Health Technology Assessment 2005; Vol. 9: No. 22

A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis

M Stevenson, M Lloyd Jones, E De Nigris,
N Brewer, S Davis and J Oakley

June 2005

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis

M Stevenson,[1*] M Lloyd Jones,[1] E De Nigris,[1] N Brewer,[1] S Davis[1] and J Oakley[2]

[1] School of Health and Related Research (ScHARR), University of Sheffield, UK
[2] Department of Probability and Statistics, University of Sheffield, UK

* Corresponding author

Declared competing interests of authors: none

Published June 2005

This report should be referenced as follows:

Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess* 2005;**9**(22).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. '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.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

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 research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 01/58/01. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis

M Stevenson,[1*] M Lloyd Jones,[1] E De Nigris,[1] N Brewer,[1] S Davis and J Oakley[2]

[1] School of Health and Related Research (ScHARR), University of Sheffield, UK

[2] Department of Probability and Statistics, University of Sheffield, UK

* Corresponding author

Objectives: To establish the clinical effectiveness and cost-effectiveness of selective oestrogen receptor modulators, bisphosphonates and parathyroid hormone (subject to licensing) for the prevention and treatment of osteoporosis and the prevention of osteoporotic fractures in postmenopausal women.

Data sources: Electronic databases.

Review methods: Studies that met the review's entry criteria were eligible for inclusion in the meta-analyses provided that they reported fracture incidence in terms of the number of patients suffering fractures. Meta-analysis was carried out using the random-effects model. A model was constructed to estimate the cost-effectiveness of osteoporosis interventions. The model calculated the number of fractures that occurred and provided the costs associated with osteoporotic fractures, and the quality-adjusted life-years (QALYs). In addition, the conditions of breast cancer and coronary heart disease (CHD) were modelled, as some interventions have been shown to affect the risk of these conditions.

Results: Ninety randomised controlled trials (RCTs) met the inclusion criteria. They related to the five interventions (alendronate, etidronate, risedronate, raloxifene and teriparatide) and to five comparators (calcium, calcium plus vitamin D, calcitriol, hormone replacement therapy and exercise), as well as placebo or no treatment. All five interventions have been shown to reduce the risk of vertebral fracture in women with severe osteoporosis with adequate calcium intakes. However, none of these drugs has been demonstrated, by direct comparison, to be significantly more effective than either each other or the other active interventions reviewed in this report. The intervention costs of treating all osteoporotic women, for a period of 5 years, were in the region of £900–1500 million for alendronate, etidronate, risedronate and raloxifene. The cost per QALY ratios fell dramatically with age. Assuming the risks of a woman with severe osteoporosis at the threshold of osteoporosis, no treatment had a cost per QALY below £35,000 at 50 years of age. At 60 years of age, the cost per QALY of raloxifene was £26,000 assuming no impact on hip fractures, and £31,000 assuming an adverse effect. However, these results are driven by the effect on breast cancer and the assumptions made regarding this disease state. No other intervention had a cost per QALY below £35,000. When analyses were conducted assuming that the fracture risk is doubled at each site, alendronate and risedronate had cost per QALY ratios below £30,000 at all ages. For women at the threshold of osteoporosis, without a prior fracture and aged 70 years, the cost per QALY of the three bisphosphonates ranged from £34,000 to £41,000. Raloxifene had a cost per QALY of £23,000, assuming no effect on hip fracture, given assumptions regarding breast cancer. At 80 years of age, the cost per QALY of alendronate and risedronate was below £20,000. This was true for etidronate when incorporating observational data, but the value rose to £69,000 when only RCT data were used. No other intervention had a cost per QALY below £35,000. It was assumed that doubling the risk of fracture for women without a prior fracture would give results similar to patients at the threshold of osteoporosis with a prior fracture.

Conclusions: Of the five interventions, only raloxifene appeared to reduce the risk of vertebral fracture in postmenopausal women unselected for low bone mineral density (BMD). However, as the full data have not been made public, there is some uncertainty regarding this result. None of the five interventions has been shown to reduce the risk of non-vertebral fracture in women unselected for low BMD. All of the proposed interventions provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY

gain for each intervention was strongly related to the age of the patient. The estimated costs varied widely for the interventions. These net costs were markedly different by age, with some interventions becoming cost-saving at higher age ranges in patients with a prior fracture. Areas for future research include: the evidence base for the efficacy of fracture prevention in the very elderly, reanalysis of raloxifene using a dedicated breast cancer and CHD model, and more trials considering the cost-effectiveness of teriparatide.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout.

Glossary

Osteopenia Bone mineral density between 1 and 2.5 standard deviations below the young adult mean (*T*-score –1 to –2.5).

Osteoporosis Bone mineral density 2.5 standard deviations or more below the young adult mean (*T*-score <–2.5).

Reference nutrient intake The level of intake of a nutrient that is sufficient to cover the needs of nearly all the population group for which it is recommended; as it is set 2 standard deviations above the estimated average requirement for that nutrient, it is considerably higher than most people need, and individuals consuming the reference nutrient intake are most unlikely to be deficient in that nutrient.[1]

Severe osteoporosis Bone mineral density 2.5 standard deviations or more below the young adult mean (*T*-score <–2.5) plus at least one documented fracture.

***T*-score** The number of standard deviations from the average bone mineral density of healthy young women.

Z-score The number of standard deviations from the average bone mineral density of women of the same age as the patient.

List of abbreviations

AOPS	Alendronate Osteoporosis Prevention Study
BMD	bone mineral density
C	control
CEAC	cost-effectiveness acceptability curve
CEE	conjugated equine estrogen
CHD	coronary heart disease
CI	confidence interval
DVT	deep venous thrombosis
DXA	dual-energy X-ray absorptiometry
EPIC	Early Postmenopausal Intervention Cohort
EQ-5D	EuroQol 5 Dimensions
FIT	Fracture Intervention Trial
FSH	follicle-stimulating hormone
GI	gastrointestinal
HRT	hormone replacement therapy
HSUV	health state utility value
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
MFP	monofluorophosphate

continued

List of abbreviations *continued*

MI	myocardial infarction
MORE	Multiple Outcomes of Raloxifene Evaluation
MPA	medroxyprogesterone acetate
NETA	norethisterone acetate
NHP	Nottingham Health Profile
NOF	National Osteoporosis Foundation
NSAID	non-steroidal anti-inflammatory drug
PEPI	postmenopausal (o)estrogen/progestin interventions
PTH	parathyroid hormone
QALY	quality-adjusted life-year
QWB	quality of well-being
RCT	randomised controlled trial
RH	relative hazard
RNI	reference nutrient intake
RR	relative risk
Rx	treatment
SD	standard deviations
SERM	selective (o)estrogen receptor modulator
SG	standard gamble
SHEMO	Sheffield Health Economic Model for Osteoporosis
TTO	time trade-off
VAS	visual analogue scale
WHI	Women's Health Initiative

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

Epidemiology and background

Osteoporosis is a common disease in the elderly, with an estimated 2.1 million female sufferers in England and Wales. It is defined as possessing a *T*-score of –2.5 standard deviations or lower. The main consequence of osteoporosis is an increased incidence of fractures, notably at the hip, spine, wrist and proximal humerus, which increases as a woman ages. These result not only in morbidity for the patient, with a risk of mortality following fractures of the hip, and possibly of the vertebra, but also in the consumption of scarce health resources. A recent estimate of the cost in the UK of osteoporotic fractures in females has put this figure at £2100 million. A woman who has suffered a fracture is defined as suffering from severe osteoporosis.

Objective

The aim of this review was to evaluate the use of alendronate, etidronate, risedronate, raloxifene or teriparatide to reduce the risk of osteoporotic fracture in postmenopausal women.

Methods

Studies that met the review's entry criteria were eligible for inclusion in the meta-analyses provided that they reported fracture incidence in terms of the number of patients suffering fractures, as this enabled calculation of the relative risk of patients in the intervention group developing a new fracture or fractures, compared with those in the control group. Ideally, only studies that had fracture as a primary end-point would have been included in the meta-analyses. However, pragmatically this was not possible as very few studies met this criterion. Meta-analysis was carried out with Review Manager, using the random-effects model, as this both allows generalisation beyond the sample of patients represented by the studies included in the meta-analysis and provides wider, more conservative, confidence intervals than the fixed-effects model. Since the end-point of interest was fracture, it seemed appropriate to include open-label studies.

To ensure comparability, the meta-analyses of vertebral fractures only pooled data from studies that used the same definition of vertebral fracture. Where possible, data were pooled from studies using a definition that required a 20% or greater reduction in anterior, middle or posterior vertebral height: as noted above, this definition was felt to identify fractures more reliably than a definition that required a 15% or greater reduction.

A model was constructed to estimate the cost-effectiveness of osteoporosis interventions. The key inputs to this model were the efficacy data for each intervention in terms of the ability to reduce the incidence of hip, vertebral, wrist and proximal humerus fractures. The model calculated the number of fractures that occurred and provided the costs associated with osteoporotic fractures, and the quality-adjusted life-years (QALYs) accrued by a cohort of 100 women with osteoporosis, with each fracture being detrimental to health. When the costs of the intervention are included, the marginal cost compared with no treatment (assumed to be a sufficient intake of calcium and vitamin D) can be calculated. When this figure is divided by the gain in QALYs, a cost per QALY ratio can be calculated. In addition to osteoporotic fractures, the conditions of breast cancer and coronary heart disease (CHD) were modelled, as some interventions have been shown to affect the risk of these diseases.

Results and conclusions

Number and quality of studies, and direction of evidence

Ninety randomised controlled trials (RCTs) met the inclusion criteria. They related to the five interventions (alendronate, etidronate, risedronate, raloxifene and teriparatide) and to five comparators [calcium, calcium plus vitamin D, calcitriol, hormone replacement therapy (HRT) and exercise], as well as placebo or no treatment.

All five interventions have been shown to reduce the risk of vertebral fracture in women with severe osteoporosis with adequate calcium intakes. Alendronate and raloxifene have also been

demonstrated to reduce the risk of vertebral fracture in women with adequate calcium or vitamin D intakes who have osteoporosis without fracture. However, only risedronate and teriparatide have also been demonstrated to reduce the risk of non-vertebral fracture in women with severe osteoporosis and adequate calcium intakes. Alendronate has been shown to do so in women with osteoporosis with or without fracture and with adequate calcium or vitamin D intakes. However, none of these drugs has been demonstrated, by direct comparison, to be significantly more effective than either each other or the other active interventions reviewed in this report.

Of the five interventions, only raloxifene appeared to reduce the risk of vertebral fracture in postmenopausal women unselected for low bone mineral density (BMD). However, as the full data have not been made public, there is some uncertainty regarding this result. None of the five interventions has been shown to reduce the risk of non-vertebral fracture in women unselected for low BMD.

Summary of benefits

All of the proposed interventions provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the age of the patient.

Costs

The intervention costs of treating all osteoporotic women, for a period of 5 years, were in the region of £900–1500 million for alendronate, etidronate, risedronate and raloxifene. Teriparatide had a much higher acquisition cost, but has been used on a small subset of the population and thus this cost has not been calculated.

The estimated costs, when the reduction in the number of fractures and breast cancer events over a 10-year period was included, varied widely for the interventions. These net costs were markedly different by age, with some interventions becoming cost-saving at higher age ranges in patients with a prior fracture.

Cost per QALY

The cost per QALY ratios fell dramatically with age. Assuming the risks of a woman with severe osteoporosis at the threshold of osteoporosis, no treatment had a cost per QALY below £35,000 at 50 years of age. At 60 years of age, the cost per QALY of raloxifene was £26,000 assuming no impact on hip fractures, and £31,000 assuming an adverse effect. However, these results are driven by the effect on breast cancer and the assumptions made regarding this disease state. No other intervention had a cost per QALY below £35,000. At 70 years of age, the cost per QALY ratios of the three bisphosphonates significantly decreased, being £10,000, £15,000 and £28,000 for alendronate, risedronate and etidronate, respectively. Etidronate had a reasonably strong observational evidence base and where this was considered the cost per QALY ratio fell to £15,000. Raloxifene, assuming no effect on hip fracture, had a cost per QALY of £24,000. At 80 years of age, both alendronate and risedronate dominated no treatment. Raloxifene, assuming no effect on hip fracture, had a cost per QALY of £28,000. This figure was £38,000 for teriparatide (when assumed to cost £2000 per annum) and £45,000 for etidronate. Incorporating the observational data into the etidronate analysis reduced the cost per QALY ratio to £6000.

Analyses were conducted assuming that the fracture risk is doubled at each site. In these circumstances alendronate and risedronate had cost per QALY ratios below £30,000 at all ages. If the observational data were incorporated, etidronate had a cost per QALY ratio below £30,000 at all ages; however, using RCT data alone the cost per QALY fell below £30,000 only at 70 years of age and above. Raloxifene (assuming no effect on hip fracture) had a cost per QALY ratio below £30,000 at all ages; however, this again was driven by breast cancer assumptions. Teriparatide (assumed to cost £3500 per annum) had a cost per QALY of £31,000 at 80 years of age.

For women at the threshold of osteoporosis, without a prior fracture and aged 70 years, the cost per QALY of the three bisphosphonates ranged from £34,000 to £41,000. Raloxifene had a cost per QALY of £23,000, assuming no effect on hip fracture, given assumptions regarding breast cancer. At 80 years of age, the cost per QALY of alendronate and risedronate was below £20,000. This was true for etidronate when incorporating observational data, but the value rose to £69,000 when only RCT data were used. No other intervention had a cost per QALY below £35,000. It was assumed that doubling the risk of fracture for women without a prior fracture would give results similar to patients at the threshold of osteoporosis with a prior fracture.

The results for 80 years of age in all scenarios should be treated with caution as the assumed efficacy for each intervention has not been proven in this age group. The results for raloxifene should be treated with caution as the major impact on quality of life is through an effect on breast cancer and not via effects on fractures.

Recommendations for research

The evidence base for the efficacy of fracture prevention in the very elderly needs to be strengthened. The results calculated for women aged 80 years assumed the applicability of results from RCTs (in which only a minority of patients were of this age). If this were not true, as possibly demonstrated by an RCT by McClung, then the results would be markedly different.

To assess accurately the true potential of raloxifene, reanalysis should be conducted using a dedicated breast cancer and CHD model. Results for women at the threshold of osteoporosis and with a prior fracture that ignore these benefits produced a high cost per QALY ratio (>£70,000), which fell significantly (<£40,000) when the effect on breast cancer was included and to under £30,000 when the effect on CHD was included. The robustness of these latter results cannot be guaranteed, owing to simplifying assumptions on the aetiology, costs and QALYs of breast cancer and CHD.

The cost-effectiveness of teriparatide is dependent on the assumed efficacy on hip fracture. At present the decrease is non-significant and a further trial is recommended to reduce the uncertainty in this parameter.

Chapter 1

Aim of the review

The review aims to establish the clinical effectiveness and cost-effectiveness of selective oestrogen receptor modulators (SERMs), bisphosphonates and parathyroid hormone (PTH) (subject to licensing) for the prevention and treatment of osteoporosis and the prevention of osteoporotic fractures in postmenopausal women, and to provide guidance to the NHS in England and Wales.

Chapter 2
Background

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 and susceptibility to fracture.[2]

The clinical significance of osteoporosis lies in the fractures that arise; without a fracture, a woman suffering from osteoporosis will not suffer morbidity. The most 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.

The incidences of fracture are strongly related to age, with a steady increase as a woman ages. The exception is for hip fracture, where the rise appears to be more exponential.

Fractures of the spine often go undetected. It is estimated that only one-third of fractures seen in trials, where morphometric criteria are used to establish the presence of a fracture, come to clinical attention. There is a good deal of uncertainty surrounding the impact of undetected 'morphometric' fractures on the quality of life of the sufferer, and on any cost impacts that such fractures have.

Osteoporotic fractures occurring at the spine and the distal radius are associated with significant morbidity, but the most serious consequences arise in patients with hip fracture, which is associated with an increase in mortality in the year following the hip fracture.[3]

It has been estimated that the cost of treating osteoporotic fractures in female postmenopausal patients was approximately £1500–1800 million in the UK per annum in 2000.[4,5] These costs have been estimated to increase to £2100 million by 2010.[5] The key components of the costs associated with osteoporotic fractures are hip fractures and subsequent nursing home care that is required for a proportion of these patients.

This report is focused on postmenopausal women, owing to the deterioration of bone quality following the menopause.

Description of osteoporosis, osteopenia and severe (established) osteoporosis

The definition has been developed since bone mineral can be measured with precision and accuracy allowing definitive diagnoses of osteoporosis. However, it is acknowledged that other factors, such as abnormalities within the skeleton and risk of falls, are also important in determining the risks of fracture. Nevertheless, bone mineral density (BMD) alone forms the basis for the diagnosis of osteoporosis.

The units used in this report for assessing the BMD of a woman will be *T*-scores and *Z*-scores. A *T*-score is defined as the number of standard deviations (SD) from the average BMD of healthy young women. A *Z*-score is defined as the number of SD from the average BMD of women of the same age as the patient.

Two thresholds of BMD have been proposed for Caucasian women based on the *T*-score.[6,7] The first, osteoporosis, denotes a value for BMD that is 2.5 SD or more below the young adult mean value (*T*-score <–2.5 SD). The second, osteopenia, denotes a *T*-score that lies between –1 and –2.5 SD.

