%) agreed to take part, and only 97 (19.1%) completed 2 years. However, study took place in relatively poor inner-city population and may not be typical of other areas • Of 165 women participated, 68 (41%) did not complete 2 years. Drop-outs said to be evenly distributed between brisk walking and control groups. Reasons for withdrawal after randomisation given as unwillingness to continue (24%), illness (6%), death (1%), exercise-related trauma (1%) and other unspecified difficulties (9%) • Women who dropped out tended to be less physically fit than others; thus those patients may have been lost who would have benefited most from intervention [a] Compliance with walking self-reported by those who completed study as good, but could not be validated • Brisk walking group experienced more falls than control group (an excess of 15.2 falls/100 person years over course of study) • Following intervention, no significant differences seen between groups' Nottingham Health Profile scores. However, brisk walking group showed greater improvements in stamina

Protein supplements

Study	Schurch, 1998[186]
Setting	Switzerland
Date of intervention	April 1992
Source of funding	Sandoz Nutrition Ltd Swiss National Research Science Foundation
Design	Randomised, double-blind, placebo-controlled, with 6-month post-treatment follow-up
Study population	Men and women, aged over 60 years, with recent osteoporotic hip fracture
Recruitment procedure used	Patients in orthopaedic ward of Geneva Hospital
Number of patients	82
Length of study	6 months with 6-month post-treatment follow-up
Main intervention/s	Oral protein supplement
Primary outcome measures	Insulin-like growth factor-1 levels and other biochemical data BMD
Secondary outcome measures	Vertebral deformity Length of hospital stay Function
Definition of incident vertebral fracture	Decrease of more than 20% in anterior, middle or posterior vertebral height from baseline
Results: vertebral fracture	Trend to fewer vertebral fractures in treatment group was not statistically significant
Results: non-vertebral fracture	–
Quality score	13/15
Comments	• All patients received single oral 200,000 IU dose of vitamin D_3 • Of 19 patients (23%) who withdrew from trial or died during 6-month intervention period, 11 (26.8%) were from treatment and eight (19.5%) from control group. Further eight (9.8%) dropped out or died during 6-month follow-up period, six (14.6%) from treatment, two (4.9%) from control group • Treatment well tolerated; no major side-effects • Four patients (9.8%) withdrew from each group because of nausea, and two (4.9%) from treatment and one (2.4%) from control group because of diarrhoea • Treatment group stayed in orthopaedic ward for 18.0 ± 1.4 days post surgery, and control group 16.9 ± 0.9 days, but after transfer to rehabilitation hospitals, median stay in treatment group was 21 days shorter than control group (p = 0.018)

Vitamin K_2

Study	Shiraki, 2000[68]
Setting	Japan
Date of intervention	Not stated
Source of funding	Not stated
Design	Randomised, open-label, placebo-controlled
Study population	Ambulatory women with osteoporosis (lumbar BMD < 70% of young adult mean, or with one or more non-traumatic vertebral fractures and lumbar BMD < 80% of young adult mean)
Recruitment procedure used	Patients with osteoporosis registered with Research Institute and Practice for Involutional Disease, Nagano, Japan
Number of patients	241
Length of study	2 years
Main intervention/s	Vitamin K_2
Primary outcome measures	Lumbar BMD Vertebral fracture
Secondary outcome measures	Biochemical markers Non-vertebral fracture
Definition of incident vertebral fracture	Decrease of 20% or more in anterior, middle or posterior vertebral height from baseline
Results: vertebral fracture	Thirteen vertebral fractures in 77 women in vitamin K_2 group compared with 30 in 64 women in control group
Results: non-vertebral fracture	One non-vertebral fracture in 77 women in vitamin K_2 group compared with five in 64 women in control group
Quality score	12/18
Comments	• Patients in both arms received elemental calcium, 150 mg daily • Patients not given any specific instructions regarding daily calcium, vitamin D or vitamin K intake, or exercise; and prohibited from taking any other drugs that affected bone or calcium metabolism during study period • Only 190 women had X-rays at 24 months, allowing them to be included in fracture analysis. No information why such data not available for remaining 51 women – 29 (24.2%) from vitamin K_2 and 22 (18.2%) from control group • Combined incidence of vertebral and non-vertebral fractures significantly (p = 0.0273) lower in vitamin K_2 than in control group • No information on side-effects or adverse events, if any

Comparisons with active treatments

Study	Abellan Perez, 1995[139]
Setting	Spain
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label RCT
Study population	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral crush fracture)
Recruitment procedure used	Through outpatient rheumatology clinics at 12 hospitals
Number of patients	88
Length of study	1 year
Main intervention/s	Intranasal synthetic salmon calcitonin and calcium compared with larger dose of calcium
Primary outcome measures	Pain New vertebral fractures
Secondary outcome measures	Limitation of movement Biochemical parameters
Definition of incident vertebral fracture	Meunier's index of spinal deformity
Results: vertebral fracture	Authors claimed statistically significant ($p < 0.001$) reduction in rate of vertebral fracture in intervention group; however, data presented in such a way that precise extent of reduction not clear
Results: non-vertebral fracture	–
Quality score	10/15
Comments	• Both intervention and control groups received elemental calcium: intervention group received 500 mg for 14/28 days and control group received 1000 mg daily throughout • Significant reductions in intensity of pain, limitation of action by pain, and analgesic use in intervention group • Only one woman from intervention group (2.3%) is stated to have withdrawn, as result of arterial hypertension which might have been treatment-related. However, other participants may have withdrawn for other reasons • Other side-effects were mild: one case of flushing and three gastrointestinal problems

Study	Adami, 1995[93]
Setting	Italy
Date of intervention	Not specified
Source of funding	Not specified
Design	RCT, double-blind between alendronate and placebo, with open-label calcitonin arm
Study population	Postmenopausal women with osteoporosis (lumbar T-score > –2), 5% of whom had vertebral fracture at entry
Recruitment procedure used	Not specified
Number of patients	286
Length of study	2 years
Main intervention/s	Alendronate Intranasal salmon calcitonin
Primary outcome measures	BMD (spine)
Secondary outcome measures	BMD (hip) Biochemical indices of bone turnover
Definition of incident vertebral fracture	Not applicable: only clinically apparent fractures were recorded
Results: all fractures	No significant trends noted between treatment groups in relation to number of fractures
Quality score	9/15
Comments	• Alendronate arm placebo-controlled but not calcitonin arm because intranasal placebo not available • Blinding not possible in relation to calcitonin arm and, although assessors of BMD scans blinded to treatment allocation, no such assurance given for fracture outcomes • All patients received elemental calcium, 500 mg daily • Of 41 women (14.3%) who withdrew from treatment, 15 (5.2%) were due to adverse events • Analysis was on an ITT basis • All treatment groups similar to placebo with regard to both overall safety profile and upper gastrointestinal adverse events • Quality score low because of lack of information, partly about method of randomisation but more about methods used to identify and confirm fractures. However, study not designed to detect significant differences in fracture rates, and fracture data only collected as part of adverse event reporting. It is thus perhaps unreasonable to expect such detail to have been provided

Comparisons with active treatments *contd*

Study	Arthur, 1990[190]
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	Randomised trial
Study population	Elderly postmenopausal women with radiographic evidence of osteopaenia; 40% had vertebral compression fractures at entry
Recruitment procedure used	Not specified
Number of patients	Fourteen in randomised study, plus four age-matched normal individuals
Length of study	1 year
Main intervention/s	Low-dose calcitriol compared with vitamin D_2
Primary outcome measures	BMD
Secondary outcome measures	Biochemical analyses Vertebral fractures
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	No-one in either group developed new compression fractures, even though each group contained two women with prevalent fractures and at high risk of new fractures
Results: non-vertebral fracture	No-one in either group suffered non-vertebral fracture
Quality score	7/15
Comments	• Initial dose of calcitriol was 0.25 µg/day, increased to 0.25 µg twice daily if (? blood or urine) calcium level remained at 10 mg/dl or less. By end of study, all patients in calcitriol group taking 0.25 µg twice daily • Patients in vitamin D_2 group received 50,000 units orally twice weekly • All patients received elemental calcium, 1 g daily • Patients not placed on calcium-restricted diet • Only data relating to two randomised treatment groups considered here • Three women (21.4%) withdrew: one from calcitriol group; two from vitamin D_2 group. Another woman (group unknown) excluded from analysis due to osteomalacia • Baseline characteristics only given for ten women who completed randomised study; no information given regarding comparability of all groups at entry • Combination of calcitriol and calcium can lead to hypercalciuria, hypercalcaemia and renal failure. Significant hypercalciuria observed in both groups and transient hypercalcaemia in one individual in vitamin D_2 group. However, patients' renal functions did not decline significantly over course of study

Comparisons with active treatments *contd*

Study	Birkenhager, 1992[164]
Setting	The Netherlands
Date of intervention	1986–
Source of funding	Organon Nederlands BV
Design	Single-blind RCT
Study population	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral compression fracture) or osteopaenia (lumbar BMD > 2 SD below normal mean of age-matched controls) (86% had fractures)
Recruitment procedure used	Not specified
Number of patients	43
Length of study	2 years
Main intervention/s	Intermittent intramuscular nandrolone decanoate + HRT compared with HRT alone
Primary outcome measures	BMD Biochemical markers
Secondary outcome measures	Vertebral fracture Phoniatrics
Definition of incident vertebral fracture	Reduction in anterior and/or mid-vertebral height of at least 20% of posterior height, or reduction of at least 20% in posterior height of one or both adjacent vertebral bodies
Results: vertebral fracture	Mean number of deformed vertebrae per individual did not increase significantly in either group
Results: non-vertebral fracture	–
Quality score	11/15
Comments	• Patients whose dietary history suggested that this necessary received oral calcium supplements up to total of at least 1000 mg/day • Seven women (16.7%) withdrew from study, five because of voice problems and two because of extent of uterine bleeding. Not stated from which groups they withdrew • Number of patients too small and follow-up too short to produce statistically significant results in relation to vertebral fracture • Substantially higher proportion of patients in nandrolone group than in control group complained of vocal changes ($p < 0.01$); these confirmed by logopaedic evaluation. Not clear whether changes would prove to be reversible • No patients complained of increased hair growth, whether facial or other • Total serum cholesterol unchanged in nandrolone but fell in control group; high density lipoprotein cholesterol fell in nandrolone but unchanged in control group • Potential for confounding not clear as baseline data only provided for some of patients in each group; hence, comparability at entry cannot be determined

Comparisons with active treatments *contd*

Study	Ebeling, 1998[70]
Setting	Australia
Date of intervention	Not specified
Source of funding	Not specified
Design	Randomised, double-masked, double-placebo controlled trial
Study population	Men with moderately severe idiopathic osteoporosis (at least one vertebral fragility fracture)
Recruitment procedure used	Not specified
Number of patients	Specified as both 39 and 41
Length of study	2 years
Main intervention/s	Calcitriol compared with calcium
Primary outcome measures	Vertebral fractures Spinal BMD
Secondary outcome measures	Non-vertebral fractures
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Significantly more patients in one arm than in other suffered vertebral fracture
Results: non-vertebral fracture	Six non-vertebral fragility fractures in one arm and none in other
Quality score	8/18
Comments	• Published in abstract form only • Abstract presents groups in masked form only • Five patients withdrew from study. It was not stated from which arm they withdrew

Study	Falch, 1987[191]
Setting	Norway
Date of intervention	Not specified
Source of funding	Not specified
Design	Single-blind RCT
Study population	Postmenopausal women with recently sustained fracture of distal left forearm
Recruitment procedure used	Not specified
Number of patients	86
Length of study	3 years
Main intervention/s	Calcitriol compared with vitamin D_3
Outcome measures	Bone mass Vertebral fractures Fractures of long bones
Definition of incident vertebral fracture	Each vertebra compared with nearest cranial vertebra. If anterior wedging or middle depression was < 85% of cranial vertebra, vertebra assigned fracture score of 1; if both measurements < 85%, fracture score was 2
Results: vertebral fracture	No significant difference between treatment groups
Results: non-vertebral fracture	No significant difference between treatment groups
Quality score	13/18
Comments	• Patients' allocation known to clinician in charge of study but not to those evaluating their skeletal status • Ten women (11.6%) withdrew, eight (17.0%) from calcitriol group and two (5.1%) from vitamin D_3 group, none because of drug-related adverse effects • Initial dose of calcitriol, 0.50 µg daily, halved if total serum calcium exceeded 2.65 mmol/L. This necessary in 11 women (28%)

Comparisons with active treatments *contd*

Study	Fujita, 1992[64]
Setting	Japan
Date of intervention	1984–90
Source of funding	Not specified
Design	Randomised, open-label, controlled
Study population	Women with established osteoporosis (at least one non-traumatic vertebral fracture)
Recruitment procedure used	From patients with established osteoporosis consulting medical outpatient clinic of Kanebo Memorial Hospital
Number of patients	32
Length of study	Not specified
Main intervention/s	Alfacalcidol, with and without low-dose, intermittent, elcatonin (eel calcitonin derivative)
Primary outcome measures	Vertebral fractures
Secondary outcome measures	–
Definition of incident vertebral fracture	Decrease of 20% in ratio of anterior or middle height of vertebral body (whichever is larger) and posterior height of same or adjacent vertebra (whichever is larger)
Results: vertebral fracture	Low-dose intermittent elcatonin failed to reduce rate of vertebral fractures. Alfacalcidol appeared effective, with effect augmented by simultaneous administration of elcatonin, but too few patients to reach a definite conclusion
Results: non-vertebral fracture	–
Quality score	11/15
Comments	• Patients not given calcium supplements; calcium intake averaged 400–500 mg/day • Starting dose of alfacalcidol 0.75 µg/day. This increased stepwise to 1.5 µg as long as urinary Ca/Cr stayed below 0.4. When exceeded 0.4, alfacalcidol temporarily discontinued, and then restarted at lower dose • No specific physical therapy prescribed but adequate exercise recommended for all patients • Two patients (6.3%) withdrew, both from alfacalcidol group (25% of group) • Study quasi-randomised, patients being allocated to groups on basis of date of first visit • Groups only approximately homogeneous in relation to age and number of vertebral deformities at baseline • Conducted from 1984 to 1990; mean duration of interventions not specified

Comparisons with active treatments *contd*

Study	Fujita, 1993[58]
Setting	Japan
Date of intervention	Not specified
Source of funding	Not specified
Design	Multicentre, double-blind placebo-controlled
Study population	Patients with postmenopausal or senile osteoporosis (scoring 4 points or more on diagnostic criteria proposed by Osteoporosis Study Groups of Japanese Ministry of Health and Welfare for diagnosis of involutional osteoporosis
Recruitment procedure used	Not specified
Number of patients	414
Length of study	48 weeks
Main intervention/s	Etidronate (compared with alfacalcidol)
Primary outcome measures	Lumbar vertebral mineral density
Secondary outcome measures	Incidence of vertebral fractures Biochemical parameters Pain relief
Definition of incident vertebral fracture	Not given in abstract
Results: vertebral fracture	Patients in two etidronate groups had fewer fractures than alfacalcidol comparison group
Results: non-vertebral fracture	–
Quality score	6/15
Comments	• Quality score very low because no translation of article available and hence data could only be extracted from abstract. Paper is long and appears detailed; it is therefore possible that quality score would increase considerably were it possible to extract full data • Some uncertainty about comparability of different arms of study. One etidronate group appeared more severely osteoporotic than other; not specified how compared with alfacalcidol group

Study	Gallagher, 1990b[74]
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	RCT
Study population	Men and women with established idiopathic spinal osteoporosis (at least one vertebral fracture)
Recruitment procedure used	Not specified
Number of patients	40
Length of study	At least 3 years
Main intervention/s	Comparison of fluoride + calcium with fluoride + calcitriol
Outcome measures	Hyperosteoidosis Total body calcium Vertebral fracture Hip fracture
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Incidence at end of first year = 60% in each arm
Results: non-vertebral fracture	Incidence during first 18 months = 6% overall
Quality score	6/18
Comments	• Abstract only • Patients included 35 women and five men. No information given on groups to which randomised • No information given on baseline characteristics at entry • At time of writing, 31 patients completed 1 year of therapy, 20 2 years and 13 3 years

Comparisons with active treatments *contd*

Study	Geusens, 1986[63]
Setting	Belgium
Date of intervention	Not specified
Source of funding	Supply of drugs only: Organon International; Organon Belgium; Leo Pharmaceutical, Belgium/Denmark; Sandoz, Basle, Switzerland
Design	Double-blind, randomised, placebo-controlled trial
Study population	Men and women with established osteoporosis (at least one vertebral fracture)
Recruitment procedure used	Consecutive patients admitted to unit because of vertebral collapse without trauma
Number of patients	60
Length of study	2 years
Main intervention/s	Intermittent intramuscular nandrolone decanoate compared with alfacalcidol and with intermittent intravenous calcium infusions
Primary outcome measures	Bone mineral content Cortical bone volume Vertebral fracture rate Biochemical variables
Secondary outcome measures	Non-vertebral fractures
Definition of incident vertebral fracture	Clear change (> 20%) in shape of anterior, middle or posterior part of vertebra
Results: vertebral fracture	Statistically nonsignificant trend to lower fracture rates in second year of treatment in nandrolone compared with alfacalcidol and intermittent calcium infusion groups. Vertebral fracture rate 40% lower in nandrolone than in other groups 2 years after end of treatment but, again, not statistically significant
Results: non-vertebral fracture	–
Quality score	10/15
Comments	• Of 26 patients (43%) who withdrew from study, one withdrew from each group because of 'subjective tolerance without organic side-effects'. Remainder, not attributed to treatment groups, withdrew because of intercurrent illness or discontinuation of treatment • Potential for confounding not clear as baseline data only provided for patients who completed study; hence, comparability of groups at entry cannot be determined. Of patients completing trial, those in calcium group significantly older than other two groups • No serious side-effects reported or noted; no signs of virilisation or disturbance of liver function in nandrolone group

Study	Guañabens, 1996[75]
Setting	Spain
Date of intervention	Not specified
Source of funding	Not specified
Design	Randomised trial
Study population	Women with established postmenopausal osteoporosis (mean lumbar BMD T-score –3.2 SD + at least one atraumatic vertebral fracture)
Recruitment procedure used	Not specified
Number of patients	125
Length of study	2 years
Main intervention/s	Fluoride compared with cyclic etidronate
Primary outcome measures	Bone mass Vertebral fracture
Secondary outcome measures	Non-vertebral fracture
Definition of incident vertebral fracture	Definition not given
Results: vertebral fracture	More patients in etidronate than in fluoride group had new vertebral fractures (26 fractures in 11 women versus nine in seven women); not statistically significant
Results: non-vertebral fracture	Rate of non-vertebral fracture said to be similar in both groups; figures not given
Quality score	7/18
Comments	• Abstract form only • All patients also took calcium, 1 g, 'regularly' • Of 36 women (28.6%) who withdrew from study, 21 (35%) were from fluoride and 15 (22.7%) from etidronate group • Four withdrawals from fluoride group due to stress fractures and eight to gastrointestinal symptoms; no withdrawals from etidronate group attributed to either cause

Comparisons with active treatments *contd*

Study	Gutteridge, 1996[79]
Setting	Australia
Date of intervention	1989–[a]
Source of funding	Australian National Health and Medical Research Council Medical Research Fund of Western Australia
Design	Open-label, randomised, two-centre, controlled
Study population	Postmenopausal women aged under 80 years with established osteoporosis (at least one vertebral fracture but no hip fracture)
Recruitment procedure used	Not specified
Number of patients	100
Length of study	27 months
Main intervention/s	Intermittent cyclic enteric-coated sodium fluoride, with or without HRT
Outcome measures	BMD Vertebral fractures
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Interim results only available. In non-HRT groups, significantly more patients in fluoride than control group suffered vertebral fractures (83% versus 36%, $p = 0.004$). Differences more marked in first 9-month cycle than second (24% versus 0%). In HRT groups, fewer patients in fluoride than control group suffered such fractures (29% versus 56%) but not statistically significant; difference most marked in first cycle (28% versus 0%)
Results: non-vertebral fracture	Eight women (18%) in fluoride and none in control groups suffered stress fractures, mostly (6/8) below knee
Quality score	6/18
Comments	• All patients received calcium, 1 g daily, + vitamin D_2, 0.25–0.5 mg (10,000–20,000 IU) weekly • Initial dose of sodium fluoride, 60 mg;[a] could be reduced or increased (to maximum of 80 mg/day) depending on vertebral radiographic and densitometric response • Of 100 patients, 35 on HRT at entry continued; randomised separately from those not on HRT • Patients not on HRT had not previously received treatment for osteoporosis (other than calcium) • Patients 'randomly adaptively assigned' to treatment • No information given on comparability of treatment and control groups at entry • Twelve women (12%) withdrew, five (14%) from HRT and seven (11%) from non-HRT groups; no reasons given

[a] *Additional information from: Gutteridge, 1993*[80]

Study	Leidig-Bruckner, 1997[76]
Setting	Germany
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, randomised
Study population	Postmenopausal women with established osteoporosis (at least one vertebral fracture)
Recruitment procedure used	Not specified
Number of patients	38
Length of study	Mean follow-up 4.7 ± 1.6 years
Main intervention/s	Sodium fluoride alone or with either HRT or nandrolone decanoate
Outcome measures	BMD Vertebral fractures
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Progression of vertebral fractures not different between groups, but highly related to severity of fracture status at beginning of therapy
Results: non-vertebral fracture	–
Quality score	7/15
Comments	• Abstract form only • All patients received calcium, 1000 mg, and vitamin D, 3000 IU, daily • Nandrolone decanoate given for 2 years; implied but not stated that other interventions given for at least 4 years • Three women (7.9%) withdrew from study; not clear from which groups they withdrew

Comparisons with active treatments *contd*

Study	Lems, 1997[192]
Setting	The Netherlands
Date of intervention	July 1991–
Source of funding	Dutch League against Rheumatism Christiansen (supplier of sodium fluoride and placebo)
Design	Randomised, double-blind, placebo-controlled
Study population	Men and women with established corticosteroid-induced osteoporosis (vertebral deformity, prior peripheral fracture or both)
Recruitment procedure used	Hospital departments of rheumatology and clinical immunology, nephrology and pulmonology
Number of patients	47
Length of study	2 years
Main intervention/s	Cyclical etidronate with or without enteric-coated sodium fluoride
Primary outcome measures	BMD
Secondary outcome measures	Vertebral fractures Peripheral fractures Biochemical markers
Definition of incident vertebral fracture	Decrease of 15% in anterior, middle or posterior vertebral height relative to baseline. Clinical vertebral deformity defined as vertebral deformity causing clinical manifestations leading to prescription of therapy (bed rest, analgesia or both)
Results: vertebral fracture	Seven patients in fluoride and four in control group suffered vertebral fractures. Difference between groups not statistically significant
Results: non-vertebral fracture	Eight patients in fluoride and five in control group suffered non-vertebral fractures. Difference between groups not statistically significant
Quality score	11/18
Comments	• All received cyclical etidronate for 2 weeks followed by 11 etidronate-free weeks • All received supplement of elemental calcium, at least 500 mg daily; those with low dietary calcium intake received 1000 mg • Patients with serum 25 hydroxyvitamin D concentration below 10 µg/L in winter and 15 µg/L in summer, received vitamin D (dihydrotachysterol, 0.2 mg, on alternate days) • All took prednisone, at least 7.5 mg daily, at start of study and were expected to continue for at least 6 months • Seven women (14.9%) withdrew from study, three (13.0%) from fluoride and four (16.7%) from control group: one from fluoride and two from control group did not wish to travel for BMD measurement; two from control group because of other severe diseases, one from fluoride group because of incomplete fractures at knee and another died of pulmonary embolism • No patient in fluoride group reported gastrointestinal complaints • Lower extremity pain syndrome reported by only one patient taking fluoride • Lumbar spine BMD significantly lower in fluoride than control group, approximately doubling risk of fracture in intervention group

Study	Lyritis, 1994[166]
Setting	Greece
Date of intervention	Not specified
Source of funding	Not specified
Design	Randomised, placebo-controlled
Study population	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral collapse)
Recruitment procedure used	Not specified
Number of patients	88
Length of study	1 year
Main intervention/s	Intramuscular nandrolone decanoate compared with alfacalcidol
Primary outcome measures	Incidence of vertebral fractures BMD Symptoms (pain, mobility)
Secondary outcome measures	Biochemical markers
Definition of incident vertebral fracture	Meunier–Vignon index
Results: vertebral fracture	No recent vertebral fractures in either group
Results: non-vertebral fracture	–
Quality score	9/15
Comments	• Number of withdrawals not specified • Nandrolone improved pain and mobility significantly more than alfacalcidol