The class of osteoporosis is further divided into patients with osteoporosis and those with severe (or established) osteoporosis, which is defined as a *T*-score <–2.5 SD plus at least one documented fracture. In this report severe osteoporosis will be used to define patients who have a *T*-score equal to or less than –2.5 SD, with a prior fracture. The term osteoporosis will be used to define patients with a *T*-score equal to or less than –2.5 SD, without a previous fracture.

Since the introduction of working definitions of osteoporosis, much attention has focused on their application to epidemiology, clinical trials and patient care. Several problems have emerged, however, largely owing to the development of new

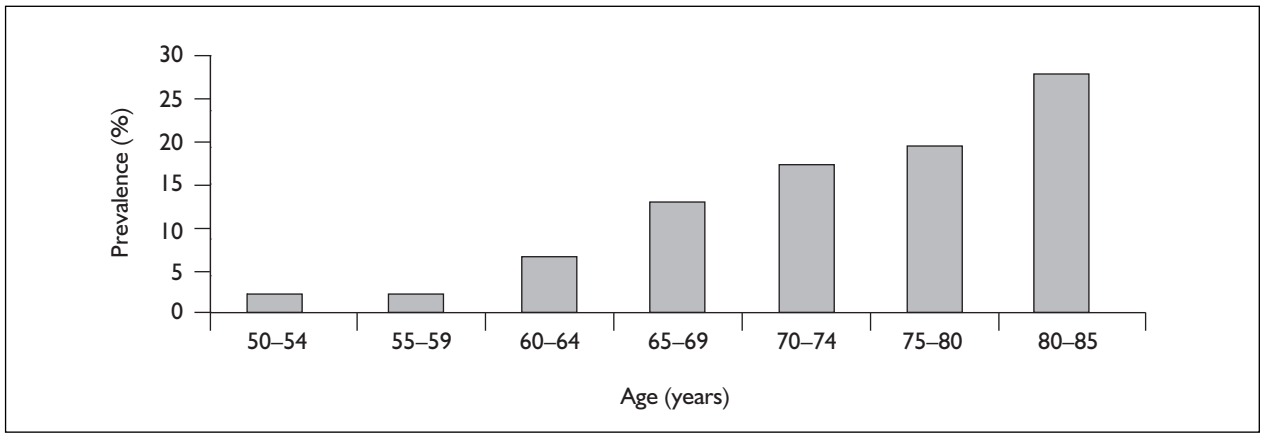

FIGURE 1 *Estimated prevalence of female osteoporosis, measured at the femoral neck, by age band*

measurement techniques applied to 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 (DXA).[8] Measurements at the hip have the highest predictive value for hip fracture.[9] Moreover, the hip is a site of greatest biological relevance since hip fracture is the dominant complication of osteoporosis in terms of morbidity and cost.

The *Z*-score is used primarily in calculating the increased risks of fracture when compared to the average population at that age. Research has shown that the *Z*-score is a better predictive variable than an absolute *T*-score value, since any value, such as –2.5 SD, will be associated with different fracture risks at the age of 50 than at 80 years.

Epidemiological data

Prevalence of osteoporosis by age

Raw data were taken from a UK population-based study by Holt and colleagues[10] and used to derive the prevalence of osteoporosis within society. This data set contained observations on 5713 women aged between 50 and 85 years.

The femoral neck was used as the measurement site and the percentage of women with a *T*-score of –2.5 SD or below was recorded. These data are shown in *Figure 1* and exhibit a marked increase with age. Multiplying these prevalence rates by the respective population of England and Wales,[11] it is estimated that there are 0.94 million women suffering with osteoporosis.

TABLE 1 *Average* T*-scores for women at the threshold of osteoporosis by age band*

Age (years)	Average UK BMD score
50–54	–0.66
55–59	–0.92
60–64	–1.17
65–69	–1.43
70–74	–1.69
75–79	–1.94
80–84	–2.20
85–89	–2.45

Data from Holt and Khaw.[10]

The average *T*-score at the femoral neck at each age band was calculated from the UK population data[10] as before. A linear relationship was assumed and *T*-score was assumed to be 2.0251–0.0512 × age (in years). The assumed average *T*-score by age band is given in *Table 1*.

Incidence of osteoporotic fractures by age

Data on the incidence of hip, wrist and proximal humerus fractures in women were taken from a large-scale Scottish study.[12] As reliable data on the incidence of clinically diagnosed vertebral fractures in the UK were scarce, an estimate was imputed for the UK using vertebral fracture rates seen in Malmö, Sweden,[13] assuming that the ratio of hip to vertebral fractures would be similar for both regions. There appears to be consistency in the pattern of different osteoporotic fractures in the Western world, which provides some validation of this approach.[14] It is noted that an unknown (but small) proportion of these fractures will not

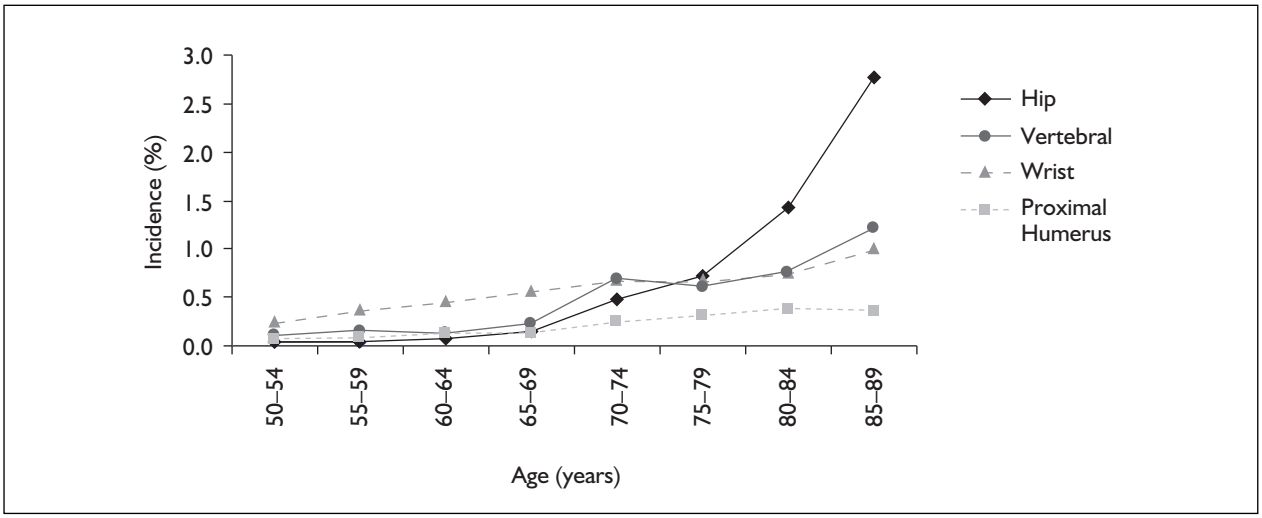

FIGURE 2 *Annual incidence of osteoporotic fracture in females by site*

TABLE 2 *Increased risk of subsequent fracture following an initial fracture*

	Location of subsequent fractures			
Prior fracture site	**Hip**	**Vertebral**	**Wrist**	**Proximal humerus**
Hip	2.3	2.5	1.4	1.9
Vertebra	2.3	4.4	1.4	1.8
Wrist	1.9	1.7	3.3	2.4
Proximal humerus[a]	2.0	1.9	1.8	1.9

Adapted from Klotzbuecher *et al.*[15]
[a] Assumed equal to the value for all non-spinal fractures in Klotzbuecher *et al.*[15]

be osteoporosis related and thus these data will overestimate fractures at these sites; however, fractures at other body sites are not included, so the introduction of large bias is not expected.

These data are presented graphically in *Figure 2*.

There is a breadth of published literature, meta-analysed by Klotzbuecher and colleagues,[15] that indicates that an initial fracture greatly increases the risk of subsequent fractures. These data have been used within the model to increase the risk of subsequent fractures following an initial fracture. The values used within the cost-effectiveness model were the point estimates presented by Klotzbuecher and colleagues.[15]

It was assumed that subsequent risks of secondary fractures at the proximal humerus are equivalent to the pooled non-spinal fractures category reported by Klotzbuecher and colleagues.[15] It was also assumed that proximal humerus had the predictive power equal to that of the 'other' category reported by Klotzbuecher and colleagues.[15] All populations were assumed to be perimenopausal or postmenopausal. There have been no prior studies on the future effect of hip fractures on wrist fractures. As a conservative estimate this risk was set at 1.4, equivalent to the lowest relative risk of all other fracture sites. These data are presented in *Table 2*.

It was assumed that for individuals who have suffered fractures in two different sites only the greatest risk adjustment will be applied in calculating the risks of subsequent fractures. For example, were a patient to have both a prior hip and wrist fracture, the relative risk (RR) adjustment for a subsequent vertebral fracture would be 2.5 (from the hip fracture), rather than 1.9 (from the wrist fracture). The relative risk adjustment for a subsequent wrist fracture would be 3.3 (from the wrist fracture), rather than 1.4 (from the hip fracture).

Increased risk of fracture for patients with low bone mass

BMD status is a significant factor in estimating the risk of fracture for a patient. Work conducted by Marshall and colleagues[16] assessed the increased probability of fracture associated with a *Z*-score of –1, when measured at the femoral neck. The point estimates of this increased risk of fracture are presented in *Table 3*. Data for proximal humerus were assumed to equal those reported by Marshall and colleagues[16] for all fractures.

TABLE 3 *Increased risk of fracture associated with a Z-score of –1 (as reported by Marshall* et al.*[16])*

Fracture site	Increased risk of fracture per *Z*-score
Hip	2.6
Vertebral	1.8
Wrist	1.4
Proximal humerus[a]	1.6

[a] Assumed equal to the value for all fractures.

TABLE 4 *Increased risk of hip fracture associated with a Z-score of –1 (as reported by Johnell* et al.*[8])*

Age (years)	Increased risk of hip fracture per *Z*-score
50–54	3.68
55–59	3.35
60–64	3.07
65–69	2.89
70–74	2.78
75–79	2.58
80–85	2.28
86–90	1.92

The equations presented in Marshall[16] are of the form $(RR)^{-Z\text{-score difference}}$, hence the increased risk for a hip fracture for patients with a *Z*-score of –2 would be 6.76 times (2.6^2). The increased risk would be 4.19 times ($2.6^{1.5}$) for a patient with a *Z*-score of –1.5.

More recent work undertaken by Johnell and colleagues[8] has shown that the increased risk of hip fracture in relation to *Z*-score is age dependent. These newer data have been used in the modelling, as contained in *Table 4*.

Calculating the risk of fracture for populations with average BMD and without a prior fracture

The RRs presented in *Table 2* are compared with patients without prior fracture, whereas those in *Table 3* are compared with patients with the average BMD for the patient age. To estimate the correct fracture risk for patients with low BMD and/or prior fracture, the risk for women with average BMD and without prior fracture needs to be calculated. Use of the average population values would overestimate the numbers of fractures because these average figures already contain a subset of women with osteoporosis and/or prior fractures, who are at greater risk than women without fractures and with normal BMD.

The estimated fracture risks for a woman with average BMD and without prior fracture are shown in *Table 5*. The methodology behind these calculations is given in Appendix 1.

The percentage reduction is influenced by a number of factors. At younger ages there will be few osteoporotic and severely osteoporotic women (see *Table 129* in Appendix 1), and thus the risk for women with average BMD scores will be close

TABLE 5 *Estimated fracture risk by age for a woman with average BMD and no prior fracture*

	Fracture risk (%) at each site			
Age (years)	Hip	Vertebral	Wrist	Proximal humerus
50–54	0.02 (26)	0.07 (6)	0.25 (3)	0.06 (4)
55–59	0.04 (32)	0.14 (11)	0.35 (7)	0.08 (9)
60–64	0.06 (41)	0.13 (20)	0.41 (12)	0.11 (16)
65–69	0.10 (48)	0.20 (29)	0.46 (19)	0.10 (24)
70–74	0.27 (55)	0.34 (37)	0.51 (27)	0.17 (32)
75–79	0.35 (50)	0.37 (38)	0.49 (30)	0.20 (34)
80–84	0.67 (50)	0.41 (42)	0.50 (34)	0.23 (38)
85–89	1.34 (47)	0.62 (45)	0.63 (37)	0.21 (41)

The percentage reduction in fracture incidence compared to the average for all women in that age band is shown in parentheses.

to the average population risk. However, at younger ages the number of *Z*-scores between an osteoporotic woman and a woman with average BMD is greater (see *Table 1*), which will increase the risk at each fracture site for osteoporotic patients and hence lower the risk for women with average BMD values. The converse argument is applicable to patients at older ages. As these factors work in different directions, the magnitudes of the reduction between the average population risk and that of a woman with average BMD at different age bands cannot be predicted intuitively.

For vertebral, wrist and proximal humerus fractures, which have relatively low increases due to *Z*-score differentials (see *Table 3*), the increased proportion of women with osteoporosis dominates the effect owing to the greater *Z*-score between average BMD and a *T*-score of –2.5 SD. As the cohort age increases, the percentage reduction compared with the average values increase.

For hip fracture, which has a relatively high risk of fracture in relation to *Z*-score at younger ages (see *Table 4*), the percentage reduction values are large even at younger ages.

The data from *Table 5* will be used in the model and multiplied as appropriate to take into account the extra risks for the assumed BMD value and prior fracture status for each patient.

Fracture risk at the threshold for osteoporosis

Table 6 and *Figure 3* give the estimated fracture risk at each site by age for women at the threshold of osteoporosis. No data on the fracture risks for patients with severe osteoporosis have been given, as the risks would be dependent on the site of the previous fracture, as detailed in *Table 2*. As a rough guide, the fracture rates for those suffering from severe osteoporosis would be approximately double those presented in *Table 6*. It can be seen that as the population age increases the risk at the threshold for osteoporosis may be lower than that

TABLE 6 *Estimated fracture risk by age for a woman with a* T*-score of –2.5 and no prior fracture*

	Fracture risk (%) at each site			
Age (years)	**Hip**	**Vertebral**	**Wrist**	**Proximal humerus**
50–54	0.07	0.24	0.63	0.14
55–59	0.07	0.26	0.77	0.17
60–64	0.10	0.19	0.79	0.22
65–69	0.16	0.28	0.82	0.17
70–74	0.43	0.73	0.84	0.28
75–79	0.56	0.56	0.71	0.30
80–84	1.09	0.63	0.66	0.32
85–89	1.90	0.89	0.75	0.27

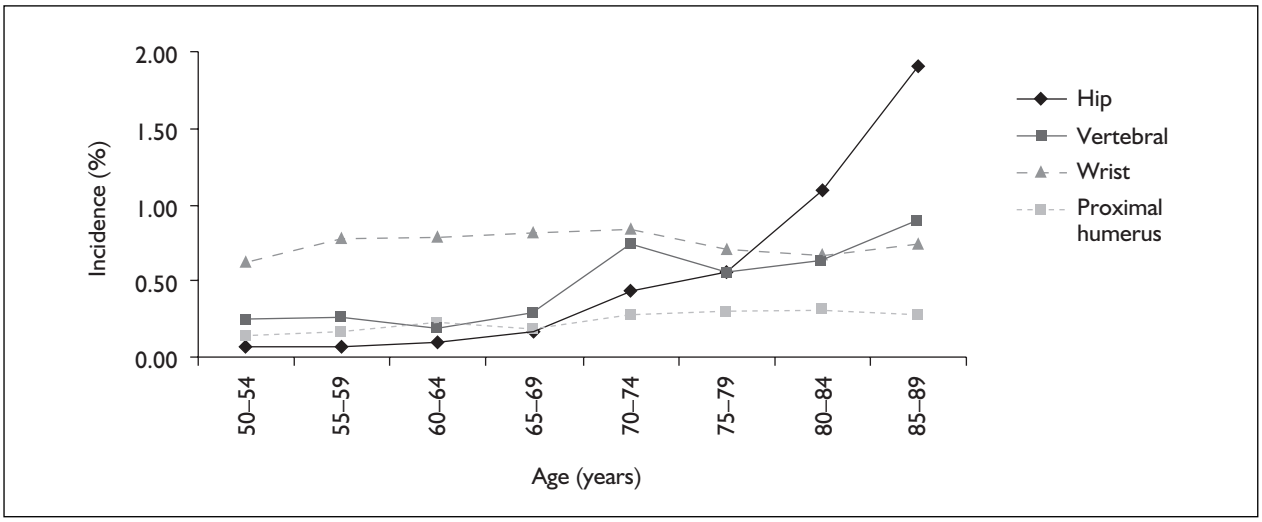

FIGURE 3 *Estimated fracture risk by age for a woman with a* T*-score of –2.5 and no prior fracture*

TABLE 7 *Assumed mortality rates directly attributable to hip fracture in the 12 months following fracture*

Residential status	Age (years)	Mortality rate (%) directly related to hip fracture
Community	50–59	2
Community	60–69	6
Community	70–79	6
Community	80–89	11
Community	⩾90	16
Nursing home	50–59	0
Nursing home	60–69	0
Nursing home	70–79	13
Nursing home	80–89	22
Nursing home	⩾90	23

of the average population. This is due both to the large proportion of women with severe osteoporosis and to the small differential between the population average BMD and the *T*-score of –2.5 that defines osteoporosis.

At a *T*-score of –2.5 SD the risk of hip fracture greatly increases from the age of 65 years. The rate of wrist and proximal humerus fractures remains fairly stable regardless of age. The risk of a vertebral fracture is broadly similar for the bands between 50 and 69 years, and broadly similar for the bands between 70 and 89 years.

Mortality following osteoporotic fractures

Mortality following a hip fracture

Excess mortality is well described after hip fracture. In the first year following hip fracture, relative mortality risk varies in women from 2.0 to greater than 10, depending on age.[9] However, case–control studies that adjust for prefracture morbidity indicate that a substantial component can be attributed to co-morbidity.[17,18]

The data used in the cost-effectiveness model are taken from unpublished data from the Second Anglian Audit of Hip Fracture,[19] which recorded deaths up to 90 days following hip fracture.

To account for mortality that was not related to the hip fracture, data were taken from Parker and Anand.[20] It was estimated that 33% of deaths 1 year after hip fracture were totally unrelated to the hip fracture, 42% were possibly related and 25% directly related. These figures were not stratified by age, gender or residential status; they have, however, been assumed to be constant for all population subsets.

It is likely that there was further mortality between 91 and 365 days that was not recorded by the audit.[19] An estimate of this can be inferred from the graph in Parker and Anand,[20] with the value assumed to be 40%. It was assumed that attributing all of the deaths possibly due to hip fractures as directly to hip fracture and including only the data to 90 days would provide an accurate estimation of the true mortality rate. The mortality rates that were assumed attributable to hip fracture are given in *Table 7*. No data were available for the age band 50–59 years and it was assumed that, as suggested by Swedish data,[9] this value was 33% that of the rate between 60 and 69 years.

Mortality following vertebral fracture

Recent data[21–23] suggest that vertebral fractures are associated with mortality, although there may be uncertainty regarding the number of mortalities that are caused by co-morbidities and the number directly related to the vertebral fracture.

Two studies looking at the increased mortality risk following a clinical vertebral fracture have reported an age-standardised risk in the mortality rate for women of 1.66 [95% confidence interval (CI) 1.51 to 1.80][21] and of 8.64 (95% CI 4.45 to 16.74).[22]

A study that included vertebral fractures defined by morphometric criteria reported that women with one or more vertebral fracture have a 1.23-fold greater age-adjusted mortality rate (95% CI 1.10 to 1.37) compared to those without vertebral fracture.[23] Assuming that only clinical fractures can cause mortality and that one-third of morphometric fractures come to clinical attention[24] then the relative risk of mortality of clinical fractures can be estimated to be 1.69 [1 + (0.23 × 3)].

It was assumed that the mortality rates reported by Center and colleagues[21] are correct, as they have tight confidence intervals and are supported by the data from Kado and colleagues.[23]

Mortality following osteoporotic fractures not at the hip or spine

It was assumed that there was no increase in mortality from forearm fractures, consistent with published surveys.[21,22,25] For proximal humerus fractures, a conservative assumption of a two-fold increase in mortality was assumed.[25]

Entry into nursing home following an osteoporotic fracture

Entry into a nursing home following a hip fracture

Data were sought to estimate what percentage of women who suffer a hip fracture move from living in the community into nursing home accommodation. Global assumptions on this percentage, as used in some models,[26] were not used as this allows nursing home costs to be incorrectly allocated to women already residing in such care.

Unpublished data from the Second Anglian Audit of Hip Fracture[19] were used in the model. These data are shown in *Table 8*. It is assumed that patients who enter a nursing home will remain there for the remainder of their lives.

A recent estimate of the costs associated with osteoporotic fractures assumed that 10% of all patients with a hip fracture would reside in a nursing home for the rest of their lives.[5] This figure looks plausible above the age of 70 years, but appears not to be applicable within the ranges 50–69 years.

Entry into a nursing home following fractures at sites other than the hip

It was assumed that fractures at sites other than the hip would not cause a woman to move from community living into nursing home accommodation.

Risk of non-skeletal events on which osteoporosis treatments may impact

Some osteoporosis treatments have effects on non-skeletal events, such as the incidence of coronary heart disease (CHD) or breast cancer. For the model to take such intervention characteristics into account these disease areas had to be modelled.

Calculating the incidence of CHD

Data on the incidence of CHD were derived from the incidence of death due to CHD [International Classification of Diseases (ICD) codes 410–414] and population figures were taken from Mortality Statistics.[27] The incidence of CHD events was imputed from a ratio of fatal to non-fatal possible myocardial infarction events as reported by Volmink and colleagues.[28] It was assumed that the fatality rates apply to all CHD, although this assumption may overestimate the CHD death rate. The study only focused on the age groups 50–79 years and linear extrapolation was undertaken to make predictions for ages above or below this range. The incidence rates for fatal and non-fatal CHD used in the model are given in *Table 9*. It is seen that the method used for extrapolating the data estimates that any CHD event in a woman above the age of 80 will result in fatality, which will overestimate the mortality associated with CHD.

CHD was originally included in the model when it was believed that oestrogen offered protection against this condition. This has subsequently been shown to be non-significant, with a mean relative risk greater than 1.[29] Raloxifene had no significant effect on CHD events across the whole population of a randomised controlled trial (RCT). However, it has been shown to have a significant reduction in cardiovascular events and stroke events in high-risk patients, but not a significant reduction in coronary death, myocardial infarction (MI) or unstable angina.[30] Given these data, the relative risk of CHD was set

TABLE 8 *Percentage of women who move from the community to a nursing home following a hip fracture*

Age (years)	% of women who move from the community to a nursing home following a hip fracture
50–59	0
60–69	4
70–79	4
80–89	12
⩾90	17

TABLE 9 *Incidence of fatal and non-fatal CHD by age band*

Age (years)	Non-fatal CHD (%)	Fatal CHD (%)
50–54	0.072	0.026
55–59	0.144	0.064
60–64	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

TABLE 10 *Incidence of breast cancer in the average female population, in women with osteoporosis and women at the threshold for osteoporosis*

Age (years)	Incidence of breast cancer (%) within subsets of the population		
	Average population	Population with average BMD values	Population at the threshold for osteoporosis
50–54	0.245	0.248	0.145
55–59	0.278	0.284	0.179
60–64	0.319	0.336	0.228
65–69	0.257	0.279	0.204
70–74	0.269	0.297	0.234
75–79	0.284	0.311	0.264
80–84	0.320	0.339	0.311
85–89	0.362	0.366	0.361

to 1 for all interventions and no treatment, effectively removing CHD incidents from the model.

Calculating the incidence of breast cancer

The incidence of breast cancer was taken from cancer registrations (*Tables 1–3*),[27] assuming a population as reported by the Office for National Statistics.[31] These figures are given in *Table 10*.

Two large cohort studies have shown that osteoporosis or low BMD is associated with a lower incidence of breast cancer.[32,33] Data from the Cauley study,[32] which reports a 1.34 increase in breast cancer risk per 1-unit increase in *Z*-score, were used in the model. The equation took the form $1.34^{\text{Increase in } Z\text{-score}}$.

Because the average population values are constructed from a population that contains both osteoporotic and non-osteoporotic women, the risk of breast cancer in a healthy woman with average BMD values was calculated using a similar methodology to that described in Appendix 1. The estimated risks of breast cancer in a population with average BMD and in an osteoporotic population are given in *Table 10*.

Mortality due to breast cancer

The cost-effectiveness model simulates individual patients, and thus standard summary data, such as total death rates due to breast cancer per year, are inappropriate. Data had to be derived on obtaining the risk of death due to breast cancer in relation to the time since diagnosis.

The data that were used are 5-year survival rates for the years 1986–1990 in England and Wales.[31] These report a 5-year survival rate of 68%.

Comparison of 1-, 5- and 10-year survival shows a steep decline in mortality followed by a flattening of the death rate after 5 years. It was assumed that patients who survive beyond 5 years will not die as a result from that episode of breast cancer.

For the 32% that die within the 5-year period, it was assumed that the survival period was 2 years. It was also assumed that these mortality rates are applicable at all ages.

Death due to other causes

These data have been taken from interim life tables[34] and are 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.[35,36] At the radius, the increase in relative risk was 1.22 per SD decrease in BMD adjusted for age,[35] and this factor has been used within the model, although it is unsure how much excess mortality may be related to co-morbidities. The data for the mortality rate in the general population and for those patients at the threshold of osteoporosis are shown in *Table 11*. The general population mortality rates have not been adjusted to take into account the osteoporotic population, meaning that these death rates are likely to be slight overestimates. As these apply to all interventions it is unlikely that this will bias the results.

A recent study[37] suggested that there may be no link between BMD value and excess mortality. The effect of making this assumption was investigated in the sensitivity analyses.

TABLE 11 *Mortality due to other causes in the general female population and in women at the threshold for osteoporosis*

	Mortality rate (%) due to other causes	
Age (years)	**General population**	**Population at the threshold for osteoporosis**
50–54	0.237	0.342
55–59	0.392	0.536
60–64	0.649	0.845
65–69	1.129	1.397
70–74	1.864	2.190
75–79	3.065	3.426
80–84	5.279	5.604
85–89	9.177	9.268

Current service provision

Data taken from the company submission for etidronate[38] state that approximately 275,000 women are being prescribed bisphosphonates, and that bisphosphonates represent 57% of all osteoporosis prescribing. The submission from Eli Lilly[39] states that approximately 22,000 women were prescribed raloxifene in 2002. This equates to approximately 5% of all osteoporosis prescribing. As teriparitide is not yet licensed in the UK, it currently has 0% of osteoporosis prescribing.

The total number of women receiving medication for osteoporosis is approximately 480,000. This equates to 23% of the female population who are expected to be suffering from osteoporosis.

Description of new interventions

Identification of patients and criteria for treatment

All postmenopausal women are potentially at risk of osteoporosis, and therefore of osteoporotic fracture. Therapy may be offered to those who already have osteoporosis (defined, in Caucasian women, as a *T*-score of –2.5 or below, as determined by single- or dual-energy X-ray absorptiometry) and to those who are perceived to be at risk of osteoporosis as a result of factors such as low BMD, family history, age and low weight.

Interventions

As noted earlier, five new interventions (alendronate, etidronate, risedronate, raloxifene and teriparatide) have been proposed for the prevention or treatment of postmenopausal osteoporosis. Four of these (alendronate, etidronate, risedronate and raloxifene) are licensed for use in postmenopausal women who have, or are at risk of, osteoporosis (see section 'Summary of product characteristics', below).

PTH has not yet been licensed in the UK for use in postmenopausal osteoporosis. However, in the USA it is indicated for patients with a history of osteoporosis-related fracture, or multiple risk factors for such fracture, or who have failed or are intolerant to other osteoporosis therapies.[40]

The evidence for the efficacy of the five interventions, in comparison with other interventions that are licensed in the UK for the prevention or treatment of postmenopausal osteoporosis [calcium, vitamin D, calcitriol, and hormone replacement therapy (HRT)] and with exercise, placebo or no treatment, will be discussed in turn below. The evidence for the comparator treatments, in comparison with placebo, no treatment or each other, will then be reviewed. Although calcitonin is also licensed for the prevention and treatment of postmenopausal osteoporosis, the evidence for its efficacy will not be reviewed in this report.

Summary of product characteristics

Alendronate (Merck Sharp & Dohme)

Alendronate is an oral bisphosphonate that is licensed in the UK at 5 mg per day for the prevention of postmenopausal osteoporosis and the treatment of corticosteroid-induced osteoporosis, and at 10 mg per day for the treatment of postmenopausal osteoporosis, corticosteroid-induced osteoporosis in postmenopausal women not receiving HRT, and osteoporosis in men. It is also licensed at 70 mg per week for the treatment of postmenopausal osteoporosis.[41]

The UK licence for alendronate is held by Merck Sharp & Dohme. It is marketed as Fosamax®. Fosamax is available in 5- and 10-mg tablets, which respectively contain 6.53 and 13.05 mg of alendronate sodium (the molar equivalent to 5 and 10 mg of alendronic acid). These are available in blister packs of 28 tablets. Fosamax is also available

in once-weekly 70-mg tablets, which contain 91.37 mg alendronate sodium trihydrate (the equivalent of 70 mg of alendronic acid). These are available in blister packs of four tablets.[42]

For adequate absorption, Fosamax must be taken with at least 200 ml or 5 fluid ounces of plain water, at least 30 minutes before the first food, beverage (including mineral water) or medication of the day.[42]

Because of the risk of oropharyngeal ulceration, patients should not chew the tablet or allow it to dissolve in the mouth. They should not lie down until after their first food of the day (at least 30 minutes after taking the tablet). Fosamax should not be taken at bedtime or before rising for the day.[42]

Fosamax is contraindicated in patients with:

- abnormalities of the oesophagus or other factors such as stricture or achalasia that delay oesophageal emptying
- inability to stand or sit upright for at least 30 minutes
- hypersensitivity to any component of the product
- hypocalcaemia.[42]

Owing to a lack of experience, Fosamax is not recommended for patients with renal impairment where the glomerular filtration rate is less than 35 ml per minute. It should not be given to pregnant or lactating women.[42]

Because Fosamax can cause local irritation of the upper gastrointestinal mucosa, caution should be used when it is given to patients with active upper gastrointestinal problems (e.g. dysphagia, oesophageal disease, gastritis, duodenitis or ulcers).[42]

Etidronate (Procter & Gamble Pharmaceuticals)
Etidronate is an oral bisphosphonate. It is licensed at a dose of 400 mg per day, given for 14 days of a 90-day cycle followed by calcium carbonate for 76 days, for the prevention and treatment of postmenopausal osteoporosis and corticosteroid-induced osteoporosis.[41]

The UK licence for etidronate is held by Procter & Gamble. It is marketed as Didronel PMO®, as a two-component therapy consisting of 14 Didronel 400-mg tablets and 76 Cacit® 500-mg effervescent tablets containing 1250 mg of calcium carbonate which, when dispersed in water, provides 500 mg of elemental calcium as calcium citrate. Didronel PMO is sold in compliance kits containing a blister pack of 14 Didronel tablets and four tubes, each containing 19 Cacit tablets.[38]

Didronel should be taken at the midpoint of a 4-hour fast (i.e. 2 hours before and 2 hours after food or medications).[38]

Didronel is contraindicated in patients with:

- severe renal impairment
- hypercalcaemia or hypercalciuria
- clinically overt osteomalacia
- hypersensitivity to any component of the product.[38]

It is also contraindicated in pregnant or lactating women.

Risedronate (Alliance for Better Bone Health: Aventis UK and Procter & Gamble Pharmaceuticals UK)
Risedronate sodium is an oral bisphosphonate that is licensed at a dose of 5 mg per day or 35 mg per week for the prevention and treatment of osteoporosis in postmenopausal women.[41]

The UK licence for risedronate is held by Procter & Gamble Pharmaceuticals UK. It is marketed as Actonel®, in 5-mg tablets which contain 5 mg risedronate sodium (equivalent to 4.64 mg risedronic acid). It is available in blister packs of 14 tablets packaged in cartons of 14, 28 or 84 tablets. Hospital packs of ten 14-tablet blister packs and two ten-tablet blister strips are also available.[43]

For adequate absorption, Actonel® must be taken, while in an upright position, with at least 120 ml of plain water, either at least 30 minutes before the first food or drink (other than water) of the day or at least 2 hours from any food or drink at any other time of day, and at least 30 minutes before going to bed. Patients should swallow the tablet whole, without sucking or chewing it, and should not lie down for 30 minutes after taking the tablet.[43]

Actonel is contraindicated in patients with:

- severe renal impairment (creatinine clearance <30 ml per minute)
- hypocalcaemia
- hypersensitivity to any component of the product.[43]

Because bisphosphonates have been associated with oesophagitis and oesophageal ulcerations,

caution should be used when risedronate is given to patients with a history of oesophageal problems that delay oesophageal transit or emptying (e.g. stricture or achalasia), or who are unable to stay upright for at least 30 minutes after taking the tablet.[43]

Because animal studies have shown reproductive toxicological effects, the significance of which to humans is unknown, risedronate should not be given to pregnant or lactating women.[43]

Hypocalcaemia and other disturbances of bone and mineral metabolism (e.g. parathyroid dysfunction and hypovitaminosis D) should be treated at the time of starting risedronate therapy.[43]

Raloxifene (Eli Lilly and Company)
Raloxifene is a selective (o)estrogen receptor modulator (SERM). It is licensed in the UK, at a dose of 60 mg per day, only for the treatment and prevention of postmenopausal osteoporosis.[41]

The UK licence for raloxifene is held by Eli Lilly. It is marketed as Evista®. Evista is available in 60-mg tablets, which contain 60 mg of raloxifene hydrochloride (equivalent to 56 mg raloxifene free base). These are available in blister boxes of 14, 28 or 84 tablets, or in bottles of 100 tablets.[39]

Evista is contraindicated in women with:

- childbearing potential
- active or past history of venous thromboembolic events, including deep venous thrombosis (DVT), pulmonary embolism and retinal vein thrombosis
- hypersensitivity to any component of the product
- hepatic impairment, including cholestasis
- severe renal impairment
- unexplained uterine bleeding
- signs or symptoms of endometrial cancer.[39]

Owing to a lack of experience, Evista should not be coadministered with systemic oestrogens. In patients with breast cancer, it should be used only after the treatment of breast cancer, including adjuvant therapy, has been completed.[39]

Evista should not be coadministered with cholestyramine (or other anion-exchange resins).[39]

Teriparatide (Eli Lilly and Company)
PTH is an anabolic agent that stimulates new formation of high-quality bone. It is also claimed to increase resistance to fracture. Teriparatide [recombinant human PTH (1–34)] is identical to the 34 N-terminal amino acid sequence of endogenous human PTH. It has recently been licensed in the USA at a dose of 20 μg per day for the treatment of osteoporosis, both in postmenopausal women at high risk of fracture and in men with primary or hypogonadal osteoporosis who are at high risk of fracture.[40]

The UK producer of teriparatide is Eli Lilly. It is produced as Forsteo®. Forsteo is administered as a once-daily subcutaneous injection in the thigh or abdomen. It is available in prefilled pens, each containing 750 μg of teriparatide and intended for 28 days of dosing; a new sterile needle must be used for every injection. The prefilled pens should be stored at 2–8°C at all times. The pens are available in packs of one or three. The packs do not include needles; insulin pen injection needles can be used.[40] Patients must be trained in proper injection techniques.[40]

The maximum total length of treatment with Forsteo should be 18 months.[40]

Forsteo is contraindicated in women with:

- hypersensitivity to any component of the product
- pre-existing hypercalcaemia
- severe renal impairment
- metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone)
- unexplained elevations of alkaline phosphatase
- prior radiation therapy to the skeleton.[40]

Forsteo should be used with caution in patients with active or recent urolithiasis or moderate renal impairment. It should not be used during pregnancy or by breastfeeding women.[40]

Personnel involved

Alendronate, risedronate and raloxifene can be prescribed by GPs, as well as in specialist osteoporosis clinics.