Comparisons with active treatments *contd*

Study	**Mamelle, 1988**[176]
Setting	France
Date of intervention	Recruitment: November 1984–December 1985
Source of funding	Merck-Clevenot Laboratories INSERM
Design	Large, open-label RCT
Study population	Men and women with established primary vertebral osteoporosis (at least one non-traumatic vertebral crush fracture)
Recruitment procedure used	Patients consulting one of 94 physicians who agreed to participate
Number of patients	466
Length of study	2 years
Main intervention/s	Sodium fluoride, calcium and vitamin D_2 compared with other regimes prescribed by French physicians
Primary outcome measures	Vertebral fractures
Secondary outcome measures	Side-effects (including non-vertebral fractures)
Definition of incident vertebral fracture	Deformation of normal vertebra to biconcave one, a fracture plate, or wedging or collapse of vertebral body
Results: vertebral fracture	Of patients who could be followed-up for 24 months, 39.2% of fluoride group had one or more new vertebral fractures compared with 50.8% of control group ($p < 0.05$)
Results: non-vertebral fracture	Of those patients who could be followed up for 24 months, 12.8% of fluoride group had one or more new non-vertebral fractures compared with 12.5% of control group
Quality score	11/18
Comments	• Approximately 10% of patients in both groups were male • Fluoride group received elemental calcium, 1 g, + vitamin D_2, 800 IU, daily • Control group received following treatments: – calcium, 1 g, + vitamin D_2, 800 IU, daily ($n = 95$) – calcitonin, 500 U daily, for 5 days/3 weeks, + phosphorus, 1–1.5 g daily ($n = 85$) – calcitonin + calcium ($n = 12$) – calcium + phosphorus ($n = 17$) – phosphorus + sodium etidronate, taken for 5 days/3 weeks ($n = 2$) • In all, 240 patients (51.5%) did not continue treatment for full 24 months, although some were followed-up for full period: 128 (49.8%) from fluoride and 112 (53.6%) from control group. In fluoride group, 24 patients (9%) discontinued treatment because of intolerance, together with 17 (8%) from control group; remainder withdrew because of death, intercurrent disease, aggravation of vertebral osteoporosis, or personal reasons unrelated to treatment, or were lost to follow-up • In all, 316 patients (68%) were followed-up for full 24 months • No significant difference between two groups in relation to osteo-articular pain, non-vertebral fractures, gastrointestinal disorders and other side-effects, although pain in lower limbs more often located in ankle and foot in fluoride group than control group (15% versus 5%, $p < 0.01$). However, full details of side-effects only given for patients who completed 24 months of treatment; these patients may have suffered lower rate of side-effects than those who withdrew from study. In total sample, side-effect data presented only as RRs and, when adjusted for previous osteo-articular symptoms, indicated that for osteo-articular pain, RR = 0.73 in control versus fluoride group – not statistically significant ($p = 0.07$); however, for ankle and foot pain, RR = 0.34 in control group – statistically significant ($p = 0.01$)

Comparisons with active treatments *contd*

Study	Pacifici, 1988[104]
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label RCT
Study population	White women with osteoporosis or osteopenia (at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation)
Recruitment procedure used	Women attending hospital for osteoporosis screening
Number of patients	128
Length of study	2 years
Main intervention/s	Cyclical potassium phosphate followed by etidronate Conjugated oestrogens and medroxyprogesterone acetate
Primary outcome measures	Bone mineral content
Secondary outcome measures	Incident vertebral fractures Total vertebral height loss Biochemical measures
Definition of incident vertebral fracture	Compression fractures: loss of posterior height greater than 15% compared with mean of posterior height of nearest (above and below) intact vertebrae Wedging and biconcave fractures: loss of anterior and central height greater than 20% compared with posterior height of same vertebra
Results: vertebral fracture	Incidence of vertebral fractures almost identical in all three groups. However, total vertebral height loss in hormone-treated group significantly lower (7.5 ± 4.4%, $p < 0.05$) than in etidronate (13.6 ± 10.6%) and control (20.8 ± 20.2%) groups, which not significantly different from each other
Results: non-vertebral fracture	–
Quality score	8/15
Comments	• All patients received calcium, 1000 mg daily • In all, 58 women (45%) withdrew from study. Numbers of withdrawals said to be evenly distributed between three groups. Reasons: financial problems, geographical relocation, loss of interest and dissatisfaction with results of treatment; however, numbers citing reasons not given • Baseline characteristics not presented in relation to 35 women who dropped out during first year of study; no information on comparability of all groups at entry • Significant side-effects said to occur only in hormone group; consisted primarily of pelvic congestion and cyclic bleeding; number affected not specified

Comparisons with active treatments *contd*

Study	Pak, 1989[193]
Setting	USA
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label, randomised trial
Study population	Men and women with osteoporosis or osteopaenia (fractures, low BMD or radiological evidence of osteopaenia) (98% had vertebral or peripheral fractures)
Recruitment procedure used	Not specified
Number of patients	44
Length of study	Maximum of 5.5 years
Main intervention/s	Intermittent slow release sodium fluoride, with or without preceding high dose of 1,25-dihydroxyvitamin D
Outcome measures	BMD Vertebral fractures Non-vertebral fractures Bone biopsy
Definition of incident vertebral fracture	Reduction of more than 15% in vertebral heights
Results: vertebral fracture	Vertebral fracture rates significantly reduced in both arms of study, especially after 1 year of treatment, compared with same patients prior to intervention. Fracture rates lower in group not receiving 1,25-dihydroxyvitamin D than in group receiving it, although former group had history of more fractures than latter
Results: non-vertebral fracture	One hip fracture in 1,25-dihydroxyvitamin D group and two other fractures in group not receiving it
Quality score	15/18
Comments	• Each group contained three men • 1,25-dihydroxyvitamin D group took it for first 2 weeks of 5-month cycle, in conjunction with a low calcium diet • For last 6 weeks of 5-month cycle, all patients took 25-hydroxyvitamin D, 50 µg twice weekly, together with calcium supplements to bring daily calcium intake to 1500 mg daily • 1,25-dihydroxyvitamin D group underwent treatment for mean of 2.7 years; group not receiving 1,25-dihydroxyvitamin D for mean of 3.1 years. Apparently only one or at most two patients in each group completed full 5 years. No reasons given for discontinuation of treatment • Baseline fracture rate higher in group not receiving 1,25-dihydroxyvitamin D than in group receiving drug • Patients originally took sodium fluoride between meals. About 10% complained of nausea; this overcome by taking it with crackers or bread • Overall, 15.9% of patients had adverse gastrointestinal or rheumatic reactions. Foot and hip pain relieved by halving dose of sodium fluoride

Comparisons with active treatments *contd*

Study	Rozhinskaya, 1999[72]
Setting	Russia
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label RCT
Study population	Women with established steroid-induced osteoporosis (at least two vertebral fractures + T-score < –2.5 at spine or femur neck)
Recruitment procedure used	Not specified
Number of patients	22
Length of study	1 year
Main intervention/s	Monofluorophosphate + calcium, with and without alfacalcidol, compared with alfacalcidol alone
Outcome measures	BMD Vertebral fractures Back pain
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Two women (17%) in pooled fluoride groups suffered vertebral fractures, as did two (20%) in group receiving alfacalcidol alone; no statistically significant difference between fluoride and non-fluoride groups
Results: non-vertebral fracture	–
Quality score	6/15
Comments	• Patients in fluoride arms received calcium, 450 mg daily • No information given on number of withdrawals • Back pain significantly reduced in both fluoride groups but not in group taking alfacalcidol alone • All side-effects mild and transient – only one woman from fluoride groups refused to continue treatment because of nausea and arthralgia

Study	Shiota, 1998[194]
Setting	Japan
Date of intervention	Not specified
Source of funding	Not specified
Design	Randomised trial
Study population	Women over 50 suffering from senile or postmenopausal osteoporosis (BMD less than 0.70 g/cm^2)
Recruitment procedure used	Consecutive patients with diagnosis of osteoporosis visiting hospital complaining of lumbodorsal pain
Number of patients	158 or 195
Length of study	2 years
Main intervention/s	Ipriflavone; elcatonin; alfacalcidol + calcium; alfacalcidol + ipriflavone + calcium
Primary outcome measures	BMD
Secondary outcome measures	Vertebral fracture
Definition of incident vertebral fracture	Criteria of Japanese Society of Bone Mineral Research
Results: vertebral fracture	Number of fractures increased in all groups but only significantly in ipriflavone and alfacalcidol + calcium groups
Results: non-vertebral fracture	–
Quality score	6/15
Comments	• Inconsistent numbers of patients given, either 158 (53, 21, 61 and 23, respectively, in four groups) or 195 (62, 25, 78 and 30, respectively) • Not clear whether groups, as randomised, comparable: data refer only to 73 patients who completed at least 18 months but these not fully comparable in terms of age and BMD • Only 73 women could be followed-up until at least 18 months. Reasons for withdrawal not given; compliance claimed to be relatively good in all groups except alfacalcidol + ipriflavone + calcium group • Author argues that, as overall vertebral fracture rate only 397/1000 patient-years, compared with 760/1000 in untreated patients in another Japanese study; treatments all suppressed incidence of such fractures

Comparisons with active treatments *contd*

Study	Shiraki, 1999[195]
Setting	Japan
Date of intervention	September 1995–August 1997
Source of funding	Banyu Pharmaceutical Company Ltd (Tokyo, Japan) Teijin Ltd (Tokyo, Japan)
Design	Double-blind, multicentre RCT
Study population	Women with primary osteoporosis (lumbar T-score < –2.5, or < –1.5 with one or more vertebral fractures)
Recruitment procedure used	Through 69 departments of 63 medical institutions and hospitals in Japan
Number of patients	210
Length of study	48 weeks
Main intervention/s	Alendronate compared with alfacalcidol
Primary outcome measures	Effect on lumbar BMD
Secondary outcome measures	Bone turnover markers Adverse effects Vertebral fracture
Definition of incident vertebral fracture	Not given
Results: vertebral fracture	Two of 61 women in alendronate group suffered vertebral fracture as did two of 64 in alfacalcidol group. Thus no difference in fracture incidence between two groups
Results: non-vertebral fracture	–
Quality score	11/15
Comments	• Aim was to evaluate efficacy and safety of alendronate in Japanese women with osteoporosis • Alendronate compared with alfacalcidol, standard treatment for osteoporosis in Japan, as ethics committees of many institutions would not allow use of inactive placebo • Alendronate dose half that recommended for Caucasians as, in recent dose-ranging study, this was found to be optimal dose for Japanese population • Patients in both arms received elemental calcium, 200 mg daily • Patients allowed analgesics if in serious pain but prohibited from taking any other drugs which affected bone or calcium metabolism during study period • Lower proportion of women had baseline fractures in alendronate (14/83, 16.9%) than in alfacalcidol group (20/79, 25.3%), but not statistically significant • Three women (one in alendronate and two in alfacalcidol group) excluded from all analyses because failed to take any medication. A further 44 (not attributed to groups) excluded from efficacy analyses because of protocol violations. However, vertebral fracture data available for only 125 women, 61 (58%) in alendronate and 64 (61%) in alfacalcidol group • Similar proportion of women in each group (19/102 (18.6%) in alendronate and 25/100 (25.0%) in alfacalcidol group) reported adverse events. These occurred primarily in first 4 weeks of treatment and mostly disappeared without additional treatment after withdrawal of study drug. Gastrointestinal symptoms evenly distributed between groups • No-one in alfacalcidol group appeared to suffer from hypercalcaemia, despite use of relatively high dose in conjunction with calcium supplementation

Comparisons with active treatments *contd*

Study	Thiébaud, 1994[115]
Setting	Switzerland
Date of intervention	Autumn 1988–end 1992
Source of funding	Ciba-Geigy AG (donated pamidronate)
Design	Small, open-label, randomised
Study population	Postmenopausal women with established osteoporosis (at least one vertebral fracture)
Recruitment procedure used	Consecutive postmenopausal women referred to outpatients clinic with established osteoporosis who did not like or could not take HRT
Number of patients	32
Length of study	2 years
Main intervention/s	Intermittent intravenous pamidronate compared with oral fluoride
Primary outcome measures	BMD
Secondary outcome measures	Incidence of vertebral fracture Incidence of other fractures Side-effects
Definition of incident vertebral fracture	Greater than 25% reduction in either anterior or posterior vertebral height
Results: vertebral fracture	Trend towards lower incidence in pamidronate group but numbers too small for statistical significance
Results: non-vertebral fracture	Trend towards lower incidence in pamidronate group but numbers too small for statistical significance
Quality score	10/18
Comments	• Authors variously describe study as 'randomised' and 'partially randomised', or that patients were 'randomly allocated alternately' • All women received calcium, 1 g, and vitamin D, 1000 U, daily • Compliance in pamidronate group was 100% and any side-effects minor • More side-effects in fluoride group: mainly transient arthralgias and mild gastric intolerance but two women (12.5%) withdrew from study following stress fractures