Equipment required

No special equipment is required to deliver any of the interventions under review. However, special equipment is required to undertake the single- or dual-energy X-ray absorptiometry necessary to determine BMD and thus ascertain the appropriateness of therapy with these or other antiosteoporotic agents.

Length of treatment

It is stipulated that the maximum total length of treatment with teriparatide should be 18 months.[40] The length of treatment with the other interventions is not specified. However, low BMD is not so much an illness that can be cured as a condition which, once developed, will continue, and may deteriorate further, without the use of some intervention. There is no evidence that, if given for a set period, these interventions will reduce the risk of fracture for the remainder of the patient's life, and the implication therefore is that treatment is long term and open ended.

Degree of diffusion

As three of the five interventions reviewed in this report can be prescribed by GPs as well as by specialist osteoporosis clinics, the degree of diffusion is substantial.

Anticipated costs

The anticipated costs depend strongly on the intervention prescribed and on the age of the patient. In analyses assuming women with a prior fracture and a *T*-score of –2.5 SD, both alendronate and risedronate are estimated to be cost-saving at the age of 80 years, when the costs associated with fractures that have been avoided are included. These results assume that the efficacy data seen in RCTs are applicable within this age group; this assumption is currently unproven. At lower ages the cost offset becomes much lower and the expected costs of an intervention are much higher; the expected net costs of treating all women with severe osteoporosis aged 65–74 years, and assuming a *T*-score of –2.5 SD, with bisphosphonates is approximately £200 million.

Assuming that the risks of fracture are doubled in these patients, alendronate becomes cost-saving and the net costs of treating with risedronate and etidronate are £68 million and £193 million, respectively.

Chapter 3

Effectiveness

Methods for reviewing effectiveness

Search strategy

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

Sources searched

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

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

Search terms

A combination of free-text and thesaurus terms was used. General population search terms (e.g. osteoporosis, bone, density, diseases, fracture) were used to identify all potentially relevant studies. Intervention terms were not used in the main searches since it was felt that these might restrict the results and cause possibly relevant articles to be missed. Utilities searches were performed for breast cancer and for osteoporosis fractures as part of the economic evaluation section of the report. Copies of the MEDLINE search strategies are included in Appendix 4. Search strategies for the other databases are available on request.

Search restrictions

No language, date or study-type restrictions were applied to the searches. However, the BIOSIS search was performed as title only, and the Citation Indexes searches were limited with brief clinical trials, systematic reviews, guidelines and economics filters, and to title only, to keep the number of hits to a sensible level. An RCT filter, an economics and quality of life evaluations filter, and a systematic reviews filter, were used in the main searches performed in MEDLINE and EMBASE to assist the identification of articles of these types (see Appendix 5). After the searches were completed, because of the large number of references retrieved, only the articles identified using these specific filters, the articles from the databases that were not searched with filters (such as BIOSIS) and the papers found through handsearching, and so on, were reviewed.

Inclusion and exclusion criteria

Inclusion criteria

- **Participants:** women with primary osteoporosis who were at least 6 months postmenopausal
- **interventions:**
  - bisphosphonates: alendronate, etidronate and risedronate
  - SERMs: raloxifene
  - teriparatide [recombinant human PTH (1–34)]
- **comparators:**
  - vitamin D
  - calcitriol (a vitamin 1α-hydroxylated derivative)
  - pharmacological doses of calcium
  - oestrogens (opposed and unopposed)
  - exercise
  - placebo
  - no treatment
- **outcome measures:** vertebral or non-vertebral fracture, associated effects, quality of life related to the study intervention, continuance and compliance
- **study design:** RCTs; trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind.

Discussion of outcome measures

Clinical, or symptomatic, vertebral fractures are those fractures that cause sufficient discomfort for the patient to bring them to the attention of a health professional. They can be identified by X-ray. However, it is also possible to suffer vertebral fractures that do not cause sufficient

discomfort to be reported by the patient, but that can also be identified by X-ray. Although some studies use only clinical fractures as their end-point, many use fractures that are identified radiographically: such fractures, which are termed radiographic or morphometric, will include both symptomatic and asymptomatic fractures. For the most part, therefore, the vertebral fracture data used in this report relate to radiographic fractures. Data from one large study that reported both clinical and radiographic fractures suggest that, as might be expected, the relative risk of the two types of fracture is very similar.[45]

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

Where necessary, the authors of included studies were asked for additional, unpublished, fracture data; some provided such data.

Because of the very large number of otherwise healthy postmenopausal women who have, or are at risk of, osteoporosis and who may be prescribed medications as a result, issues relating to drug toxicity are important. RCTs generally cannot provide definitive information about drug toxicity. They may underestimate the incidence of drug-related adverse events, both because their populations may not be wholly typical of the target population (as they tend to exclude older participants and those with co-morbidities) and because they are not powered to identify rare, although potentially serious, adverse events; moreover, they do not always measure all potential side-effects.[46] For this reason, in addition to data drawn from the studies under review, evidence from other sources has been used when relevant in discussing the various incidental effects, whether adverse or beneficial, associated with the various treatments for postmenopausal osteoporosis.

Vertebral and non-vertebral fractures are known to affect the quality of life. However, the review of clinical effectiveness only reports on the impact of the study medication itself on other aspects of health-related quality of life, as otherwise the quality of life impact of the medication becomes confused with its efficacy in reducing fracture incidence.

Continuance and compliance take on particular importance in relation to preventive therapies. Continuance is here understood to mean continuing in principle to take the relevant medication, while compliance relates to taking it consistently and in accordance with the dosage regimen. The risk of non-continuance or non-compliance with prescribed medication is particularly high in patients with asymptomatic chronic diseases or risk factors that require long-term preventive medication;[47] postmenopausal women with, or at risk of, osteoporosis clearly fall into this category. Continuance and compliance depend on a number of properties of the medication in question, including tolerability, convenience of administration, the patient's perception of its safety and quality of life while on treatment.[47] Adherence to, and compliance with, medication are clearly important in relation to the actual, rather than theoretical, efficacy of the interventions under study and therefore, as with adverse effects, data drawn from the studies under review will be supplemented with data from other sources when relevant.

Exclusion criteria

Studies were excluded if they included participants with secondary osteoporosis (e.g. related to therapy with corticosteroids), or drew their participants exclusively from patients with specific diseases known to affect fracture rates (e.g. Parkinson's disease).

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

It had originally been intended to include all relevant studies, whatever the language of publication. However, for practical reasons, it was possible only to include those published in English, French, German, Italian or Spanish. This led to the exclusion of one possibly relevant study published only in Japanese.[48]

Sifting

In principle, the references identified by the literature searches were sifted in two stages, being

screened for relevance first by title and then by abstract. However, as it was not possible to identify all relevant studies with fracture outcomes from titles alone, the title sifting stage was used essentially to reject studies that were clearly irrelevant. Following this, the abstracts of all studies that used the relevant interventions in the relevant populations were screened (for studies that did not provide abstracts, the full studies were screened). Twenty-eight studies that had been identified by the literature searches were not identified as relevant at the abstract sifting stage, but were identified from other reviews as reporting fracture outcomes.[24,49–75] The reason for this was that, as fracture was only a secondary outcome measure in many studies, it was not reported in the abstract.

Data extraction strategy

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

Where available, the following data will be reviewed:

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

Quality assessment strategy

The methodological quality of all trials that met the inclusion criteria was assessed using the tool developed by Gillespie and colleagues.[76] This tool was selected because it was intended specifically for the assessment of randomised or quasi-randomised trials of interventions designed to prevent fractures associated with osteoporosis.

The quality assessment tool included the following items:

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

Definitions of the various levels of randomisation and concealment of randomisation derived from Prendiville and colleagues[77] were incorporated in the tool (see Appendix 6).

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

Blinding of the quality assessors to author, institution or journal was not considered necessary.[78,79]

The quality assessment of studies included in the review of clinical effectiveness was carried out by one researcher.

Meta-analysis strategy

Studies that met the review's entry criteria were eligible for inclusion in the meta-analyses provided that they reported fracture incidence in terms of the number of subjects suffering fractures, as this enabled calculation of the relative risk of subjects in the intervention group developing a new fracture or fractures, compared with subjects in the control group. Studies that reported only numbers of fractures, or fracture rates (i.e. numbers of fractures per 100 or 1000 patient-years) could not be included in the meta-analyses unless it was possible to obtain from the authors unpublished information on the number of subjects who suffered fractures. The meta-analysis of data relating to numbers of fractures or fracture rates would have violated the basic statistical assumption that the occurrence of one event does not increase the likelihood of a subsequent event,[80] since once a subject has suffered an osteoporotic fracture, the risk of a subsequent fracture increases.[81,82]

Ideally, only those studies that had fracture as a primary end-point would have been included in the meta-analyses. However, pragmatically this was not possible as very few studies met this criterion (see Appendix 7). Meta-analysis was carried out with Review Manager (RevMan, Cochrane Collaboration; 2000), using the random-effects model, as this both allows generalisation beyond the sample of patients represented by the studies included in the meta-analysis and provides wider, more conservative confidence intervals than the fixed-effects model.[46]

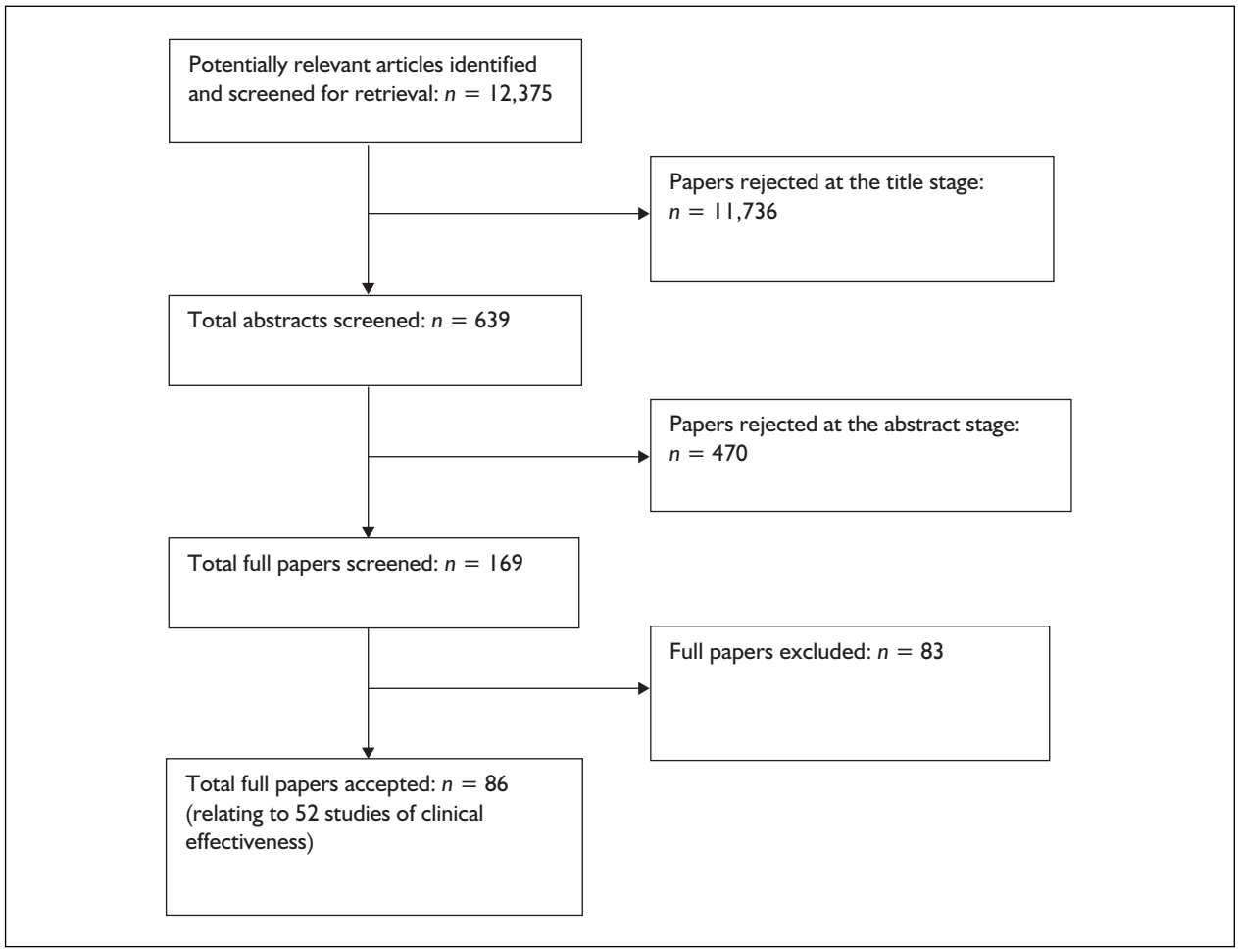

FIGURE 4 *Summary of study selection and exclusion: electronic literature searches*

Since the end-point of interest was fracture, it seemed appropriate (with due respect to Meunier[83]) to include open-label studies.

To ensure comparability, the meta-analyses of vertebral fractures only pooled data from studies that used the same definition of vertebral fracture. Where possible, data were pooled from studies using a definition that required a 20% or greater reduction in anterior, middle or posterior vertebral height: as noted above, this definition was felt to identify fractures more reliably than a definition that required a 15% or greater reduction.

Results: quantity and quality of research available

Number of studies of clinical efficacy identified

The electronic literature searches identified 12,375 potentially relevant articles. Of these, 86 articles related to 52 trials that compared an intervention of interest with a relevant comparator (*Figure 4*).

As noted earlier, 28 studies that had been identified by the electronic literature searches were initially rejected at either the title or the abstract stage; it was only realised that they contained relevant data as a result of references in other sources. In addition, a further ten relevant studies[39,84–92] were identified only from citations.

Number and type of studies included

A total of 90 individual RCTs met the review inclusion criteria; these are listed in Appendix 8. Given the volume of the evidence, it was not felt necessary to include other study designs.

Number and type of studies excluded, with reasons

As detailed above, a very large number of studies that did not meet the inclusion criteria were therefore excluded as part of the sifting process. Details are therefore given only of those studies

that were excluded at the full paper stage, and then only if the reason for exclusion was not immediately apparent from the full text. Such studies, and the reasons for their exclusion, are listed in Appendix 9.

Tabulation of quality of studies

This report reviews evidence relating to a large number of interventions and comparators. The quality of studies relating to each intervention is therefore tabulated and discussed in turn as part of the discussion of the nature of the evidence relating to that intervention.

Tabulation and discussion of results; assessment of effectiveness

The results relating to the five interventions of interest (alendronate, etidronate, risedronate, raloxifene and teriparatide) are tabulated and discussed in turn in the following sections; their effectiveness is also assessed in those sections. In each case, studies that compare the intervention with other active interventions are discussed before those that compare the intervention with placebo or no treatment. Comparisons of the comparator treatments with placebo, no treatment or each other are reviewed in the section 'Results: comparator treatments' (p. 52). Particular emphasis will be given to the results of studies that use the interventions in their current licensed doses.

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

Where appropriate, evidence from other studies will be used to supplement data from the studies under review in relation to the non-skeletal beneficial and adverse effects of the interventions, and in relation to continuance and compliance with treatment (see 'Inclusion criteria', p. 15).

Alendronate

Quantity and quality of research available: alendronate in postmenopausal osteoporosis or osteopenia

Fourteen RCTs were identified that compared alendronate with the other interventions and comparators reviewed in this report, in postmenopausal osteoporosis or osteopenia, and that reported fracture outcomes.[52,54,60,93–103] Two of these were comparative studies.[52,94] One study[60] specifically studied the effects of alendronate in ambulatory residents of long-term care facilities. Another study looked specifically at the impact of alendronate in women who were already taking HRT.[101]

One 3-year study[100] pooled data from two multicentre dose-ranging trials with identical designs. The pooling of data from the two trials, and from the three alendronate groups within each study, was preplanned as it was anticipated that neither trial alone, nor any one dose group, would be large enough to demonstrate a treatment effect in relation to fracture outcomes. Data relating to a 4-year extension of this study were not used, as the study was no longer truly randomised.[104]

One of the comparative studies[52] compared alendronate with oestrogen, either alone or in combination with alendronate; it was limited to hysterectomised women to avoid any possible confounding effects of progestin therapy or withdrawal bleeding. All participants received supplementary calcium. The other comparative study compared alendronate with teriparatide; both groups received supplementary calcium and vitamin D (for details, see Appendix 10, *Tables 132* and *133*).[94]

Thirteen studies[52,54,93,95–103] compared alendronate with placebo or no treatment. In eight of these trials, all women, including those in the placebo or no treatment group, received elemental calcium at a dose of 500 mg[52,54,93,95,96,101,103] or 1000[97] mg per day. In the Fracture Intervention Trial (FIT),[98,99] women whose dietary calcium intake at baseline was less than 1000 mg per day were given 500 mg per day of elemental calcium and 250 IU per day of vitamin D; another study[60] gave such a supplement to all women whose daily dietary calcium intake was less than 1500 mg, while all participants received 400 IU vitamin D daily. In another study,[103] all subjects were counselled to achieve a dietary calcium intake of 1200 mg, using supplements if necessary. Finally, another study[101] provided participants whose daily calcium intake at baseline was less than 1000 mg per day with supplements to achieve a daily intake of at least 1000 mg; all participants were given 400 IU vitamin D daily.

In most of the studies that compared alendronate with placebo or no treatment, some or all of the subjects received alendronate at a dose of 10 mg per day.[52,54,60,93,96,97,100–102] The Fracture Intervention Trial[98,99] used a dose of 5 mg per day for the first 24 months, followed by 10 mg per day for the remainder of the study period. One of the remaining studies[103] used a dose of 20 mg per

TABLE 12 *Alendronate 10 mg per day in postmenopausal osteoporosis: comparisons with active treatment*

Study	Comparator	Type of fracture	No. of subjects suffering fracture		RR of fracture (95% CI): alendronate vs comparator
			Alendronate	Comparator	
Body, 2002[94]	Teriparatide (40 mg per day)	Non-vertebral fracture	10/73	3/73	3.33 (0.96 to 11.62)
Bone, 2000[52]	CEE (0.625 mg per day)	All clinical fractures	5/92	10/143	0.78 (0.27 to 2.20)
Bone, 2000[52]	CEE (0.625 mg per day) plus alendronate	All clinical fractures	5/92	8/140	0.95 (0.32 to 2.82)

CEE, conjugated equine oestrogen.

day, and another[95] a range of low doses (1.0, 2.5 and 5.0 mg per day) (see Appendix 10, *Table 132*).

One study was carried out in women with severe osteoporosis,[98] four studies were conducted in women with osteoporosis,[52,94,96,100] eight in women with osteoporosis or osteopenia,[60,93,95,97,99,101–103] and one study in women with osteopenia[54] (see Appendix 10, *Tables 132* and *133* for details).

As published, the quality of many of the studies of alendronate in women with osteoporosis or osteopenia appeared to be poor: in particular, few provided evidence of appropriately masked randomisation or of blinded outcome assessment. However, the largest studies, the two arms of the Fracture Intervention Trial,[98,99] were reported to have been of high quality. In addition, Merck Sharp & Dohme have confirmed that all the studies that they conducted[54,60,93,95,100–102] used masked randomisation and blinded outcome assessment. These comments have been taken into account in assessing the quality of those studies. However, as no detail was provided of the methods used to mask randomisation, a score of 2 was given to those studies that lacked published evidence that the method used did not allow disclosure of assignment (see Appendix 10, *Table 134*).

Assessment of effectiveness of alendronate in postmenopausal osteoporosis or osteopenia

Comparisons with active treatment

Both of the comparative studies[52,94] used alendronate at the dose (10 mg per day) currently licensed in the UK for treatment of osteoporosis. One study[52] reported only clinical fractures: most of these were non-vertebral, occurring at sites such as foot, ankle and rib, most frequently as a result of trauma. There were no significant differences in terms of the numbers of women suffering such fractures between alendronate alone, oestrogen, and combined alendronate/oestrogen therapy. The other study[94] compared alendronate with teriparatide; it reported the numbers of women suffering non-vertebral fracture. Although the point estimate favoured teriparatide, the confidence intervals cross unity (*Table 12*). Vertebral fractures were not reported, but back pain was reported significantly more frequently by women in the alendronate group (19%) than by those in the teriparatide group (6%, $p = 0.012$). Mean height did not change from baseline in either group.

Comparisons with placebo or no treatment

Vertebral fracture

Only seven of the non-comparative studies[54,95–100,103] provided any information on the incidence of radiographic vertebral fractures. Two of these[54,103] reported that there had been no vertebral fractures; they did not state what fracture definition had been used. Only three of the remaining five stated that they used a 20% fracture definition.[97–100] Of these, one only presented pooled data on the number of women receiving alendronate at different doses who suffered vertebral fracture;[100] another (the Fracture Intervention Trial)[98,99] did not use the current licensed dose for the full length of the study (*Table 13*).

The only study that provided usable data on the impact of alendronate at a dose of 10 mg per day on vertebral fracture rates, measured using a 20% fracture definition, was the study by Dursun and colleagues.[97] This found that the relative risk of

TABLE 13 *Alendronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: vertebral fracture data*

Study	Alendronate dose	Fracture definition	No. of women in each group suffering vertebral fracture
Adami, 1995[93]	10 and 20 mg per day	NA	Clinical fracture data only presented; site not specified
Bone, 1997[95]	1, 2.5 and 5 mg per day	20%	Alendronate 1 mg: 4 Alendronate 2.5 mg: 3 Alendronate 5 mg: 4 Placebo: 6 RR not calculable as denominators not available; difference between groups said by investigators not to be statistically significant
Bone, 2000[52]	10 mg per day	NA	Clinical fracture data only presented
Carfora, 1998[96]	5 and 10 mg per day; 20 mg per day for 15 months/placebo for 15 months	Not given	Alendronate 5 mg: 5.88% Alendronate 10 mg: 2.94% Alendronate 20 mg: 8.82% Placebo: 11.8% As the actual numbers of women suffering fracture were not stated, RRs could not be calculated
Chesnut, 1995[54]	5, 10, 20 and 40 mg per day	Not given	There were no vertebral fractures in any subject
Dursun, 2001[97]	10 mg per day	20%	Alendronate: 12/38 Control: 14/40 RR 0.90 (95% CI 0.48 to 1.69)
FIT: women with pre-existing fractures[98]	5 mg per day increased after 2 years to 10 mg per day	20%	Alendronate: 78/981 Placebo: 145/965 RR 0.53 (95% CI 0.41 to 0.69)
FIT: women without pre-existing fractures[99]	5 mg per day increased after 2 years to 10 mg per day	20%	Alendronate: 43/2057 Placebo: 78/2077 RR 0.56 (95% CI 0.39 to 0.80) (the reduction in relative risk was significant in those women whose initial *T*-score was ≤ -2.5 (RR 0.50, 95% CI 0.31 to 0.82), but not in those with initial *T*-scores >-2.5)
Greenspan, 2002[60]	10 mg per day	NA	Clinical fracture data only presented; site not specified
Liberman, 1995[100]	5, 10 and 20 mg per day decreased to 5 mg per day after 2 years	20%	Pooled alendronate groups: 17/526 Placebo: 22/355 RR 0.52 (95% CI 0.28–0.97) [this decreased risk was still seen when stratified by age (<65 or $\geqslant 65$ years) or the presence or absence of a previous vertebral fracture]
Lindsay, 1999[101]	10 mg per day	NA	No symptomatic vertebral fractures were identified in either group
Pols, 1999[102]	10 mg per day	NA	Vertebral fractures not investigated
Rossini, 1994[103]	20 mg per day	Not stated	No subjects suffered vertebral fracture during the study period

NA, not applicable.

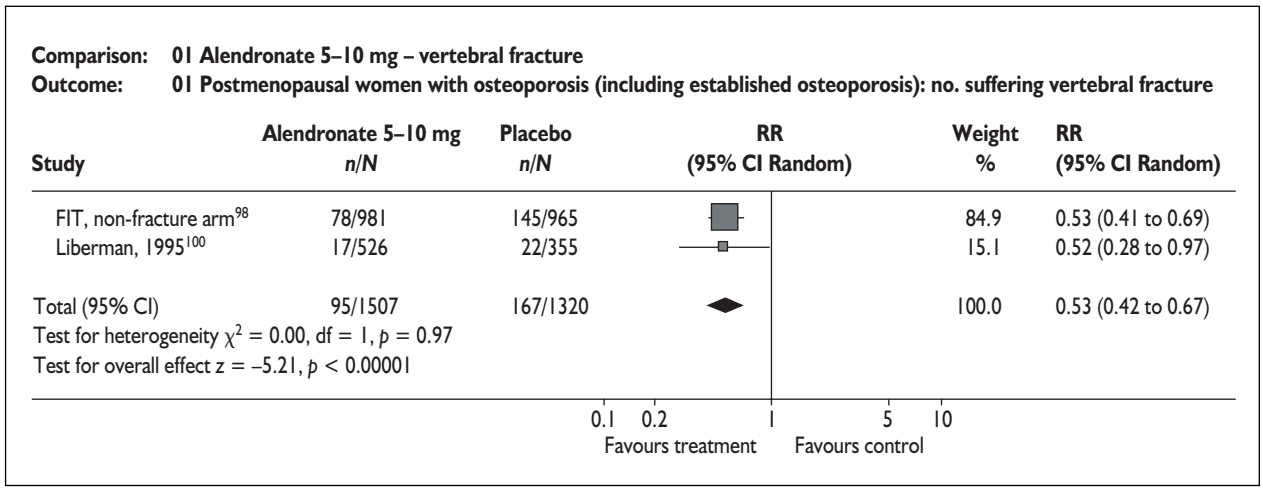

FIGURE 5 *Alendronate: vertebral fracture in severe postmenopausal osteoporosis or osteoporosis*

vertebral fracture in women with osteoporosis or osteopenia treated with alendronate, compared with controls, was 0.90 (95% CI 0.48 to 1.69). However, this was a small, relatively short (1-year), study whose quality, as reported, seems relatively low. Despite using a dose of only 5 mg for its first 2 years, the non-fracture arm of the much larger, high-quality, Fracture Intervention Trial demonstrated a greater treatment effect, finding a relative risk of vertebral fracture of 0.56 (95% CI 0.39 to 0.80) compared with placebo in women with osteoporosis or osteopenia and without pre-existing fracture who received alendronate,[99] and of 0.53 (95% CI 0.41 to 0.68) in women with severe osteoporosis who received alendronate.[98] The result in women with severe osteoporosis was consistent regardless of age, BMD, number of pre-existing fractures or history of postmenopausal fracture.[98] It therefore does not seem appropriate to regard the results of the Fracture Intervention Trial as irrelevant to contemporary practice simply because it did not use a dose of 10 mg for the full length of the study. The same argument can also be applied to another study that used a 20% vertebral fracture definition, that of Liberman and colleagues,[100] which presented pooled data relating to women with osteoporosis without fracture who received alendronate at doses of 5 and 10 mg for 3 years and at 20 mg for 2 years followed by 5 mg for 1 year.

Pooling of data from the fracture arm of the Fracture Intervention Trial[98] and from the study by Liberman and colleagues[100] indicates a relative risk of vertebral fracture of 0.53 (95% CI 0.42 to 0.67) in women with osteoporosis or severe osteoporosis receiving alendronate, compared with controls (*Figure 5*). This is very similar to the figures obtained in a preplanned analysis of women with osteoporosis or severe osteoporosis from both the fracture and the non-fracture arm of the Fracture Intervention Trial: this found a relative risk of radiographic fracture of 0.52 (95% CI 0.42 to 0.66, $p < 0.001$), and of clinically apparent vertebral fractures of 0.55 (95% CI 0.36 to 0.82, $p = 0.003$) in treated women compared with controls. The relative risk of multiple radiographic vertebral fractures in treated women was 0.13 (95% CI 0.07 to 0.25, $p < 0.001$).[45]

Pooling of data from the non-fracture arm of the Fracture Intervention Trial[99] with data from studies by Dursun and colleagues[97] and Liberman and colleagues[100] indicates a relative risk of vertebral fracture in women with osteoporosis without fracture or osteopenia who received alendronate, compared with controls, of 0.60 (95% CI 0.46 to 0.80) (*Figure 6*). This is slightly higher than the relative risk seen in women with severe osteoporosis or osteoporosis, suggesting that alendronate may be less effective in women with osteopenia than in those with osteoporosis. This is supported by the fact that the non-fracture arm of the Fracture Intervention Trial found a significant reduction in relative hazard (RH) of vertebral fracture in those women whose initial *T*-score was –2.5 or less (RH 0.50, 95% CI 0.31 to 0.82), but not in those with initial *T*-scores between –2.5 and –2.0 (RH 0.54, 95% CI 0.28 to 1.04) or between –2.0 and –1.6 (RH 0,82, 95% CI 0.33 to 2.07).[99] These data were not presented in a form that permitted the calculation of relative risks, and thus are not wholly comparable with the other results presented here.

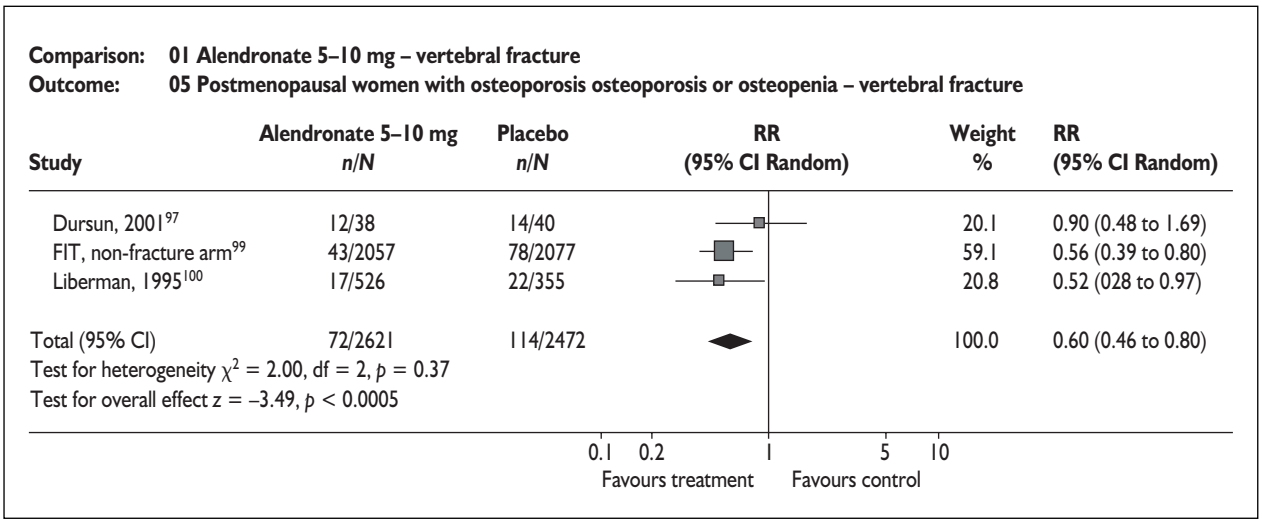

FIGURE 6 *Alendronate: vertebral fracture in postmenopausal osteoporosis or osteopenia*

Alendronate thus appears to reduce the risk of vertebral fracture both in women with severe osteoporosis and in those with osteoporosis without fracture. However, it is not clear that it reduces the risk of vertebral fracture in women with osteopenia.

Non-vertebral fracture

Eleven studies presented data relating to non-vertebral fracture (*Table 14*).

Only two of the studies that used a dose of 10 mg per day in women who were not taking HRT provided non-vertebral fracture data in a form that could be used in a meta-analysis.[102,105] One of these studied women with osteoporosis without vertebral fracture,[105] the other women with osteoporosis or osteopenia.[102] Pooling of data from these studies indicated a relative risk of non-vertebral fracture in such women of 0.56 (95% CI 0.36 to 0.89). Addition of data from the non-fracture arm of the Fracture Intervention Trial[99] indicated a relative risk of non-vertebral fracture of 0.74 (95% CI 0.52 to 1.06) for women with osteoporosis or osteopenia treated with alendronate (*Figure 7*). However, subgroup analysis of data from the non-fracture arm of the Fracture Intervention Trial[99] suggests that, although alendronate has a significant effect on non-vertebral fractures in osteoporotic women (RR 0.64, 95% CI 0.58 to 0.82), it does not in those who are only osteopenic (RR 1.08, 95% CI 0.87 to 1.35).