Study	Tilyard, 1992[124]
Setting	New Zealand
Date of intervention	Not specified
Source of funding	Not specified
Design	Large, multicentre, open-label, randomised
Study population	Healthy postmenopausal women with established osteoporosis (at least one non-traumatic vertebral compression fracture)
Recruitment procedure used	Women diagnosed in 1986 and 1987 by 123 primary care physicians as having history of previous fracture of wrist or hip, loss of height, dowager's hump or chronic back pain
Number of patients	622
Length of study	3 years
Main intervention/s	Calcitriol compared with calcium
Primary outcome measures	Rate of new vertebral fractures
Secondary outcome measures	Peripheral fractures Safety of calcitriol at the study dosage
Definition of incident vertebral fracture	Reduction of 15% or more in anterior or posterior vertebral height in any 1 year
Results: vertebral fracture	Significant reduction in number suffering new fractures in calcitriol versus calcium group. However, effect only evident after 2 years of treatment and only in women with mild-to-moderate osteoporosis (five or fewer vertebral fractures at baseline) or aged 65 years or older
Results: non-vertebral fracture	Significant reduction in non-vertebral fractures in calcitriol group (11 fractures compared with 24 in calcium group, $p < 0.05$)
Quality score	16/18
Comments	• Randomisation codes used to assign women to treatment groups but both patients and physicians subsequently aware of treatment assignment • Patients given no specific instructions in relation to dietary calcium but instructed to take no calcium supplements other than those supplied for study • Mean dietary calcium intake 880 mg/day • Of 190 (30.5%) who withdrew from study, 101 (32.2%) from calcitriol and 89 (28.9%) from calcium group; 27 (8.6%) withdrew from calcitriol and 20 (6.5%) from calcium group due to adverse events ($p > 0.05$) • Gastrointestinal symptoms led to 13 withdrawals from calcitriol and 12 from calcium group. Persistently elevated serum calcium led to two withdrawals from calcitriol but none from calcium group • Calcium absorption status had no effect on rate of fractures in treatment groups

Comparisons with active treatments *contd*

Study	Watts, 1990[109]
Setting	USA
Date of intervention	Not specified
Source of funding	Norwich Eaton Pharmaceuticals
Design	Multicentre, randomised, double-blind, placebo-controlled
Study population	Healthy postmenopausal white or Asian women with established osteoporosis (at least one but no more than four vertebral crush fractures)
Recruitment procedure used	Media announcements and letters to physicians
Number of patients	429
Length of study	2 years
Main intervention/s	Oral etidronate, with or without phosphate
Primary outcome measures	Spinal BMD Incidence of new vertebral fractures
Secondary outcome measures	Incidence of non-vertebral fractures
Definition of incident vertebral fracture	Reduction of 20% or more in anterior, middle or posterior height, plus reduction of 10% or more in area of previously unfractured vertebra
Results: vertebral fracture	Five patients (5.1%) in etidronate-only and three (3.1%) in etidronate–phosphate group suffered new vertebral fractures, compared with seven (7.6%) in phosphate-only and ten (11.0%) in placebo group. Difference between etidronate–phosphate and placebo group statistically significant (p = 0.034). Effect greatest in subgroup with baseline BMD below 50th percentile of baseline values for total study population: of these, three (5.8%) in etidronate-only and three (6.1%) in etidronate–phosphate groups suffered new vertebral fractures, compared with seven (17.5%) in phosphate-only and ten (21.3%) in placebo groups
Results: non-vertebral fracture	No apparent differences between treatment groups in number of non-vertebral fractures attributal to osteoporosis
Quality score	14/18
Comments	• All patients took elemental calcium, 500 mg, for days 18–91 of 91-day cycle • All counselled in ways to achieve dietary calcium intake of at least 700 mg/day • Exceptions to stated entry criteria granted to nine women whose weight exceeded 80 kg and to five whose age exceeded 75 years • Of 66 (15.4%) who withdrew from study, six withdrew after randomisation but before beginning of regimen. Of remaining 60, 27 (12.8%) received etidronate and 33 (15.6%) placebo • Baseline characteristics not given for six women who withdrew immediately after randomisation • Only seven (1.6%) withdrew because of adverse events, one (0.9%) in phosphate-only, three (2.9%) in etidronate-only, one (0.9%) in etidronate–phosphate and two (1.9%) in placebo group • Adverse effects were mild, generally infrequent and comparably distributed between treatment groups; 5–6% in all groups suffered nausea during days 1–17 (phosphate/placebo and etidronate/placebo phases of cycle); however, during days 1–3 (phosphate/placebo phase), 39% of those receiving phosphate suffered diarrhoea compared with 9% receiving placebo • Pooling of results from etidronate-treated groups and those not receiving etidronate indicated significantly fewer etidronate-treated patients with new vertebral fractures (8 versus 17, p = 0.044) • Pooling of results for low BMD subgroup indicated significantly fewer etidronate-treated patients with new vertebral fractures (6 versus 17, p = 0.006) • Pooling of treatment groups and subgroup analysis in terms of BMD not pre-planned • Combination of etidronate and phosphate resulted in no apparent additional benefits beyond those offered by etidronate alone • Following initial 2 years, patients could choose to continue original blinded treatment or take calcium alone.[a] Patients completing full 3 years, whether on blinded therapy or calcium, eligible for inclusion in 2-year open-label follow-up study in which all patients took intermittent cyclical etidronate. They were then re-randomised to receive intermittent cyclical therapy with either etidronate or placebo.[b] However, only results of original 2-year, double-blinded RCT included in this review.

Additional information from: [a] *Harris*, et al., *1993*; [b] *Miller*, et al., *1997*

Comparisons with active treatments *contd*

Study	Wimalawansa, 1998[110]
Setting	UK
Date of intervention	Not specified
Source of funding	Not specified
Design	Open-label RCT
Study population	Postmenopausal women with established osteoporosis (spinal T-score –2 and at least one but no more than four atraumatic thoracic vertebral crush fractures)
Recruitment procedure used	Not specified
Number of patients	72
Length of study	4 years
Main intervention/s	HRT plus etidronate, given separately and in combination
Primary outcome measures	BMD
Secondary outcome measures	Biochemical markers Non-vertebral fractures New vertebral fractures Height loss
Definition of incident vertebral fracture	Reduction of 20% or more in anterior, middle or posterior vertebral height plus reduction of 15% or more in area in previously unaffected vertebra. Further deterioration in height or area of previously affected vertebra not considered new fracture
Results: vertebral fracture	Trend to fewer vertebral fractures in treatment than control group (two in patients taking HRT alone, three in patients taking etidronate alone, one in patients taking combined therapy, and five in control group). However, numbers too small for results to be statistically significant, even when expressed as fractures/1000 patient years
Results: non-vertebral fracture	No statistically significant difference between groups in terms of non-vertebral fracture
Quality score	14/18
Comments	• All participants received elemental calcium, 1 g, + vitamin D_2, 400 units (10 µg), daily • All participants received advice on lifestyle, dietetic modifications, and encouraged to walk about 2 miles/day • Of 14 (19.4%) who withdrew, three were from HRT, three from etidronate, four from combined therapy and four from control group. Five withdrew as result of oestrogen-related adverse effects, two from inability to tolerate medications, five for other medical problems, one died and one was lost to follow-up. Withdrawals due to toxicity distributed as follows: HRT 3, etidronate 1, combined therapy 2, control 1 • Through all groups, 23 women complained of minor side-effects attributable to calcium but continued supplementation • Six women (35%) taking etidronate alone complained of nausea; no-one from any other group complained of this • Although quality of trial relatively good, numbers were too small to produce significant results in relation to fractures as opposed to BMD

Appendix 5

Summary of intervention studies* and quality assessment

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* NB. The reference numbers quoted are the principal ones for each particular trial. For details of other relevant references, see 'Trials meeting the inclusion criteria' (page 125).

Bisphosphonate: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Adami, 1995[93]	2	BMD (spine)	Postmenopausal women with osteoporosis (lumbar T-score > –2), 5% had vertebral fracture at entry	59 (48–76)	Group 1: oral alendronate, 10 mg/day Group 2: oral alendronate, 20 mg/day All patients received elemental calcium, 500 mg/day	Placebo + elemental calcium, 500 mg
Bone, 1997[94]	2	Lumbar BMD	Postmenopausal women with osteopaenia or osteoporosis (T-score < –2 but no more than one lumbar crush fracture), 37% of whom had vertebral fracture at entry	70.7 (60–85)	Group 1: oral alendronate, 1.0 mg/day Group 2: oral alendronate, 2.5 mg/day Group 3: oral alendronate, 5.0 mg/day All patients received elemental calcium, 500 mg/day	Placebo + elemental calcium, 500 mg
Carfora, 1998[95]	2.5	BMD* Vertebral fractures* Biochemical markers*	Postmenopausal women with osteoporosis (lumbar spine T-score < –2.5)	(44–73)	Group 1: oral alendronate, 5 mg/day Group 2: oral alendronate, 10 mg/day Group 3: oral alendronate, 20 mg/day for 15 months, placebo for 15 months All patients received elemental calcium, 500 mg/day	Placebo + elemental calcium, 500 mg
Chesnut, 1995[96]	2	Lumbar BMD	Postmenopausal women with osteopaenia (maximum lumbar spine BMD 0.88 g/cm^2) but no vertebral or hip fractures attributable to osteoporosis	63 (42–75)	Group 1: oral alendronate, 5 mg/day Group 2: oral alendronate, 10 mg/day Group 3: oral alendronate, 20 mg/day for 1 year, placebo for 1 year Group 4: oral alendronate, 40 mg/day for 1 year, placebo for 1 year Group 5: oral alendronate, 40 mg/day for 3 months, 2.5 mg/day for 21 months All patients received elemental calcium, 500 mg/day	Placebo + elemental calcium, 500 mg
Clemmesen, 1997[97]	2	BMD at spine	Postmenopausal women with established osteoporosis (at least one but no more than four vertebral fractures)	68 (53–81)	Group 1: oral risedronate, 2.5 mg/day Group 2: oral risedronate, 2.5 mg/day for 2 weeks, followed by placebo for 10 weeks of a 12-week cycle All patients received calcium, 1 g/day	Placebo + calcium, 1 g/day
FIT, 1996[98] Women with pre-existing fractures	2.9 (mean)	Proportion of women with new vertebral fractures	Postmenopausal women with established osteoporosis (at least one existing vertebral fracture)	70.8 (55–81)	Oral alendronate, 5 mg/day, increased at 24 months to 10 mg/day	Placebo
FIT, 1998[99] Women without pre-existing fractures	4.2 (mean)	Proportion of women with incident non-pathological non-traumatic clinical fractures (non-vertebral and symptomatic vertebral fractures)	Postmenopausal women with osteopaenia (femoral neck BMD 0.68 g/cm^2) but no vertebral fractures	67.7 (54–81)	Oral alendronate, 5 mg/day, increased at 24 months to 10 mg/day	Placebo

continued

Bisphosphonate: general information *contd*

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Harris, 1999[100]	3	Incidence of new vertebral fractures Incidence of radiographically confirmed non-vertebral fractures Changes from baseline BMD	Postmenopausal women with established osteoporosis (either at least two vertebral fractures or one vertebral fracture and lumbar-spine T-score of –2)	69	Group 1: oral risedronate, 2.5 mg/day Group 2: oral risedronate, 5 mg/day All patients received elemental calcium, 1 g/day	Placebo + elemental calcium, 1 g/day
Liberman, 1995[101]	3	Effect on BMD at lumbar spine Safety and tolerability of daily oral alendronate Effect on calcium-regulating hormones Effect on biochemical indices of bone turnover	Postmenopausal women with osteoporosis (lumbar T-score < –2.5) but no vertebral fractures	64 (45–80)	Group 1: oral alendronate, 1.5 mg/day Group 2: oral alendronate, 10 mg/day Group 3: oral alendronate, 20 mg/day, years 1–2, 5 mg/day, year 3 All patients received elemental calcium, 500 mg/day	Placebo + elemental calcium, 500 mg
Lindsay, 1999[102]	1	BMD at lumbar spine	Postmenopausal women with osteopaenia already receiving HRT (T-score at lumbar spine or femoral neck < –2 and at other site < 1.5), 57% of whom had previous fracture	61.7 (> 40)	Oral alendronate, 10 mg/day, + vitamin D, 400 IU	Placebo + vitamin D, 400 IU
McClung, 1998[77]	1.5	BMD at lumbar spine	Postmenopausal women with osteopaenia (T-score at lumbar spine < –2)	68	Group 1: oral risedronate, 2.5 mg/day Group 2: oral risedronate, 5 mg/day All patients received elemental calcium, 1 g/day	Placebo + elemental calcium, 1 g/day
Montessori, 1997[103]	3	BMD	Postmenopausal women with osteopaenia (lumbar Z-score < –1), 36% of whom had vertebral fracture on entry	62.5 (45–73)	Oral etidronate, 400 mg/day, for days 1–14, + calcium, 500 mg/day, for days 15–90 of 90-day cycle	Calcium, 500 mg/day
Pacifici, 1988[104]	2	Bone mineral content	Women with osteoporosis or osteopaenia (at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation)	58 (26–80)	Potassium phosphate, 500 mg, on days 1–3, + oral etidronate, 200 mg/day on days 4–17 of 73-day cycle, + calcium carbonate, 1 g/day	Calcium carbonate, 1 g/day
Pols, 1999[105]	1	Lumbar BMD	Postmenopausal women with osteopaenia (lumbar T-score < –2)	62.8 (39–84)	Oral alendronate, 10 mg/day, + elemental calcium, 500 mg	Placebo + elemental calcium, 500 mg
Reginster, 2000[106]	3	Proportion of patients with at least one incident vertebral fracture	Postmenopausal women with established osteoporosis (at least two vertebral fractures)	71	Group 1: oral risedronate, 2.5 mg/day Group 2: oral risedronate, 5 mg/day All patients received calcium, 1 g/day	Placebo + calcium, 1 g/day
Reid, 1994[107]	2	BMD	Postmenopausal women with established osteoporosis (at least one vertebral fracture)	66	Oral pamidronate, 150 mg/day, + elemental calcium, 1 g/day	Placebo + elemental calcium, 1 g/day

continued

Bisphosphonate: general information *contd*

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Storm, 1990[108]	3	Bone mineral content at lumbar spine and distal nondominant forearm Spinal deformity index Loss of height Rate of new vertebral fractures	Postmenopausal women with established osteoporosis (at least one but no more than four atraumatic vertebral crush fractures)	68.3 (56–75)	Oral etidronate, 400 mg/day, for weeks 1–2 of 15-week cycle + elemental calcium, 500 mg/day, + vitamin D, 400 IU/day	Placebo + elemental calcium, 500 mg/day, + vitamin D, 400 IU/day
Watts, 1990[109]	2 as RCT	Spinal BMD Rates of new vertebral fractures	Postmenopausal women with established osteoporosis (at least one but no more than four vertebral crush fractures)	65.1	Group 1: oral etidronate, 400 mg/day, on days 4–17, and elemental calcium, 500 mg/day, on days 18-91, of 91-day cycle Group 2: sodium-potassium phosphate, 2 g/day on days 1–3, oral etidronate, 400 mg/day on days 4–17, and elemental calcium, 500 mg/day on days 18–91 of 91-day cycle	Placebo + elemental calcium, 500 mg/day on days 18–91 of 91-day cycle
Wimalawansa, 1998[110]	4	BMD	Postmenopausal women with established osteoporosis (spinal T-score –2 and at least one but no more than four atraumatic thoracic vertebral crush fractures)	64.9 (58–72)	Group 1: oral etidronate, 400 mg/day, for weeks 1–2 of 12-week cycle Group 2: Premarin®, 0.625 mg daily, + Norgestrel®, 150 µg, for 12 days/month + oral etidronate, 400 mg/day, for weeks 1–2 of 12-week cycle All patients received elemental calcium, 1 g, + vitamin D, 400 U, daily	Elemental calcium, 1 g, + vitamin D, 400 U, daily

* *Does not differentiate between primary and secondary outcome measures*

Bisphosphonate: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Adami, 1995[93]	1	1	3	3	1	0	9/15 (73)	Group 1: 68 Group 2: 72 Control group: 71	14.3	Not specified
Bone, 1997[94]	1	1	3	3	3	3	14/18 (78)	Group 1: 86 Group 2: 89 Group 3: 93 Control group: 91	36.5	Pharmaceutical company
Carfora, 1998[95]	1	1	1	3	0	1	7/15 (47)	Group 1: 34 Group 2: 34 Group 3: 34 Control group: 34	Not specified	Not specified
Chesnut, 1995[96]	1	1	3	2	1	1	9/18 (50)	V1: 32 Group 2: 30 Group 3: 32 Group 4: 32 Group 5: 31 Control group: 31	18.1	Pharmaceutical company
Clemmesen, 1997[97]	1	3	3	3	1	2	13/18 (72)	Group 1: 44 Group 2: 44 Control group: 44	29.6	Not specified
FIT, 1996; 1998; 1999	3	3	3	3	3	3	18/18 (100)	Women with pre-existing fracture: Group 1: 1022 Control group: 1005 Women without pre-existing fracture: Group 1: 2214 Control group: 2218	Not specified	Pharmaceutical company
Harris, 1999[100]	3	3	3	3	3	3	18/18 (100)	Group 1: 817 Group 2: 821 Control group: 820	42 (excluding Group 1)	Pharmaceutical company
Liberman, 1995[101]	1	3	3	1	1	3	12/18 (67)	Group 1: 202 Group 2: 196 Group 3: 199 Control group: 397	16.3	Pharmaceutical company
Lindsay, 1999[102]	1	1	3	3	1	1	10/18 (56)	Group 1: 214 Control group: 214	7.9	Pharmaceutical company

continued

Bisphosphonate: methodological quality *contd*

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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
McClung, 1998[77]	1	1	3	1	1	0	7/15 (47)	Group 1: 212 Group 2: 216 Control group: 220	38	Not specified
Montessori, 1997[103]	2	3	3	3	1	3	15/18 (83)	Group 1: 40 Control group: 40	20	Pharmaceutical company
Pacifici, 1988[104]	1	1	2	1	0	3	8/15 (53)	128	45.3	Not specified
Pols, 1999[105]	1	1	3	3	3	0	11/15 (73)	Group 1: 950 Control group: 958	11.1	Pharmaceutical company
Reginster, 2000[106]	1	1	3	3	3	3	14/18 (78)	Group 1: 410 Group 2: 408 Control group: 408	42 (excluding Group 1)	Pharmaceutical company
Reid, 1994[107]	1	1	2	1	0	3	8/15 (53)	Group 1: 31 Control group: 30	21.3	Not specified
Storm, 1990[108]	2	3	2	3	1	3	14/18 (78)	Group 1: 33 Control group: 33	39.4	Pharmaceutical company
Watts, 1990[109]	2	3	3	3	1	3	14/18 (78)	Group 1: 105 Group 2: 107 Control group: 104	15.4	Pharmaceutical company
Wimalawansa, 1998[110]	2	3	2	3	1	3	14/18 (78)	Group 1: 17 Group 2: 19 Control group: 18	19.4	Not specified

Vitamin D derivatives: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Aloia, 1988[117]	2	BMD* Incidence of vertebral fracture* Biochemical measures* Bone biopsy*	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral compression fracture)	64.5	Oral calcitriol, mean dose 0.8 µg/day, + vitamin D, 400 IU/day	Vitamin D, 400 IU/day
Dykman, 1984[63]	1.5	Forearm bone mass	Rheumatic disease patients with glucocorticoid-induced osteopaenia	48.7	Oral calcitriol, mean dose 0.25 µg/day, + elemental calcium, 500 mg/day, + vitamin D, 400 IU/day	Placebo, + elemental calcium, 500 mg/day, + vitamin D, 400 IU/day
Fujita, 1992[64]	Not specified	Vertebral fractures	Women with established osteoporosis (at least one non-traumatic vertebral fracture)	80.3	Group 1: oral alfacalcidol, 0.75–1.5 µg/day Group 2: oral alfacalcidol, 0.75–1.5 µg/day, + intramuscular calcitonin, 10 units twice weekly	No treatment
Gallagher, 1989[118]	1 (as RCT)	Vertebral fracture rates	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral fracture)	63.2	Oral calcitriol, 0.5 µg/day, increased to 0.75 or 1.0 µg/day at investigator's discretion	Placebo
Gallagher, 1990a[119]	2	Safety BMD	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral fracture)	69.7	Oral calcitriol, mean dose 0.62 µg/day, + vitamin D_2, 400 IU/day	Placebo + vitamin D_2, 400 IU/day
Orimo, 1987[120]	1.7–2.1 (mean)	Vertebral crush fractures	Women with established senile osteoporosis (decreased vertebral density and at least one crush fracture)	71.7	Group 1: oral alfacalcidol, 1 µg/day Group 2: oral alfacalcidol, 1 µg/day + calcium, 1 g/day	Control group 1: no treatment Control group 2: calcium, 1 g/day
Orimo, 1994[121]	1	BMD* New vertebral fractures* Non-vertebral fractures*	Postmenopausal women with established osteoporosis (62.5% had fracture of spine, femur neck or radius at entry)	71.9	Oral alfacalcidol, 1 µg/day, + elemental calcium, 300 mg/day	Placebo + elemental calcium, 300 mg/day
Ott, 1989[122]	2	Change in bone mass	Postmenopausal women with established osteoporosis (at least two non-traumatic vertebral compression fractures)	67.5	Oral calcitriol, mean dose 0.43 µg/day	Placebo
Shiraki, 1996[68]	2	BMD Vertebral and non-vertebral fractures	Postmenopausal women with diagnosis of probable or definite osteoporosis (49% had at least one vertebral fracture at entry)	72.4	Oral alfacalcidol, 0.75 µg/day + elemental calcium, 300 mg/day	Placebo + elemental calcium, 300 mg/day

* *Does not differentiate between primary and secondary outcome measures*

Vitamin D derivatives: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Aloia, 1988117	1	3	2	1	0	1	8/15 (53)	Group 1: 17 Control group: 17	20.6	Not specified
Dykman, 1984[63]	1	1	2	1	3	1	9/18 (50)	30	23.3	Not specified
Fujita, 1992[64]	1	3	2	2	0	3	11/15 (73)	Group 1: 8 Group 2: 8 Control group: 8	6.2	Not specified
Gallagher, 1989[118]	1	3	2	1	0	2	9/15 (60)	Group 1: 38 Control group: 33	12.7	Research body/ pharmaceutical company
Gallagher, 1990a[119]	3	1	2	1	0	2	9/15 (60)	Group 1: 25 Control group: 25	20	Pharmaceutical company
Orimo, 1987[120]	1	3	1	2	0	3	10/15 (67)	Group 1: 22 Group 2: 16 Control group 1: 23 Control group 2: 25	Not specified	Not specified
Orimo, 1994[121]	2	3	2	1	1	3	12/18 (67)	Group 1: 38 Control group: 42	7.5	Not specified
Ott, 1989[122]	3	1	2	3	1	2	12/18 (67)	Group 1: 43 Control group: 43	16.3	Research body/ pharmaceutical company
Shiraki, 1996[68]	2	3	1	3	1	3	13/18 (72)	Group 1: 57 Control group: 56	30.1 (?)	Not specified

Calcitonin: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Adami, 1995[93]	2	BMD (spine)	Postmenopausal women with osteoporosis (lumbar T-score > –2); 5% had vertebral fracture at entry	59 (48–76)	Intranasal calcitonin, 100 IU/day, + oral elemental calcium, 500 mg/day	Oral elemental calcium, 500 mg/day
Agrawal, 1981[61]	2	Total body calcium* Bone mineral content* New vertebral events* Biochemical indices* Peripheral fractures*	Men with established osteoporosis (at least one non-traumatic vertebral compression fracture)		Subcutaneous calcitonin, 100 MRC units/day, + oral calcium, 1 g/day, + vitamin D_2, 500 IU/day	Control group 1: oral calcium, 1 g/day, + vitamin D_2, 500 IU/day Control group 2: vitamin D_2, 800 IU/day
Cristallini, 1993[128]	2	BMD Vertebral fractures	Postmenopausal women with established osteoporosis (at least two non-traumatic vertebral fractures)	63.5 (41–73)	Group 1: cyclical intramuscular calcitonin, 100 U/day, + potassium phosphate, 2 g/day, days 1–30; oral cholecalciferol, 0.25 µg/day, + elemental calcium, 1 g/day, days 31–75 of 90-day cycle Group 2: cyclical intramuscular calcitonin, 100 U/day, + potassium phosphate, 2 g/day, days 1–30; cholecalciferol, 0.25 µg/day, + elemental calcium, 1 g/day, + sodium fluoride, 40 mg/day, days 31–75 of 90-day cycle	Cholecalciferol, 0.25 µg/day, + elemental calcium, 1 g/day
Ellerington, 1996[129]	2	BMD of lumbar spine and hip	Postmenopausal women with osteopaenia (T-score in spine or hip < –1.2)	55.8 (48–64)	Group 1: intranasal calcitonin, 100 IU/day Group 2: intranasal calcitonin, 200 IU 3 times weekly	Placebo
Fujita, 1992[64]	Not specified	Vertebral fractures	Women with established osteoporosis (at least one non-traumatic vertebral fracture)	79	Group 1: intramuscular calcitonin, 10 units twice weekly Group 2: intramuscular calcitonin, 10 units twice weekly, + alfacalcidol, 0.75–1.5 µg/day	No treatment
Gennari, 1985[65]	1	Bone mineral content of lumbar spine and femoral diaphysis* Vertebral fractures* Serum and urinary parameters*	Postmenopausal women with established osteoporosis (at least two non-traumatic vertebral compression fractures)	58.7 (44–70)	Group 1: subcutaneous calcitonin, 100 MRC units, on alternate days Group 2: subcutaneous calcitonin, 100 MRC units/day All patients received oral calcium, 1 g/day	Calcium, 1 g/day
Hizmetli, 1998[130]	2	Lumbar and femoral neck BMD Vertebral fracture	Postmenopausal women newly diagnosed as osteoporotic (T-score < –2.5)	58.0	Group 1: intranasal calcitonin, 50 IU/day Group 2: intranasal calcitonin, 100 IU/day All patients received elemental calcium, 1000 mg/day, + vitamin D, 400 IU/day or 50,000 IU/week	Elemental calcium, 1000 mg/day, + vitamin D, 400 IU/day or 50,000 IU/week