Meta-analysis combining data from the fracture arm of the Fracture Intervention Trial[98] with data from the Liberman study[100] indicated a relative risk of non-vertebral fracture of 0.81 (95% CI 0.66 to 0.98) in women with severe osteoporosis or osteoporosis treated with alendronate (*Figure 8*).

The study of alendronate in women receiving HRT[101] did not produce a statistically significant result in relation to non-vertebral fracture (RR in the alendronate group 1.67, 95% CI 0.75 to 3.73).

Thus, alendronate has been shown to reduce the risk of non-vertebral fracture in women with osteoporosis without fracture. Moreover, a preplanned analysis of women with osteoporosis or severe osteoporosis from both the fracture and the non-fracture arm of the Fracture Intervention Trial found that the relative risk of any non-vertebral fracture in such women receiving alendronate was 0.73 (95% CI 0.61 to 0.87, $p < 0.001$), and of an osteoporotic non-vertebral fracture was 0.64 (95% CI 0.51 to 0.80, $p = 0.002$).[45] These figures are not inconsistent with those obtained by combining data from the fracture arm of the Fracture Intervention Trial[98] and from the Liberman study[100] (see above).

Hip, wrist and other non-vertebral fractures

Few studies reported specifically on hip, wrist or other non-vertebral fractures (*Tables 15–17*).

Pooling of data in women with osteoporosis or osteopenia[99,100] indicated a relative risk of hip fracture of 0.68 (95% CI 0.30 to 1.54) and of wrist fracture of 0.67 (95% CI 0.19 to 2.32) in those receiving alendronate (*Figures 9* and *10*).

By comparison, a greater antifracture effect was seen when data were pooled relating to women

TABLE 14 *Alendronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: non-vertebral fracture data*

Study	Alendronate dose	No. of women in each group suffering non-vertebral fracture
Adami, 1995[93]	10 and 20 mg per day	Alendronate 10 mg: 1/68 Alendronate 20 mg: 1/72 Placebo: 3/71 (may include clinical vertebral fractures) RR, alendronate 10 mg vs placebo, 0.35 (95% CI 0.04 to 3.26)
Bone, 1997[95]	1, 2.5 and 5 mg per day	Alendronate 1 mg: 15/86 Alendronate 2.5 mg: 9/89 Alendronate 5 mg: 9/93 Placebo: 16/91 RR, alendronate 5 mg vs placebo, 0.55 (95% CI 0.25 to 1.08)
Bone, 2000[52]	10 mg per day	Alendronate 10 mg: 4/92 Placebo: 4/50 RR 0.68 (95% CI 0.19 to 2.42) Includes clinical vertebral fractures. Most fractures were non-vertebral, occurring at sites such as foot, ankle and rib, and most occurred as a result of trauma
Carfora, 1998[96]	5, 10 and 20 mg per day	RR, alendronate vs placebo, 0.55 (authors' calculation; confidence intervals and numbers of women suffering fractures not supplied)
Chesnut, 1995[54]	5, 10, 20 and 40 mg per day	13 non-vertebral fractures occurred in 12 subjects. These were evenly distributed across treatment groups and were not considered related to therapy
FIT: women with pre-existing fractures[98]	5 mg per day increased after 2 years to 10 mg per day	Alendronate: 122/1022 Placebo: 148/1005 RR 0.81 (95% CI 0.65 to 1.01)
FIT: women without pre-existing fractures[99]	5 mg per day increased after 2 years to 10 mg per day	Alendronate: 261/2214 Placebo: 294/2218 RR 0.89 (95% CI 0.76 to 1.04)
Greenspan, 2002[60]	10 mg per day	Alendronate: 13 (8%) Placebo: 18 (11%) As the number of women in each group was not stated, it was not possible to calculate RR
Liberman, 1995[100]	5, 10 and 20 mg per day decreased to 5 mg per day after 2 years	Alendronate: 45/597 Placebo: 38/397[105] RR 0.79 (95% CI 0.52 to 1.19)
Lindsay, 1999[101]	10 mg per day	Alendronate: 15/214 Control: 9/214 RR 1.67 (% CI 0.75 to 3.73)
Pols, 1999[102]	10 mg per day	Alendronate: 19/950 Control: 36/958 RR 0.52 (95% CI 0.30 to 0.89)

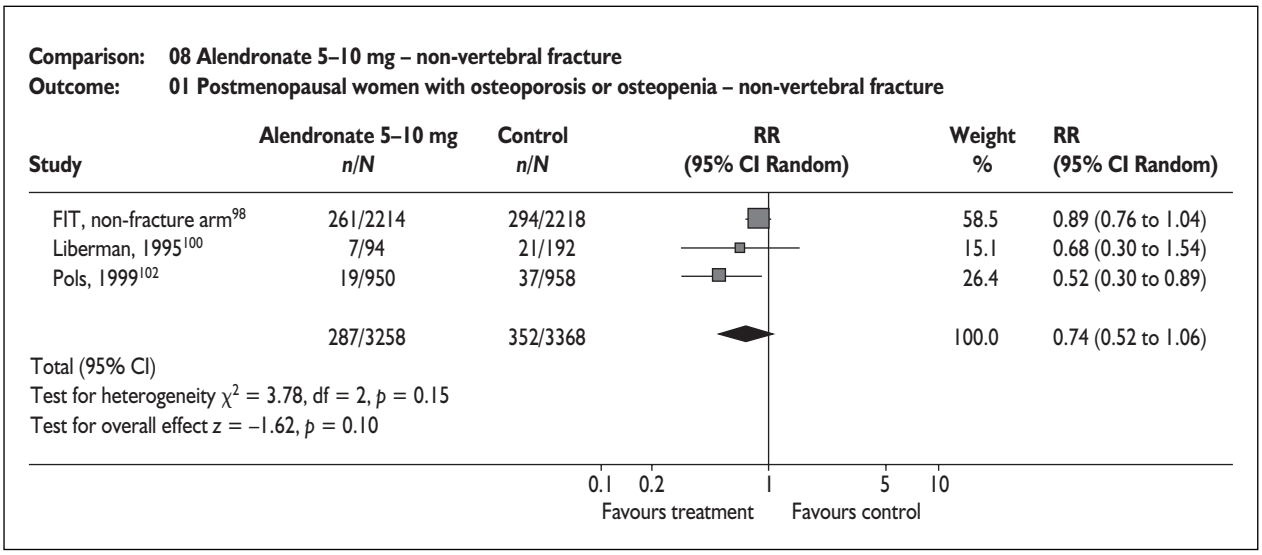

FIGURE 7 *Alendronate: non-vertebral fracture in postmenopausal osteoporosis or osteopenia*

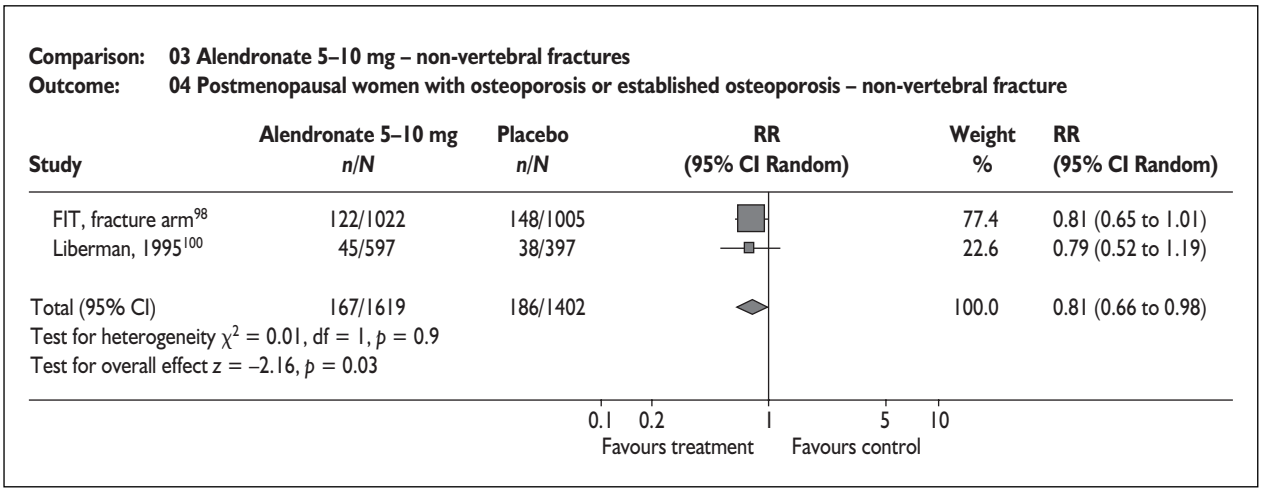

FIGURE 8 *Alendronate: vertebral fracture in severe postmenopausal osteoporosis or osteoporosis*

TABLE 15 *Alendronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: hip fracture data*

Study	Alendronate dose	No. of women in each group suffering hip fracture
FIT: women with pre-existing fractures[98]	5 mg per day increased after 2 years to 10 mg per day	Alendronate: 11/1022 Placebo: 22/1005 RR 0.49 (95% CI 0.24 to 1.01)
FIT: women without pre-existing fractures[99]	5 mg per day increased after 2 years to 10 mg per day	Alendronate: 19/2214 Placebo: 24/2218 RR 0.79 (95% CI 0.44 to 1.44)
Greenspan, 2002[60]	10 mg per day	Alendronate: 2 Placebo: 4 As the number of women in each group was not stated, it was not possible to calculate RR
Liberman, 1995[100]	5, 10 and 20 mg per day decreased to 5 mg per day after 2 years	Alendronate: 1/597 Placebo: 3/397[105] RR 0.22 (95% CI 0.02 to 2.12)

TABLE 16 *Alendronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: wrist fracture data*

Study	Alendronate dose	No. of women in each group suffering wrist fracture
FIT: women with pre-existing fractures[98]	5 mg per day increased after 2 years to 10 mg per day	Alendronate: 22/1022 Placebo: 41/1005 RR 0.55 (95% CI 0.32 to 0.88)
FIT: women without pre-existing fractures[99]	5 mg per day increased after 2 years to 10 mg per day	Alendronate: 83/2214 Placebo: 70/2218 RR 1.19 (95% CI 0.87 to 1.62)
Liberman, 1995[100]	5, 10 and 20 mg per day decreased to 5 mg per day after 2 years	Alendronate: 8/597 Placebo: 16/397[105] RR 0.33 (95% CI 0.14 to 0.77)

TABLE 17 *Alendronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: other non-vertebral fracture data*

Study	Alendronate dose	No. of women in each group suffering other non-vertebral fracture
FIT: women with pre-existing fractures[98]	5 mg per day increased after 2 years to 10 mg per day	Alendronate: 100/1022 Placebo: 99/1005 RR 0.99 (95% CI 0.75 to 1.29)
FIT: women without pre-existing fractures[99]	5 mg per day increased after 2 years to 10 mg per day	Alendronate: 182/2214 Placebo: 227/2218 RR 0.79 (95% CI 0.67 to 0.97)

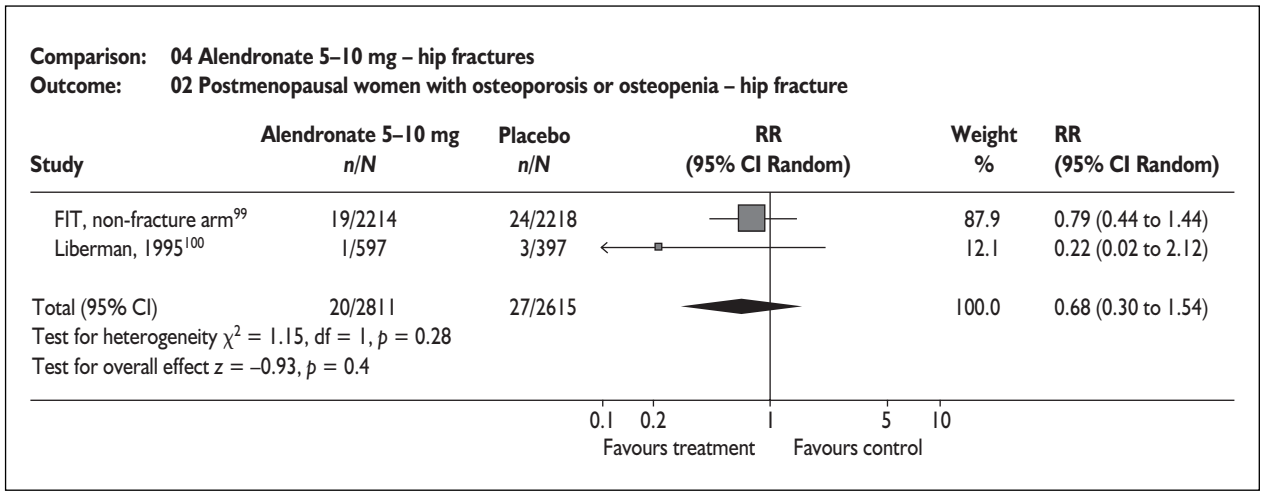

FIGURE 9 *Alendronate: hip fracture in postmenopausal osteoporosis or osteopenia*

with severe osteoporosis or osteoporosis: the relative risk of hip fracture was 0.46 (95% CI 0.23 to 0.91) and of wrist fracture was 0.48 (95% CI 0.31 to 0.75) in women treated with alendronate (*Figures 11* and *12*).

These results are consistent with those obtained in a preplanned analysis of women with osteoporosis or severe osteoporosis from both the fracture and the non-fracture arm of the Fracture Intervention Trial, which found that the relative risk of hip fracture in such women receiving alendronate was 0.47 (95% CI 0.26 to 0.79) and of wrist fracture was 0.70 (95% CI 0.49 to 0.98).[45]

Thus, alendronate has been shown to reduce the risk of non-vertebral fracture in women with osteoporosis without fracture. Moreover, a preplanned analysis of women with osteoporosis or severe osteoporosis from both the fracture and the

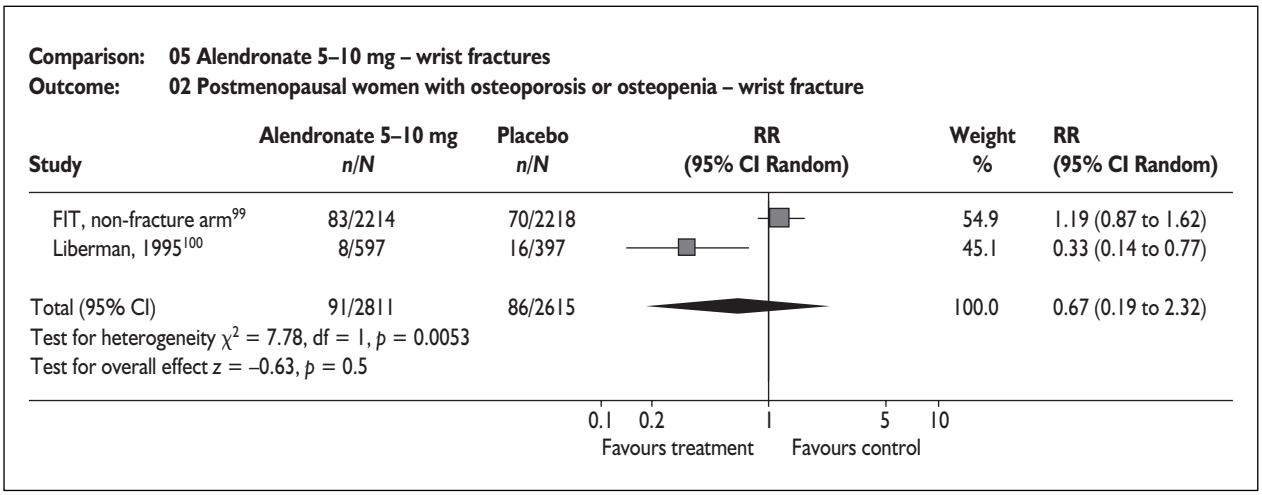

FIGURE 10 *Alendronate: wrist fracture in postmenopausal osteoporosis or osteopenia*

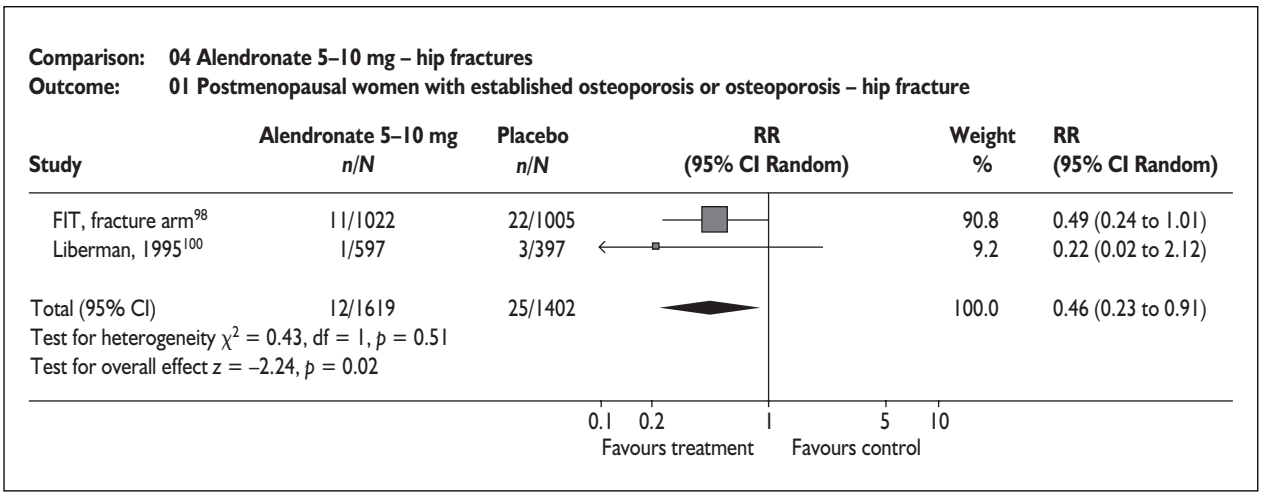

FIGURE 11 *Alendronate: hip fracture in severe postmenopausal osteoporosis or osteoporosis*