continued

Calcitonin: general information *contd*

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Hodsman, 1997[131]	2	Change in BMD at lumbar spine	Postmenopausal women with established osteoporosis (at least one vertebral compression fracture)	67	Human parathyroid hormone, 800 IU equivalent/day, days 1–28; subcutaneous calcitonin, 75 IU/day, days 29–70; elemental calcium; 500 mg/day, days 71–90 of 90-day cycle	hPTH, 800 IU equivalents/day, , days 1–28; placebo days 29–70; elemental calcium, 500 mg/day, days 71–90 of 90-day cycle
Overgaard, 1992[60]	2	Bone mineral content of distal forearm and lumbar spine Rates of vertebral and peripheral fractures	Elderly women with moderate osteoporosis (T-score at distal forearm < –2); 6% had vertebral fractures at entry	70 (68–72)	Group 1: intranasal calcitonin, 50 IU/day Group 2: intranasal calcitonin, 100 IU/day Group 3: intranasal calcitonin, 200 IU/day All patients received oral calcium, 500 mg/day	Placebo + calcium, 500 mg/day
Pontiroli, 1991[132]	0.5	Pain Metabolic indices Bone mineral content	Women with postmenopausal or senile osteoporosis (at least 1 vertebral fracture)	71 (60–83)	Intranasal calcitonin, 100 IU, on alternate days	Intramuscular calcitonin, 100 IU, on alternate days
PROOF study[78]	5	Incidence of new vertebral fractures	Postmenopausal women with established osteoporosis (at least one but not more than five non-traumatic vertebral fractures, and T-score at lumbar spine < –2)	68.3 (45–95)	Group 1: intranasal calcitonin, 100 IU/day Group 2: intranasal calcitonin, 200 IU/day Group 3: calcitonin, 400 IU/day All patients received calcium, 1000 mg/day, + vitamin D, 400 IU/day	Placebo calcitonin + calcium, 1000 mg/day, + vitamin D, 400 IU/day
Rico, 1992[134]	2	Vertebral fracture rate	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral crush fracture)	68.3	Intramuscular calcitonin, 100 IU/day, for 10 days/month + oral elemental calcium, 500 mg/day, for 10 days/month	Elemental calcium, 500 mg/day, for 10 days/month
Rico, 1995[135]	2	Spinal deformity Vertebral fracture	Postmenopausal women with established osteoporosis (more than one non-traumatic vertebral fracture)	69.2	Intramuscular calcitonin, 100 IU/day, for 10 days/month + oral elemental calcium, 500 mg/day, for 10 days/month	Elemental calcium, 500 mg/day, for 10 days/month
Ringe, 1987[136]	0.5	Vertebral fractures/deformities* Pain* Adverse effects* Non-vertebral fracture*	Men and women with 'incipient to severe signs' of steroid-induced osteoporosis	49.5	Subcutaneous calcitonin, 100 IU, on alternate days	No treatment
Ringe, 1990[137]	1	Pain* Vertebral and non-vertebral fractures* BMD* Bone biopsy*	Men and women with primary osteoporosis (undefined)	60.8	Group 1: subcutaneous calcitonin, 100 IU/day Group 2: subcutaneous calcitonin, 100 IU, on alternate days All patients received calcium, 1 g/day	Calcium, 1 g/day

* *Does not differentiate between primary and secondary outcome measures*

Calcitonin: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Adami, 1995[93]	1	1	3	3	1	0	9/15 (73)	Group 1: 68 R Group 2: 72 Control group: 71	14.3	Not specified
Agrawal, 1981[61]	1	3	2	1	0	1	8/15 (53)	39	43.6	Research body/ pharmaceutical company
Cristallini, 1993[128]	1	1	2	1	0	1	6/15 (40)	Group 1: 40 Group 2: 40 Control group: 45	38.4	Not specified
Ellerington, 1996[129]	1	1	2	3	0	3	10/15 (67)	Group 1: 36 Group 2: 35 Control group: 46	17.1	Research body/ pharmaceutical company
Fujita, 1992[64]	1	3	2	2	0	3	11/15 (73)	Group 1: 8 Group 2: 8 Control group: 8	6.2	Not specified
Gennari, 1985[65]	1	1	2	1	0	1	6/15 (40)	82	67%	Not specified
Hizmetli, 1998[130]	1	1	2	3	0	2	9/15 (73)	Group 1: 35 Group 2: 41 Control group: 31	18.7	Not specified
Hodsman, 1997[131]	1	1	2	3	1	3	11/18 (61)	39	23.1	Research body/ pharmaceutical company
Overgaard, 1992[60]	1	3	2	3	3	3	15/18 (83)	Group 1: 52 Group 2: 52 Group 3: 52 Control group: 52	15.4	Research body/ pharmaceutical company
Pontiroli, 1991[131]	1	1	2	1	0	1	6/15 (40)	Group 1: 7 Control group: 8	20	Not specified
PROOF study[78]	1	3	3	1	0	3	11/15 (73)	Group 1: 316 Group 2: 316 Group 3: 312 Control group: 311	9.8	Not specified
Rico, 1992[134]	1	3	2	3	1	3	13/18 (72)	Group 1: 32 Control group: 28	5	Government body

continued

Calcitonin: methodological quality *contd*

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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Rico, 1995[135]	1	3	2	3	1	3	13/18 (72)	Group 1: 36 Control group: 36	5.6	Not specified
Ringe, 1987[136]	1	1	2	3	1	1	9/18 (50)	Group 1: 19 Control group: 19	5.3	Not specified
Ringe, 1990[137]	1	1	2	1	1	1	7/18 (39)	67	11.9	Not specified

Calcium studies: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Gutteridge, 1993[80]	Not clear, but over 1	BMD* Vertebral fractures*	Postmenopausal women with established osteoporosis (at least one vertebral fracture following minor trauma)	Not specified	Calcium, 1 g/day, + vitamin D_2, 0.5 mg (20,000 IU)/week	No treatment
Recker, 1996[142]	4.3 (mean)	Incidence of vertebral fractures Forearm bone mass changes	Elderly women with low self-chosen calcium intakes and prevalent vertebral fractures	74.9	Calcium, 1.2 g/day	Placebo

* *Does not differentiate between primary and secondary outcome measures*

Calcium: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Gutteridge, 1993[80]	1	1	1	1	0	1	5/15 (33)	Group 1: 8 Control group: 9	Not specified	Not specified
Recker, 1996[142]	1	3	3	3	0	2	12/15 (80)	Prevalent fractures group Group 1: 53 Control group: 41	Not specified	Dairy industry/ government body/ pharmaceutical company

Oestrogen: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Lufkin, 1992[178]	1	Bone turnover assessed by biochemical markers and iliac bone histomorphometry* BMD* Vertebral fracture rate*	Postmenopausal women with established osteoporosis (low BMD and at least one vertebral fracture)	64.8 (47–75)	Transdermal 17β oestradiol, 0.1 mg, on days 1–21 + oral medroxyprogesterone acetate, 10 mg, on days 11–21 of 28-day cycle	Placebo
Pacifici, 1988[104]	2	Bone mineral content	Women with osteoporosis or osteopaenia (at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation)	58 (26–80)	Conjugated oestrogens, 0.625 mg/day, for 25 days/month, medroxyprogesterone, 10 mg/day, on days 15–25 + calcium carbonate, 1000 mg/day	Calcium carbonate, 1000 mg/day
Wimalawansa, 1998[110]	4	BMD	Postmenopausal women with established osteoporosis (spinal T-score –2 and at least one but no more than four atraumatic thoracic vertebral crush fractures)	64.9 (58–72)	Premarin®, 0.625 mg/day, daily + Norgestrel®, 150 µg/day, for 12 days/month + elemental calcium, 1 g/day + vitamin D_2, 400 U/day	Elemental calcium, 1 g/day, + vitamin D_2, 400 U/day
Zarcone, 1997[144]	64 months	BMD at lumbar spine Vertebral fractures	Postmenopausal women with osteoporosis (maximum BMD at lumbar spine 0.88 g/cm^2)	(45–63)	Group 1: conjugated equine oestrogen, 0.15 mg/day Group 2: conjugated equine oestrogen, 0.3 mg/day Group 3: conjugated equine oestrogen, 0.625 mg/day	Placebo

* *Does not differentiate between primary and secondary outcome measures*

Oestrogen: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Lufkin, 1992[178]	1	1	3	3	0	3	11/15 (73)	Group 1: 36 Control group: 39	10.7	Pharmaceutical company
Pacifici, 1988[104]	1	1	2	1	0	3	8/15 (53)	128	45.3	Not stated
Wimalawansa, 1998[110]	2	3	2	3	1	3	14/18 (78)	Group 1: 17 Group 2: 19 Control group: 18	19.4	Not stated
Zarcone, 1997[144]	1	1	2	1	1	1	7/18 (39)	132	9	Not stated

Oestrogen-like molecules: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Maugeri, 1994[157]	2	BMD Bone metabolism marker parameters	Elderly women with established osteoporosis (at least one vertebral fracture, and T-score at distal radius of < –2)	69.9	Ipriflavone, 600 mg/day, + calcium, 1 g/day	Placebo + calcium, 1 g/day
Passeri, 1992[158]	1	Bone mass Biomarkers	Elderly women with established osteoporosis (at least one vertebral fracture, and T-score at distal radius of < –2)	69 (65–85)	Ipriflavone, 200 mg/day, + calcium (carbonate and gluconate), 1 g/day	Placebo + calcium (carbonate and gluconate), 1 g/day
Passeri, 1995[159]	2	BMD Safety	Elderly women with established osteoporosis (at least one vertebral fracture, and forearm Z-score of < –2)	69.5 (65–79)	Ipriflavone, 600 mg/day, + elemental calcium, 1 g/day	Placebo + elemental calcium, 1 g/day

Oestrogen-like molecules: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Maugeri, 1994[157]	1	1	2	2	0	1	7/15 (47)	100	16	Not specified
Passeri, 1992[158]	1	3	3	3	0	1	11/15 (73)	Group 1: 14 Control group: 14	4	Not specified
Passeri, 1995[159]	1	3	3	3	3	2	15/18 (83)	Group 1: 25 Control group: 24	44.9	Pharmaceutical company

Anabolic steroids: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Chesnut, 1983[96]	29 months	Total body calcium Bone mass Biochemical markers	Postmenopausal women with vertebral osteopaenia or one or more atraumatic spinal compression fractures	68.7 (50–80)	Stanozolol, 6 mg, 3 weeks in 4	Placebo

Anabolic steroids: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Chesnut, 1983[96]	1	1	3	3	0	2	10/15 (67)	Group 1: 23 Control group: 23	18.6	Pharmaceutical company/ government body

Fluoride: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Brockstedt, 1996[73]	3	BMD* Bone markers* Vertebral fractures* Adverse events*	Women with osteoporosis	67.2	Fluoride (as sodium monofluorophosphate), 26.4 mg/day, for 3 months in every 6 + calcium carbonate, 1000 mg/day	Fluoride (as sodium monofluorophosphate), 26.4 mg/day, + calcium carbonate, 1000 mg/day
Gutteridge, 1993[80]	Not clear, but over 1	BMD* Vertebral fractures*	Postmenopausal women with established osteoporosis (at least one vertebral fracture following minor trauma)	Not specified	Enteric-coated sodium fluoride, 60 mg/day, for months 1–6 of 9-month cycle + calcium, 1 g/day, + vitamin D_2, 0.5 mg (20,000 IU)/week	Control group 1: calcium, 1 g/day, + vitamin D_2, 0.5 mg (20,000 IU)/week Control group 2: no treatment
Gutteridge, 1996[79]	2.25	BMD at lumbar spine, upper femur and lower tibia and fibula* Incident vertebral fractures*	Postmenopausal women with established osteoporosis (at least one vertebral fracture)	Not specified	Enteric-coated sodium fluoride, 60 mg/day, for months 1–6 of 9-month cycle + calcium, 1 g/day, + vitamin D_2, 0.25–0.5 mg/week	Calcium, 1 g/day, + vitamin D_2, 0.25–0.5 mg/week
Hansson, 1987[167]	3	Spinal bone mineral content	Postmenopausal women with established osteoporosis (at least one and maximum of three vertebral compression fractures sustained during minor trauma)	65.9	Group 1: sodium fluoride, 30 mg/day Group 2: sodium fluoride, 10 mg/day All patients received calcium, 1 g/day (combination of bicarbonate, lactate and gluconate)	Control group 1: calcium (combination of bicarbonate, lactate and gluconate), 1 g/day Control group 2: placebo
Kleerekoper, 1991[168]	4	Vertebral fracture	Postmenopausal women with established osteoporosis (at least one vertebral compression fracture or two or more non-contiguous vertebral wedge deformities)	70.0	Sodium fluoride, 75 mg/day (average initial dose), + calcium, 1500 mg/day	Placebo + calcium, 1500 mg/day
Meunier, 1998[169]	2	Percentage of patients with at least one new vertebral fracture between T4 and L5 after 2 years	Postmenopausal women with established osteoporosis (at least one vertebral fracture)	65.7 (47–76)	Group 1: sodium fluoride, 50 mg/day Group 2: monofluorophosphate, 150 mg/day Group 3: monofluorophosphate, 200 mg/day All patients received calcium carbonate, 1 g/day, + vitamin D_2, 800 IU/day	Calcium carbonate, 1 g/day, + vitamin D_2, 800 IU/day
Pak, 1995[170]	4	Incident vertebral fractures	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral fracture)	67.6 (55–81)	Slow-release sodium fluoride, 50 mg/day, + calcium citrate, 800 mg/day	Placebo + calcium citrate, 800 mg/day
Reginster, 1998[171]	4	Number of patients with new vertebral fractures during the 4-year treatment period	Postmenopausal women with moderate osteoporosis (lumbar spine T-score of –2.5), 2% of whom had vertebral fractures at entry	63	Sodium monofluorophosphate, 152 mg/day, + calcium carbonate, 2500 mg/day (equivalent to calcium, 1000 mg/day)	Calcium carbonate, 2500 mg/day (equivalent to 1000 mg/day calcium)
Riggs, 1990[172]	4	Vertebral fractures Side-effects, including non-vertebral fractures	Postmenopausal women with established osteoporosis (low BMD at lumbar spine and at least one vertebral fracture)	68 (median) (50–75)	Sodium fluoride, 75 mg/day, + elemental calcium, 1500 mg/day	Placebo + elemental calcium, 1500 mg/day

continued

Fluoride: general information *contd*

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Ringe, 1998[173]	3	BMD of lumbar spine	Men with early idiopathic osteoporosis (T-score < –2.5 but no significant deformity or signs of previous vertebral fractures)	53 (33–68)	Sodium monofluorophosphate, 114 mg/day, + calcium, 500 mg/day for 3 months in 4, 1000 mg/day for remaining month	Calcium, 1000 mg/day
Ringe, 1999[174]	3	BMD Incidence of vertebral fractures	Postmenopausal women with established osteoporosis (T-score < –2.5 and at least one osteoporotic vertebral fracture)	64.0	Group 1: monofluorophosphate, 114 mg/day for 3 months in 4 Group 2: monofluorophosphate, 152 mg/day All patients received calcium, 1000 mg/day	Calcium, 1000 mg/day
Sebert, 1995[175]	2	Variations in lumbar BMD	Men and women with severe osteopaenia (lumbar T-score < –2) but with no vertebral fractures	60.3 (50–70)	Sodium monofluorophosphate, 100 mg/day, + calcium carbonate, 2500 mg/day (equivalent to calcium, 1000 mg/day)	Placebo + calcium carbonate, 2500 mg/day (equivalent to 1000 mg/day calcium)

Fluoride: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Brockstedt, 1996[73]	1	1	1	1	0	1	5/15 (33)	92	41.3	Not specified
Gutteridge, 1993[80]	1	1	1	1	0	1	5/15 (33)	Group 1: 6 Control group 1: 8 Control group 2: 9	Not specified	Not specified
Gutteridge, 1996[79]	1	1	1	1	1	1	6/18 (33)	65	10.8	Government/ research council
Hansson, 1987[167]	1	1	1	1	0	1	5/15 (33)	Group 1: 25 Group 2: 25 Group 3: 25 Control group: 25	12	Research council/ charitable funding
Kleerekoper, 1991[168]	1	1	3	2	1	1	9/18 (50)	Group 1: 46 Control group: 36	47.6	Government
Meunier, 1998[169]	1	3	3	3	1	3	14/18 (78)	Group 1: 73 Group 2: 68 Group 3: 67 Control group: 146	37.3	Not specified
Pak, 1995[170]	1	3	2	3	1	3	13/18 (72)	Group 1: 54 Control group: 56	30.9	Government/ institutional funding (pharmaceutical company, drugs only)
Reginster, 1998[171]	3	3	3	3	1	3	16/18 (89)	Group 1: 100 Control group: 100	39	Pharmaceutical company
Riggs, 1990[172]	1	3	3	3	3	3	16/18 (89)	Group 1: 101 Control group: 101	33.2	Government body
Ringe, 1998[173]	1	3	3	2	1	3	13/18 (72)	Group 1: 32 Control group: 32	21.9	Not specified
Ringe, 1999[174]	1	3	3	2	1	3	13/18 (72)	Group 1: 49 Group 2: 48 Control group: 48	27.6	Not specified
Sebert, 1995[175]	1	1	3	3	3	3	14/18 (78)	Group 1: 45 Control group: 49	37.2	Not specified

SERMs: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Ettinger, 1999[182]	3	Proportion of women with one or more new non-traumatic vertebral fractures BMD	Postmenopausal women with osteoporosis (low BMD and/or vertebral fractures); 37% had at least one vertebral fracture at entry	67 (31–80)	Group 1: raloxifene, 60 mg/day Group 2: raloxifene, 120 mg/day All patients received calcium, 500 mg/day, + vitamin D_3, 400–600 IU	Placebo + calcium, 500 mg/day, + vitamin D_3, 400–600 IU
Lufkin, 1998[178]	1	BMD Biochemical markers Adverse events	Postmenopausal women with established osteoporosis (low BMD and at least one non-traumatic vertebral fracture)	68.4	Group 1: raloxifene, 60 mg/day Group 2: raloxifene, 120 mg/day All patients received calcium, 750 mg/day, + vitamin D to bring daily intake to 800 IU	Placebo + calcium, 750 mg/day, + vitamin D to bring daily intake to 800 IU

SERMs: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Ettinger, 1999[182]	3	3	3	3	1	3	16/18 (89)	Group 1: 2557 Group 2: 2572 Control group: 2576	23.4	Pharmaceutical company
Lufkin, 1998[178]	1	1	3	2	1	3	11/18 (61)	Group 1: 48 Group 2: 47 Control group: 48	7	Pharmaceutical company

Protein supplements: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Schurch, 1998[186]	0.5	Insulin-like growth factor-I levels and other biochemical data BMD	Elderly men and women with recent osteoporotic hip fracture	80.7	Protein, 20 g, 5 days/week + vitamin D_3, 200,000 IU, at entry to study	Isocaloric placebo + vitamin D_3, 200,000 IU, at entry to study

Protein supplements: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Schurch, 1998[186]	2	3	2	3	0	3	13/15 (87)	Group 1: 41 Control group: 41	23.2	Pharmaceutical company/ government body

Vitamin K_2: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Shiraki, 2000[68]	2	Lumbar BMD Vertebral fracture	Ambulatory women with osteoporosis (lumbar BMD < 70% of young adult mean, or with one or more non-traumatic vertebral fractures and lumbar BMD < 80% of young adult mean)	67.2	Vitamin K_2, 45 mg/day, + elemental calcium, 150 mg/day	Elemental calcium, 150 mg/day

Vitamin K_2: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Shiraki, 2000[68]	1	3	1	3	1	3	12/18 (67)	Group 1: 120 Control group: 121	21.2	Not stated

Exercise: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Ebrahim, 1997[187]	2	BMD	Postmenopausal women with established osteoporosis (upper limb fracture in past 2 years)	68.0	Brisk walking, building to 40 minutes three times weekly	Upper limb exercises

Exercise: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Ebrahim, 1997[187]	2	3	2	2	1	2	12/18 (67)	Group 1: 81 Control group: 84	41	Charitable trust

Comparisons with active treatments: general information

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Abellan Perez, 1995[139]	1	Pain New vertebral fractures	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral crush fracture)	62.4	Intranasal calcitonin, 100 IU, + oral elemental calcium, 500 mg/day, for 14 days out of 28	Elemental calcium, 1000 mg/day
Adami, 1995[93]	2	BMD (spine)	Postmenopausal women with osteoporosis (lumbar T-score > –2); 5% had vertebral fracture at entry	59 (48–76)	Group 1: alendronate, 10 mg/day Group 2: alendronate, 20 mg/day All patients received calcium, 500 mg/day	Intranasal calcitonin, 100 IU/day, + calcium, 500 mg/day
Arthur, 1990[190]	1	BMD	Postmenopausal women with radiographic evidence of osteopaenia; 40% had vertebral compression fractures at entry	66.4	Oral calcitriol, 0.25–0.50 µg/day, + elemental calcium, 1 g/day	Elemental calcium, 1 g/day, + vitamin D_2, 50,000 U twice weekly
Birkenhager, 1992[164]	2	BMD Biochemical markers	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral compression fracture) or osteopaenia (lumbar BMD > 2 SD below normal mean of age-matched controls) (86% had fractures)	61.7 (50–70)	Intramuscular nandrolone decanoate, 50 mg every 4 weeks, + oestradiol valerate, 2 mg/day, days 1–25 of month + medroxyprogesterone acetate, 10 mg/day, days 16–25 of month	Oestradiol valerate, 2 mg/day, days 1–25 of month + medroxyprogesterone acetate, 10 mg/day, days 16–25 of month
Ebeling, 1998[70]	2	Vertebral fractures Spinal BMD	Men with moderately severe idiopathic osteoporosis (at least one vertebral fragility fracture)		Calcitriol, 0.50 µg/day	Calcium, 1000 mg/day
Falch, 1987[191]	2	Bone mass* Vertebral fractures* Fractures of long bones*	Postmenopausal women with established osteoporosis (fracture of distal left forearm)	59.6 (50–65)	Calcitriol, 0.5 µg/day (reduced to 0.25 µg/day in 28% of cases)	Vitamin D_3, 400 IU/day
Fujita, 1992[64]	Not specified	Vertebral fractures	Women with established osteoporosis (at least one non-traumatic vertebral fracture)	81	Intramuscular calcitonin, 10 units, twice weekly	Alfacalcidol, 0.75–1.5 µg/day
Fujita, 1993[58]	48 weeks	Lumbar vertebral mineral density	Patients with postmenopausal or senile osteoporosis	Not specified	Group 1: etidronate, 200 mg/day, for 2 weeks of 12-week cycle + placebo (alfacalcidol) Group 2: etidronate, 400 mg/day, for 2 weeks of 12-week cycle + placebo (alfacalcidol) Group 3: placebo (etidronate) for 2 weeks of 12-week cycle + alfacalcidol, 1 µg/day	
Gallagher, 1990b[74]	3	Hyperosteoidosis* Total body calcium* Vertebral fractures* Hip fractures*	Men and women with established idiopathic spinal osteoporosis (at least one vertebral fracture)	Not specified	Fluoride ('standard regime') + calcium, 2 g/day	Fluoride ('standard regime') + calcitriol, 0.5 µg/day
Geusens, 1986[163]	2	Bone mineral content Cortical bone volume Vertebral fracture rate Biochemical variables	Men and women with established osteoporosis (at least one vertebral fracture)	Only median per group given	Group 1: intramuscular nandrolone decanoate, 50 mg, every 3 weeks + placebo (alfacalcidol and calcium infusions) Rx2: alfacalcidol, 1 µg/day, + placebo (nandrolone and calcium infusions) Rx3: intravenous calcium infusions, 15 mg/kg body weight, for 12 consecutive days annually + placebo (nandrolone and alfacalcidol)	