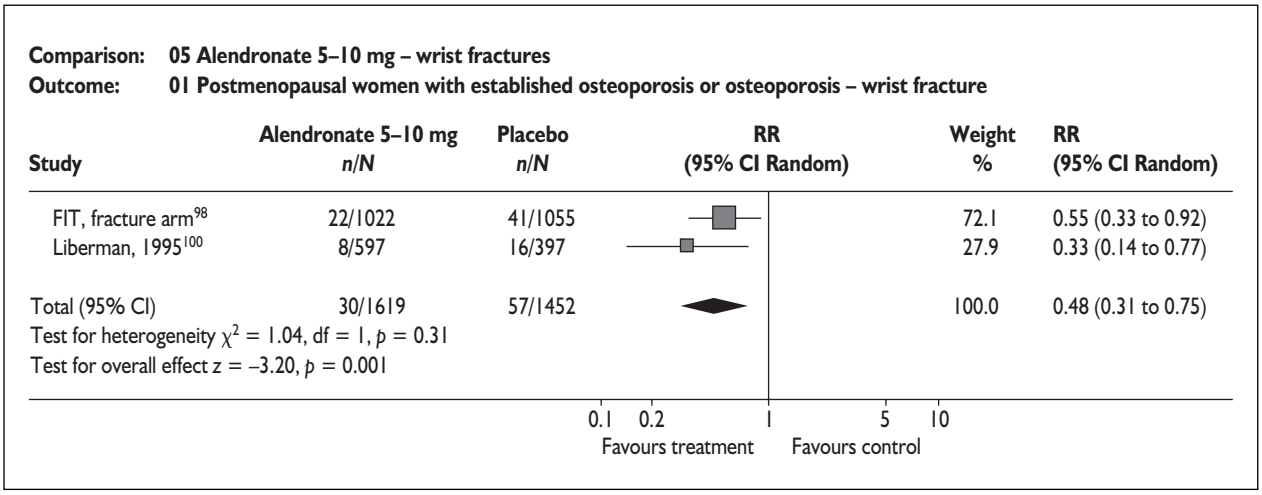

FIGURE 12 *Alendronate: wrist fracture in severe postmenopausal osteoporosis or osteoporosis*

non-fracture arm of the Fracture Intervention Trial found that the relative risk of any non-vertebral fracture in such women receiving alendronate was 0.73 (95% CI 0.61 to 0.87, $p < 0.001$) and of an osteoporotic non-vertebral fracture was 0.64 (95% CI 0.51 to 0.80, $p = 0.002$). The relative risk of hip fracture was 0.47 (95% CI 0.26 to 0.79, $p = 0.005$) and of wrist fracture was 0.70 (95% CI 0.49 to 0.98, $p = 0.038$).[45] These figures are not inconsistent with those obtained by combining data from the fracture arm of the FIT study[98] and from the Liberman study[100] (see above).

Quality of life

Only one study[97] set out to measure the effect of alendronate treatment on health-related quality of life, as measured by the Nottingham Health Profile (NHP). At 12 months, there were statistically significant mean reductions (indicating improvements) in the alendronate group, but not in the control group, in the NHP scores for pain, social isolation, energy level and physical ability. In addition, pain, as measured on a visual analogue scale (VAS), decreased significantly from baseline in the alendronate group but not in the control group. As the baseline emotional reaction score was significantly lower in the alendronate group than in the control group, the authors recognised that this might have affected the reliability of their result in terms of that parameter of quality of life.

The vertebral fracture arm of the Fracture Intervention Trial also collected data on the effects of alendronate on back pain and days of functional limitation or bed rest. Women in the treatment group had significantly fewer days in bed due to back pain than the placebo group (mean of 1.9 days over a 3-year period versus 5.1 days, $p = 0.001$) and fewer days of limited activity because of such pain (mean of 61.8 days versus 73.2, $p = 0.04$).[106]

Quantity and quality of research available: alendronate in early postmenopausal women not selected for low BMD

Two RCTs[66,107] were found that studied the use of alendronate in early postmenopausal women who were not specifically selected for low BMD, and that reported fracture outcomes. One of these, the Alendronate Osteoporosis Prevention Study (AOPS),[66] compared doses of 1, 5 and 10 mg per day, and 20 mg per day for 2 years followed by placebo for 1 year, with placebo in postmenopausal women with normal BMD or osteopenia. The other, the Early Postmenopausal Intervention Cohort (EPIC) study,[71,107] compared various regimens involving alendronate in doses of 2.5 or 5 mg per day with HRT and with placebo in women, no more than 10% of whom had low BMD. In addition, Merck Sharp & Dohme have confirmed that both studies used masked randomisation and blinded outcome assessment. These comments have been taken into account in assessing the quality of those studies. However, as no detail was provided of the methods used to mask randomisation, a score of 2 was given to both studies in the absence of evidence that the method used did not allow disclosure of assignment (see Appendix 10, *Tables 135–137*, for details).

As yet, only two planned interim analyses from the EPIC study have been published. The 2-year analysis[107] described the study as having four arms (placebo, alendronate 2.5 mg, alendronate 5 mg, and oestrogen/progestin); it was not indicated that these would be further subdivided. When the 4-year analysis was published,[71] the four groups had become six (placebo, placebo for 4 years followed by alendronate 5 mg per day for 2 years, alendronate 2.5 mg, alendronate 2.5 mg per day for 2 years followed by placebo, alendronate 5 mg per day, alendronate 5 mg per day for 2 years followed by placebo, and oestrogen/progestin); again, it was not made clear that further subdivision was planned. However, by 6 years, the study had nine arms (Hosking DJ: personal communication) (placebo for 6 years, placebo for 4 years followed by alendronate 5 mg per day for 2 years, alendronate 2.5 mg for 6 years, alendronate 2.5 mg for 4 years followed by placebo for 2 years, alendronate 2.5 mg per day for 2 years followed by placebo for 2 years, alendronate 5 mg per day for 6 years, alendronate 5 mg per day for 4 years followed by placebo for 2 years, alendronate 5 mg per day for 2 years followed by placebo for 4 years, and oestrogen/progestin for 4 years only).

All participants in the AOPS[66] received a daily supplement of calcium carbonate (Os-Cal 500 or equivalent) unless their dietary calcium intake exceeded 1000 mg per day. In the EPIC study,[107] all women whose daily calcium intake was lower than that dictated by the local standard of care were advised to increase their intake through dietary changes or supplementation.

Assessment of effectiveness of alendronate in early postmenopausal women not selected for low BMD

Both studies of alendronate in early postmenopausal women who were not specifically selected for low BMD[66,107] included some subjects

who received alendronate at 5 mg per day, the dose currently licensed in the UK for the prevention of osteoporosis. The latest published data from the EPIC study reported combined data on all clinical fractures, whether vertebral or non-vertebral; at 4 years, the relative risk of any symptomatic fracture in the group receiving alendronate at a dose of 5 mg per day was 1.01 (95% CI 0.62 to 1.62) compared with placebo.[71] Unpublished 6-year fracture data were kindly made available for this review by one of the study investigators (Hosking DJ: personal communication) (*Table 18*). As the numbers of women suffering fractures are so small, the confidence intervals for the relative risks obtained by comparing all the groups individually with either the placebo or the oestrogen arm cross unity. Thus, the relative risk of any non-vertebral fracture in the arm receiving the licensed dose of 5 mg per day alendronate was 1.27 (95% CI 0.53 to 3.03) compared with oestrogen at 4 years and 0.88 (95% CI 0.47 to 1.64) compared with placebo at 6 years.

Fracture data from the AOPS[66] have not been published. Although a published meta-analysis[108] has indicated that the study found a relative risk of vertebral fracture of 0.34 (95% CI 0.04 to 3.25) and of non-vertebral fracture of 0.28 (95% CI 0.28 to 2.24) in women receiving alendronate compared with controls, unfortunately the raw data could not be obtained to allow meta-analysis of the non-vertebral fracture data with those from the EPIC study.

Alendronate in postmenopausal osteoporosis and osteopenia and in early postmenopausal women not selected for low BMD: summary

The best evidence for the relative risk of vertebral and non-vertebral fracture in women taking alendronate at or near the current licensed dose, compared with placebo or no treatment, is summarised in *Table 19*. All results relate to women who either were receiving supplementary calcium or were considered to have an adequate dietary calcium intake; some also received supplementary vitamin D.

As may be seen, alendronate has a protective effect in relation to vertebral fracture in women with severe osteoporosis or osteoporosis. Moreover, subgroup analysis of data from the fracture arm of the Fracture Intervention Trial has indicated that it is effective even in those women at highest risk of fracture because of advanced age or multiple vertebral fractures.[109]

However, subgroup analysis from the Fracture Intervention Trial suggests that alendronate does not reduce the risk of vertebral fracture in women with osteopenia, nor has it been shown to do so in early postmenopausal women not selected for low BMD (*Table 19*).

Although the aggregated results suggest that alendronate offers protection against non-vertebral fractures in women with severe osteoporosis or osteoporosis on the one hand, and in those with severe osteoporosis, osteoporosis or osteopenia on the other, when these results are disaggregated the studies have insufficient power to demonstrate a statistically significant result either in women with severe osteoporosis on the one hand or in women with osteoporosis or osteopenia on the other: in both cases, the point estimates suggest a reduction in risk, but the confidence intervals cross unity. Although the same is true in relation to hip fracture, a protective effect relative to wrist fracture has been demonstrated in women with severe osteoporosis (*Table 19*).

TABLE 18 *EPIC study: fracture data at 6 years*

Study arm (treatment by 2-year period)	No. of subjects suffering fractures				
	Clinical vertebral	All non-vertebral	Hip	Wrist	Other non-vertebral
Alendronate 5/5/5 (n = 168)	1	14	0	2	13
Alendronate 5/5/placebo (n = 165)	2	13	1	1	12
Alendronate 5/placebo/placebo (n = 165)	1	18	0	7	11
Placebo/placebo/alendronate 5 mg (n = 250)	1	18	0	1	18
Alendronate 2.5/2.5/2.5 (n = 165)	2	14	0	6	10
Alendronate 2.5/2.5/placebo (n = 165)	1	20	0	2	18
Alendronate 2.5/placebo/exit (n = 169)	5	15	0	3	12
Oestrogen/progestin for 4 years only (n = 110)	0	6	0	0	6
Placebo/placebo/placebo (n = 252)	5	24	0	4	20

TABLE 19 *Relative risk of fracture: alendronate versus controls*

Group	Vertebral fracture	All non-vertebral fracture	Hip fracture	Wrist fracture	Other non-vertebral fracture
Women with severe osteoporosis	0.53 (0.41 to 0.68)[a]	0.81 (0.65 to 1.01)[a]	0.49 (0.24 to 1.01)[a]	0.52 (0.33 to 0.92)[a]	0.99 (0.76 to 1.29)[a]
Women with severe osteoporosis or osteoporosis	0.53 (0.42 to 0.67)[b]	0.81 (0.66 to 0.98)[b]	0.46 (0.23 to 0.91)[b]	0.48 (0.31 to 0.75)[b]	No data
Women with severe osteoporosis, osteoporosis or osteopenia	0.56 (0.46 to 0.68)[c]	0.86 (0.76 to 0.97)[d]	0.62 (0.40 to 0.98)[d]	0.64 (0.30 to 1.35)[d]	0.87 (0.71 to 1.07)[e]
Women with osteopenia or osteoporosis	0.60 (0.46 to 0.80)[f]	0.74 (0.52 to 1.06)[g]	0.68 (0.30 to 1.54)[g]	0.67 (0.19 to 2.32)[g]	0.80 (0.67 to 0.97)[h]
Women with severe osteoporosis, osteoporosis or osteopenia receiving HRT	No data	1.67 (0.75 to 3.73)[i]	No data	No data	No data
Early postmenopausal women not selected for low BMD	0.34 (0.04 to 3.25)[j]	0.88 (0.47 to 1.64)[k]	Insufficient data	Insufficient data	0.97 (0.50 to 1.91)[k]

Data are shown as RR (95% CI).
[a] Based on data from FIT fracture arm.[98]
[b] Based on data from FIT fracture arm[98] Liberman *et al*. (1995).[100]
[c] Based on data from Dursun *et al*. (2000),[97] FIT fracture[98] and non-fracture arms[99] and Liberman *et al*. (1995).[100]
[d] Based on data from FIT fracture[98] and non-fracture arms[99] and Liberman *et al*. (1995).[100]
[e] Based on data from FIT fracture[98] and non-fracture arms.[99]
[f] Based on data from Dursun *et al*. (2000),[97] FIT non-fracture arm[99] and Liberman *et al*. (1995).[100]
[g] Based on data from FIT non-fracture arm[99] and Liberman *et al*. (1995).[100]
[h] Based on data from FIT non-fracture arm.[99]
[i] Based on data from Lindsay *et al*. (1999).[101]
[j] Based on data from McClung study, as reported by Cranney *et al*. (2002).[108]
[k] Based on data from the EPIC study (Hosking DJ: personal communication).

There is no evidence that alendronate offers protection against non-vertebral fracture in early postmenopausal women without osteoporosis.

There is no direct comparative evidence that alendronate is more effective than other interventions in reducing the risk of osteoporotic fracture. Although the point estimates suggest that it is less effective than teriparatide in women with osteoporosis, and than oestrogen in early postmenopausal women, in neither case is the result statistically significant.

Alendronate: side-effects

Bisphosphonates have been associated with adverse upper gastrointestinal events. However, although the RCTs of alendronate included in this review reported adverse upper gastrointestinal events such as nausea, dyspepsia, mild oesophagitis/gastritis and abdominal pain in up to almost half their participants, in no case was the overall incidence of such events said to be significantly higher in subjects treated with alendronate than in those receiving placebo (see Appendix 10, *Table 138*). In one study, the proportion of women suffering abdominal pain and dysphagia was significantly higher in women receiving 10 mg per day alendronate than in the placebo group, but the incidence of other gastrointestinal adverse events was not significantly different. In most cases, abdominal pain occurred early in the study, and was mild and transient.[110]

Other clinical adverse events reported in these RCTs include skin rash,[54,96] musculoskeletal pain and headache.[42]

The RCT evidence is consistent with postmarketing studies which indicate that around one-third of alendronate users report gastrointestinal adverse events.[111] Some users have developed chemical oesophagitis, including severe ulcerations, which mostly resolved when alendronate was stopped.[112] Most patients who suffered oesophageal complications did so soon

after the start of alendronate administration, and in many instances these complications seemed to be associated with failure to take the drug with adequate quantities of water, or to remain upright afterwards, or both.[112]

A UK questionnaire survey gathered information relating to 1523 patients who had been prescribed alendronate. Dyspepsia, nausea/vomiting and abdominal pain were the most frequently reported adverse events, and the most common reasons for discontinuing alendronate. Possible oesophageal reactions to alendronate were experienced by 1.3% of all patients.[113] However, there is evidence to suggest that such gastrointestinal symptoms may not be exceptional in elderly women. A US retrospective cohort study compared the incidence of hospitalisations for gastric or duodenal perforations, ulcers and bleeding among 6432 patients dispensed 10 mg per day alendronate and an age- and gender-matched unexposed group. This found that, after adjustment for age, gender, chronic disease score, recent exposure to prescription non-steroidal anti-inflammatory drugs (NSAIDs) or oral corticosteroids, and number of hospitalisations in the year preceding alendronate prescription (or the referent date for the non-exposed group), there was no statistically significant difference between the two groups in terms of the risk of hospitalisation for the specified causes (RR alendronate versus controls 1.8, 95% CI 0.8 to 3.9).[114]

All of the studies reviewed in this report used a daily dose of alendronate. However, alendronate is also licensed for the treatment of postmenopausal osteoporosis using a weekly dose of 70 mg. A 2-year randomised study which compared a weekly dose of 70 mg, a twice-weekly dose of 35 mg and a daily dose of 10 mg in 1258 postmenopausal women with osteoporosis found the weekly dose to be equivalent to the daily dose in terms of BMD outcomes and clinical fracture incidence. The groups were also comparable in terms of the incidence of upper gastrointestinal adverse events, both overall and in terms of the most commonly reported events (abdominal pain, nausea, dyspepsia and acid regurgitation); the trend for a lower occurrence of oesophageal and gastric/duodenal adverse events and of more severe adverse events in the once-weekly and twice-weekly groups did not reach statistical significance.[115]

Alendronate has no documented extraskeletal benefits.