continued

Comparisons with active treatments: general information *contd*

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Guañabens, 1996[75]	2	Bone mass Vertebral fracture	Women with established postmenopausal osteoporosis (mean lumbar BMD T-score –3.2 SD plus at least one atraumatic vertebral fracture)	64.5	Oral fluoride, 50 mg/day, + calcium, 1 g, 'regularly'	Etidronate, 400 mg/day, for 14 days out of 74 + calcium, 1 g 'regularly'
Gutteridge, 1996[79]	2.25	BMD* Vertebral fractures*	Postmenopausal women with established osteoporosis (at least one vertebral fracture)	69.6	HRT + enteric-coated sodium fluoride, 60 mg/day, for months 1–6 of 9-month cycle + calcium, 1 g/day	HRT + calcium, 1 g/day
Leidig-Bruckner, 1997[76]	4.7 ± 1.6	BMD* Vertebral fractures*	Postmenopausal women with established osteoporosis (at least one vertebral fracture)	64.4	Group 1: sodium fluoride, 75 mg/day Group 2: sodium fluoride, 75 mg/day, + oestradiol valerate, 1 mg/day, or oestradiol valerate, 1.25 mg/day, + medroxyprogesterone acetate, 5 mg/day Group 3: sodium fluoride, 75 mg/day, + intramuscular nandrolone decanoate, 50 mg, every 4 weeks for 2 years All patients received calcium, 1000 mg, + vitamin D, 3000 IU, daily	
Lems, 1997[192]	2	BMD	Men and women with established corticosteroid-induced osteoporosis (vertebral deformity, prior peripheral fracture or both)	58	Etidronate, 400 mg/day, for 2 weeks of 13-week cycle + sodium fluoride, 50 mg/day, + calcium, 50–100 mg/day	Etidronate, 400 mg/day, for 2 weeks of 13-week cycle + placebo (fluoride + calcium, 50–100 mg/day)
Lyritis, 1994[166]	1	Vertebral fractures BMD Symptoms (pain, mobility)	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral collapse)	66.9	Intramuscular nandrolone decanoate, 50 mg, every 3 weeks + placebo (alfacalcidol)	Alfacalcidol, 1 µg/day, + placebo (nandrolone)
Mamelle, 1988[176]	2	Vertebral fractures	Men and women with established osteoporosis (at least one non-traumatic vertebral crush fracture)	70.9 (50–92)	Sodium fluoride, 50 mg/day, elemental calcium, 1 g/day, + vitamin D_2, 800 IU/day	One of other regimes prescribed by French physicians (calcium + vitamin D_2, *n* = 95; cyclical calcitonin + phosphorus, *n* = 85; calcitonin + calcium, *n* = 12; calcium + phosphorus, *n* = 17; phosphorus + cyclical etidronate, *n* = 2)
Pacifici, 1988[104]	2	Bone mineral content	Women with osteoporosis or osteopaenia (at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation)	58 (26–80)	Potassium phosphate, 1500 mg/day, on days 1–3 and etidronate, 400 mg/day, on days 4–17 of 73-day cycle + calcium, 1000 mg/day	Conjugated oestrogens, 0.625 mg/day, for 25 days/month, medroxyprogesterone, 10 mg/day, days 15–25 + calcium, 1000 mg/day
Pak, 1989[193]	2.9 (mean)	BMD* Vertebral fractures* Non-vertebral fractures* Bone biopsy*	Men and women with osteoporosis or osteopaenia (fractures, low BMD or radiological evidence of osteopaenia) (98% had vertebral or peripheral fractures)	62.4 (29–82)	Weeks 1–2 of 5-month cycle: 1,25-hydroxyvitamin D, 2 mg/day; weeks 3–14: sodium fluoride, 50 mg/day, + 25-hydroxyvitamin D, 50 µg, twice weekly + calcium supplements to bring daily intake to 1500 mg/day; weeks 15–20: 25-hydroxyvitamin D, 50 µg, twice weekly + calcium supplements to bring daily intake to 1500 mg/day	Weeks 3–14 of 5-month cycle: sodium fluoride, 50 mg/day, + 25-hydroxyvitamin D, 50 µg, twice weekly + calcium supplements to bring daily intake to 1500 mg/day; weeks 15–20: 25-hydroxyvitamin D, 50 µg, twice weekly + calcium supplements to bring daily intake to 1500 mg/day

continued

Comparisons with active treatments: general information *contd*

Study	Length of study (years)	Primary outcome measure/s	Population	Mean age (range) (years)	Intervention/dose	Comparison/s
Rozhinskaya, 1999[72]	1	BMD Vertebral fractures Back pain	Women with established steroid-induced osteoporosis (at least two vertebral fractures + T-score < –2.5 at spine or femur neck)	56.3	Group 1: fluoride, 15 mg/day, + calcium, 450 mg/day Group 2: fluoride, 15 mg/day, + alfacalcidol, 0.5 µg/day, + calcium, 450 mg/day Group 3: alfacalcidol, 0.75 µg/day	
Shiota, 1998[194]	2	BMD	Women aged over 50 years with postmenopausal or senile osteoporosis (BMD less than 0.70 g/cm^2)	68.1	Group 1: ipriflavone, 600 mg/day Group 2: subcutaneous calcitonin, 20 IU/week Group 3: alfacalcidol, 0.5 µg/day, + calcium lactate, 2 g/day Group 4: alfacalcidol, 2 µg/day, for weeks 1–2, and 0.5 µg/day for weeks 7–14; ipriflavone, 600 mg/day, for weeks 3–6; calcium lactate, 2 g/day, for weeks 7–14 of 14–week cycle	
Shiraki, 1999[195]	48 weeks	Lumbar BMD	Women with primary osteoporosis (lumbar T-score < –2.5, or < –1.5 with one or more vertebral fractures)	63.3	Oral alendronate, 5 mg/day + elemental calcium, 200 mg/day	Alfacalcidol, 1 µg/day, + elemental calcium, 200 mg/day
Thiébaud, 1994[115]	2	BMD	Postmenopausal women with established osteoporosis (at least one vertebral fracture)	65.9	Intravenous pamidronate, 300 mg/month, + calcium, 1 g/day, and vitamin D, 1000 U/day	Fluoride, 20–30 mg/day, + calcium, 1 g/day, and vitamin D, 1000 U/day
Tilyard, 1992[124]	3	Rate of new vertebral fractures	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral compression fracture)	63.7 (50–79)	Oral calcitriol, 0.25 µg/day	Elemental calcium, 1 g/day
Watts, 1990[109]	2 (as RCT)	Spinal BMD Rate of new vertebral fractures	Postmenopausal women with established osteoporosis (at least one but no more than four vertebral crush fractures)	65.1	Group 1: sodium-potassium phosphate, 2 g/day, on days 1–3 + placebo (etidronate) on days 4–17 of 91-day cycle Group 2: placebo (sodium-potassium phosphate) on days 1–3 + etidronate, 400 mg/day, on days 4–17 of 91-day cycle Group 3: sodium-potassium phosphate, 2 g/day, on days 1–3, etidronate, 400 mg/day, on days 4–17 of 91-day cycle All patients received calcium, 500 mg/day, on days 18-91 of 91-day cycle	
Wimalawansa, 1998[110]	4	BMD	Postmenopausal women with established osteoporosis (spinal T-score –2 and at least one but no more than four atraumatic thoracic vertebral crush fractures)	64.9 (58–72)	Group 1: Premarin®, 0.625 mg/day, + Norgestrel®, 150 µg, for 12 days/month Group 2: etidronate, 400 mg/day, for weeks 1–2 of 12-week cycle Group 3: Premarin®, 0.625 mg/day, + Norgestrel®, 150 µg, for 12 days/month + etidronate, 400 mg/day, for weeks 1–2 of 12-week cycle All patients received elemental calcium, 1 g/day, and vitamin D, 400 U/day	

Comparisons with active treatments: 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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Abellan Perez, 1995[139]	2	1	2	3	0	3	10/15 (67)	Group 1: 43 Control group: 45	Not specified	Not specified
Adami, 1995[93]	1	1	3	3	1	0	9/15 (73)	Group 1: 68 Group 2: 72 Group 3: 75	14.3	Not specified
Arthur, 1990[190]	1	3	1	1	0	1	7/15 (47)	14	28.6	Not specified
Birkenhager, 1992[164]	1	3	2	1	0	3	10/15 (67)	43	16.3	Pharmaceutical company
Ebeling, 1998[70]	1	3	1	1	1	1	8/18 (44)	Group 1: 20 Group 2: 19	12%	Not specified
Falch, 1987[191]	1	3	2	3	1	3	13/18 (72)	Group 1: 47 Control group: 39	11.6	Not specified
Fujita, 1992[64]	1	3	2	2	0	3	11/15 (73)	Group 1: 8 Group 2: 8 Control group: 8	6.2	Not specified
Fujita, 1993[58]	1	1	1	2	0	1	6/15 (40)	414	Not specified	Not specified
Gallagher, 1990b[74]	1	1	1	1	1	1	6/18 (33)	40	Not specified	Not specified
Geusens, 1986[163]	1	3	2	1	0	3	10/15 (67)	60	56.7	Pharmaceutical company (drugs only)
Guañabens, 1996[75]	1	1	2	1	1	1	7/18 (39)	Group 1: 60 Group 2: 65	28.8	Not specified
Gutteridge, 1996[79]	1	1	1	1	1	1	6/18 (33)	Group 1: 14 Group 2: 16	14.3	Government/ research council
Leidig-Bruckner, 1997[76]	1	1	1	3	0	1	7/15 (47)	Group 1: 17 Group 2: 8 Group 3: 13	7.9	Not specified
Lems, 1997[192]	1	1	2	1	3	3	11/18 (61)	Group 1: 24 Group 2: 23	14.9	Charitable foundation/ pharmaceutical company
Lyritis, 1994[166]	1	1	3	3	0	1	9/15 (60)	Group 1: 44 Group 2: 44	0	Not specified

continued

Comparisons with active treatments: methodological quality *contd*

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 (%)	Number of patients randomised to study	Lost to follow-up (%)	Source of funding
Mamelle, 1988[176]	1	1	3	2	1	3	11/18 (61)	Group 1: 257 Group 2: 209	13	Pharmaceutical company/ government agency
Pacifici, 1988[104]	1	1	2	3	0	3	10/15 (67)	128	45.3	Not specified
Pak, 1989[193]	1	3	3	2	3	3	15/18 (83)	Group 1: 23 Group 2: 21		Not specified
Rozhinskaya, 1999[72]	1	1	2	1	0	1	6/15 (40)	Group 1: 6 Group 2: 6 Group 3: 10		Not specified
Shiota, 1998[194]	1	1	1	1	0	2	6/15 (40)	Not clear	Not clear	Not specified
Shiraki, 1999[195]	3	1	1	3	0	3	11/15 (73)	Group 1: 105 Group 2: 105	40.5	Pharmaceutical company
Thiébaud, 1994[115]	1	1	2	3	1	2	10/18 (56)	Group 1: 16 Control group: 16	6.2	Drug donated by pharmaceutical company
Tilyard, 1992[124]	2	3	3	3	3	2	16/18 (89)	Group 1: 314 Control group: 308	30.6	Not specified
Watts, 1990[109]	2	3	3	3	1	3	15/18 (83)	Group 1: 107 Group 2: 105 Group 3: 107	15.4	Pharmaceutical company
Wimalawansa, 1998[110]	2	3	2	3	1	3	14/18 (78)	Group 1: 18 Group 2: 17 Group 3: 19	19.4	No information

Appendix 6

Economics literature search strategy

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 exp models, economic/
8 Economics, pharmaceutical/
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 or/1–13
15 exp Osteoporosis/
16 Bone diseases, metabolic/
17 osteoporo$.tw.
18 15 or 16 or 17
19 (bone adj6 densit$).tw.
20 Bone density/
21 (bone or bones).mp.
22 exp Densitometry/
23 Tomography, x-ray computed/
24 densit$.tw.
25 23 and 24
26 22 or 25
27 21 and 26
28 19 or 20 or 27
29 Colles' fracture/
30 exp Hip fractures/
31 Spinal fractures/
32 29 or 30 or 31
33 Fractures/
34 colles$.tw.
35 9hip or hips).tw.
36 (femur adj6 neck).tw.
37 (femoral adj6 neck).tw.
38 (spine or spinal).tw.
39 vertebra$.tw.
40 Lumbar vertebrae/
41 34 or 35 or 36 or 37 or 38 or 39 or 40
42 33 and 41
43 fractur$.tw.
44 34 or 35 or 36 or 37 or 38 or 39
45 (fractur$ adj6 (colles$ or (hip or hips) or (femur adj6 neck) or (femoral adj6 neck) or (spine or spinal) or vertebra$)).tw.
46 32 or 42 or 45
47 Estrogen replacement therapy/
48 estrogen replacement therapy.tw.
49 oestrogen replacement therapy.tw.
50 hormone replacement therapy.tw.
51 ert.tw.
52 ort.tw.
53 hrt.tw.
54 47 or 48 or 49 or 50 or 51 or 52 or 53
55 exp Menopause/
56 Climacteric/
57 menopaus$.tw.
58 postmenopaus$.tw.
59 climacteric.tw.
60 55 or 56 or 57 or 58 or 59
61 54 or 60
62 46 and 61
63 18 or 28 or 62
64 14 and 63

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The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278