Alendronate: continuance and compliance

In the studies reviewed in this section, the percentage of subjects receiving alendronate who completed the protocol ranged from 100% in a very small 18-month study[103] to 50% at 6 years (EPIC study, Hosking DJ: personal communication). In the Fracture Intervention Trial, discontinuation of the study medication was found to be greatest in the first month postrandomisation: 4.8% of participants had withdrawn at 3 months and 11.1% at 12 months. Clinical adverse events formed the most common reason for withdrawal, causing 6.9% of women to withdraw. The proportion of women discontinuing treatment was comparable in the alendronate and placebo groups, and the strongest predictor of discontinuation was fair to poor self-rated health (RR 2.10, 95% CI 1.47 to 2.99).[116]

A US survey of continuance in 813 women treated with alendronate found that 28.7% stated that they had discontinued treatment, while prescription refill records suggested that 30.2% had actually discontinued. Gastrointestinal problems were most commonly given as the reason for discontinuation, being cited by 51.9% of women who had stopped taking the drug.[117]

In the intervention arms of the Fracture Intervention Trial, 89% of surviving subjects in the fracture trial and 81% in the non-fracture trial were still taking the study medication at the final visit; in both cases, 96% of those who continued to take the medication had taken at least 75% of their pills since the last clinic visit.[98,99] Another study stated that over 90% of subjects in the intervention arm were at least 90% compliant with the study medication.[101] A comparative study found that median compliance with treatment, assessed by pill counts of oral medication and measurement of volume of injectable medication returned at each study visit, was 71% in women taking alendronate, compared with 67% in those taking teriparatide.[94]

Etidronate

Quantity and quality of research available: etidronate in postmenopausal osteoporosis and osteopenia

Eight RCTs[118–125] were identified that compared etidronate with the other interventions or comparators reviewed in this report in postmenopausal osteoporosis or osteopenia, and that reported fracture outcomes. Four of these[118,119,122,125] were comparative studies, all but one of which[119] also included an untreated control arm. One study[118] was only available in abstract form.

No studies reported quality of life outcomes.

Three of the comparative studies compared etidronate with HRT.[118,122,125] In two of these studies, all subjects received calcium either alone[122] or with vitamin D;[125] one also compared etidronate alone with etidronate plus HRT.[125] The fourth study compared etidronate plus calcium with a higher dose of calcium.[119]

Seven studies compared cyclical etidronate (either alone or preceded by 3 days of treatment with phosphate) either with placebo[123,124] or with no treatment.[118,120–122,125] In six studies, subjects in all arms received similar quantities of calcium, either alone[121,122,124] or with vitamin D.[120,123,125] In the seventh study,[118] subjects were not said to have been given calcium and/or vitamin D (for details see Appendix 10, *Table 139*).

Five studies were conducted in women with severe osteoporosis,[118,120,123–125] one in women with osteoporosis with or without vertebral fracture[119] and two in women with osteoporosis or osteopenia[121,122] (for details, see Appendix 10, *Tables 139* and *140*).

One study was set up as a 2-year double-blind, randomised, placebo-controlled trial.[124] However, after the initial 2 years, subjects were allowed to choose whether to continue the original blinded treatment or to take calcium alone; those who completed this third year, whether on blinded therapy or on calcium, were then eligible for inclusion in a 2-year open-label follow-up study in which all subjects took intermittent cyclical etidronate.[126] They were subsequently rerandomised to receive, in years 6 and 7, intermittent cyclical therapy with either etidronate or placebo.[127] Only the results of the original 2-year double-blind RCT have been used here.

Another study[123] was set up as a placebo-controlled RCT of 150 weeks' duration. All subjects who completed this study were invited to enrol in an open-label follow-up study in which all were given cyclical etidronate.[128] As the study was no longer either randomised or controlled, only the results of the original 150-week study have been used here.

As reported, the quality of these studies was variable: some[118–120,122] provided no evidence of appropriately masked randomisation or blinded outcome assessment, whereas the reported quality of others[121,123–125] was reasonably high (see Appendix 10, *Table 141*).

Assessment of effectiveness of etidronate in postmenopausal osteoporosis and osteopenia

None of the identified studies used etidronate in precisely the regimen currently licensed for use in the UK (i.e. 400 mg per day for 14 days, followed by 1.25 g calcium carbonate per day for 76 days in a 90-day cycle). The two Japanese studies[118,119] used 200 mg per day of etidronate for 14 days of a similar cycle: one[118] did not state that calcium was also used, while in the other[119] subjects were not given supplementary calcium, but were "strictly encouraged" to consume 800 mg per day calcium and 400 IU per day vitamin D in their meals. A US study also used a 200-mg dose of etidronate, preceded by 500 mg per day of potassium phosphate for 3 days; 1 g per day of calcium carbonate was taken throughout the 73-day cycle.[122] The remaining five studies[120,121,123–125] used a 400-mg dose, in most cases[120,121,123,124] with only a 500-mg daily dose of calcium; one preceded the etidronate with 5 days of 1,25-dihydroxyvitamin D_3 at 2 μg per day.[120] With one exception,[118] all trials with a placebo or no treatment arm stated that subjects in those arms received calcium (and, where relevant, vitamin D) in quantities comparable to those given in the etidronate arm (for details of regimens used, see Appendix 10, *Table 139*).

Comparisons with active treatment

Only one study that compared etidronate with another active intervention used a 400-mg dose in women with severe osteoporosis.[125] Two used a 200-mg dose of etidronate, one in women with severe osteoporosis[118] and the other in women with severe osteoporosis or osteoporosis.[119] Another used a 200-mg dose in women with osteoporosis or osteopenia.[122]

Three of the comparative studies provided separate data relating to vertebral fracture.[119,122,125] Two used a 20% definition for all fractures;[119,125] the third[122] used a 20% definition for wedging and biconcave fractures but a 15% definition for compression fractures. However, two of these studies did not state the number of women suffering vertebral fractures. One[122] only provided information on the mean number of new vertebral fractures per subject, stating that the number of such fractures was almost identical in all groups; although information on the numbers of women in each group who suffered vertebral fractures was sought, the records had not been retained (Pacifici R: personal communication, 2002). The other study only stated the number of vertebral fractures in each group.[125] Relative risks could therefore not be calculated for these studies.

TABLE 20 *Etidronate in postmenopausal osteoporosis or osteopenia: comparisons with active treatment*

Study	Comparator	Type of fracture	No. of women suffering fracture		RR of fracture (95% CI): etidronate vs comparator
			Etidronate	Comparator	
Ishida, 2001[118]	HRT	Vertebral + non-vertebral	3%	0%	Not calculable
Pacifici, 1988[122]	HRT	Vertebral	No. of women with vertebral fractures not stated. The incidence of vertebral fractures was almost identical in the etidronate and HRT groups		Not calculable
Wimalawansa, 1998[125]	HRT	Non-vertebral	1/17	1/18	1.06 (0.07 to 15.62)
Wimalawansa, 1998[125]	Etidronate + HRT	Non-vertebral	1/17	1/19	1.12 (0.08 to 16.52)
Iwamoto, 2001[119]	Calcium	Vertebral	2/25	6/24	0.32 (0.07 to 1.43)

One study[118] only provided pooled data relating to vertebral and non-vertebral fractures, and presented these only as percentages of women suffering fractures (*Table 20*), so again the relative risk of fracture could not be calculated. Thus, the only comparison with an active intervention for which a relative risk of vertebral fracture could be calculated was the comparison with calcium;[119] this was a small study, which did not produce a statistically significant result (*Table 20*).

Only one comparative study[125] provided data relating to the number of women suffering any non-vertebral fracture; again, this was a small study that did not produce a statistically significant result (*Table 20*). Another study[119] stated that no subjects suffered hip, wrist or shoulder fractures.

Comparisons with placebo or no treatment

Most of the studies that compared etidronate with placebo or no treatment used a 400-mg dose (see Appendix 10, *Table 139*). Five of these studies were carried out in women with severe osteoporosis,[118,120,123–125] one in women with severe osteoporosis, osteoporosis or osteopenia[121] and one in women with osteoporosis or osteopenia.[122]

Vertebral fracture

Seven studies provided some information relating to the incidence of radiographic vertebral fracture.[118,120–125] Five[120,121,123–125] used a 20% fracture definition, but only three of these[120,121,124] provided data on the number of women suffering incident vertebral fracture (*Table 21*).

Meta-analysis of the data provided by Lyritis[120] and Watts[124] indicated a relative risk of vertebral fracture of 0.43 (95% CI 0.20 to 0.91) in women with severe osteoporosis receiving cyclical etidronate at a dose of 400 mg per day, compared with untreated controls (*Figure 13*). The remaining study with usable data[121] was a small study that did not produce a statistically significant result, yielding a relative risk of 0.14 (95% CI 0.01 to 2.68) for a similar regimen in women with severe osteoporosis, osteoporosis or osteopenia. Thus, cyclical etidronate at a dose of 400 mg per day has been shown to reduce the risk of vertebral fracture only in women with severe osteoporosis.

There is no evidence that etidronate reduces the risk of vertebral fracture in postmenopausal women with osteoporosis without fracture or osteopenia.

The study[124] that compared etidronate with and without cyclical phosphate found that the combination resulted in no apparent additional benefits beyond those offered by etidronate alone.

Non-vertebral fracture

Six studies presented data relating to non-vertebral fracture (*Table 22*).

TABLE 21 *Etidronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: vertebral fracture data*

Study	Etidronate dose	Fracture definition	No. of women in each group suffering vertebral fracture
Ishida, 2001[118]	200 mg	Not stated	Provides pooled vertebral and non-vertebral fracture data only
Lyritis, 1997[120]	400 mg	20%	Etidronate: 4/39 Control: 9/35 RR 0.40 (95% CI 0.13 to 1.18)
Montessori, 1997[121]	400 mg	20%	Etidronate: 0/39 Control: 3/39 RR 0.14 (95% CI 0.01 to 2.68)
Pacifici, 1988[122]	200 mg	Compression fractures 15%, wedging and biconcave fractures 20%	No. of women with vertebral fractures not stated. The incidence of vertebral fractures was almost identical in the etidronate and control groups (mean of 0.30 ± 0.40 new fractures in the etidronate group and 0.25 ± 0.46 in the control group)
Storm, 1990[123]	400 mg	20%	No. of women with vertebral fractures not stated. Although there was no significant difference between the overall rate of fracture in the treatment and control groups from baseline to the end of the study (18 and 43 per 100 patient-years, respectively), after approximately 1 year of treatment etidronate was associated with a significant decrease in the rate of new vertebral fractures (6 and 54 per 100 patient-years, respectively, $p = 0.023$)
Watts, 1990[124]	400 mg	20%	Etidronate: 5/98 Placebo: 10/91 RR 0.46 (95% CI 0.16 to 1.31)
Wimalawansa, 1998[125]	400 mg	20%	No. of women with vertebral fractures not stated. There were three vertebral fractures in subjects taking etidronate alone, two in subjects taking HRT alone, one in the etidronate/HRT group and five in the control group

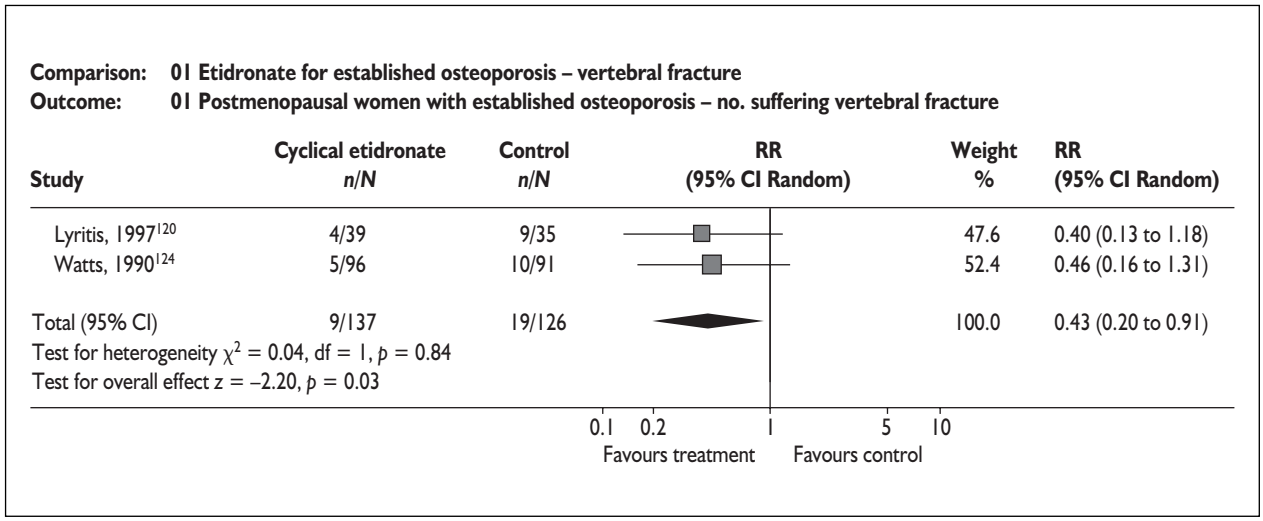

FIGURE 13 *Etidronate: vertebral fracture in severe postmenopausal osteoporosis*

TABLE 22 *Etidronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: non-vertebral fracture data*

Study	Etidronate dose	No. of women in each group suffering non-vertebral fracture
Ishida, 2001[118]	200 mg	Etidronate: 3% Control: 10% (pooled vertebral and non-vertebral fracture data)
Lyritis, 1997[120]	400 mg	Etidronate: 3/50 Control: 5/50 RR 0.60 (95% CI 0.15 to 2.38)
Montessori, 1997[121]	400 mg	Etidronate: 0/40 Control: 0/40
Storm, 1990[123]	400 mg	Etidronate: 5/33 Control: 6/33 RR 0.83 (95% CI 0.28 to 2.46)
Watts, 1990[124]	400 mg	Etidronate: 20/105 Control: 16/104 RR 1.24 (95% CI 0.68 to 2.25)
Wimalawansa, 1998[125]	400 mg	Etidronate: 1/17 Control: 1/18 RR 1.06 (95% CI 0.64 to 1.69)

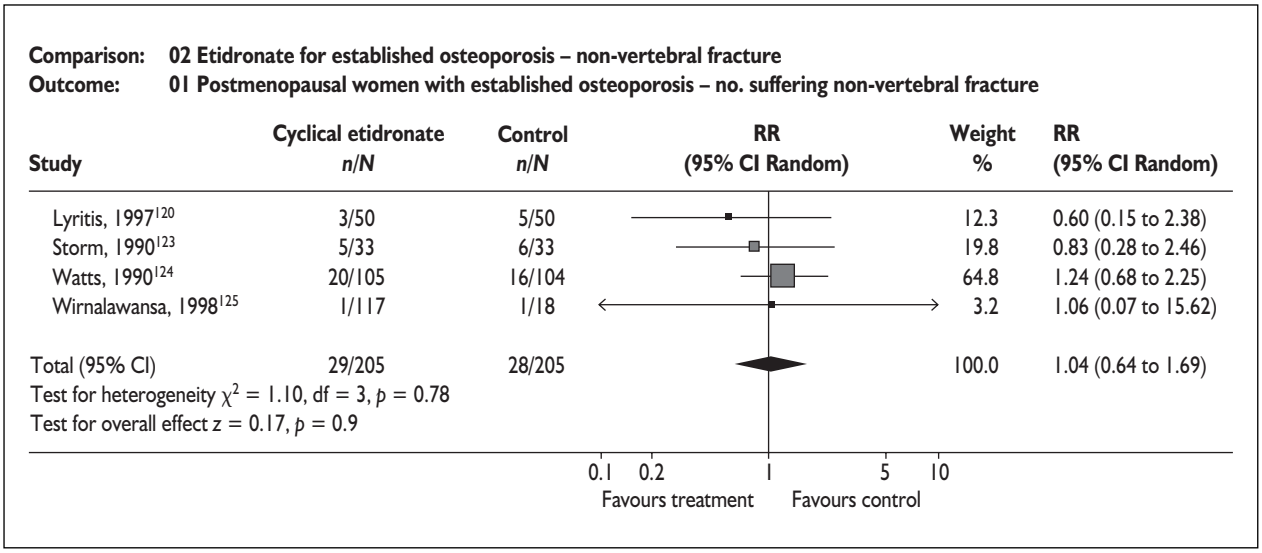

FIGURE 14 *Etidronate: non-vertebral fracture in severe postmenopausal osteoporosis*

Pooled data from the four studies conducted in women with severe osteoporosis that provided usable data[120,123–125] suggest a relative risk of non-vertebral fracture in such women of 1.04 (95% CI 0.64 to 1.69) compared with controls (*Figure 14*). The studies were so small that, even when their results were pooled, they were unable to demonstrate a significant difference between etidronate and placebo or no treatment in terms of the risk of non-vertebral fracture in women with severe osteoporosis.

Hip and other non-vertebral fracture

Only one study[120] provided separate information on hip and other non-vertebral fractures: in neither case were the results significant (relative risk for the etidronate group versus controls of 0.50, 95% CI 0.05 to 5.34, for hip fracture; and 0.67, 95% CI 0.12 to 3.82, for non-hip, non-wrist fracture).

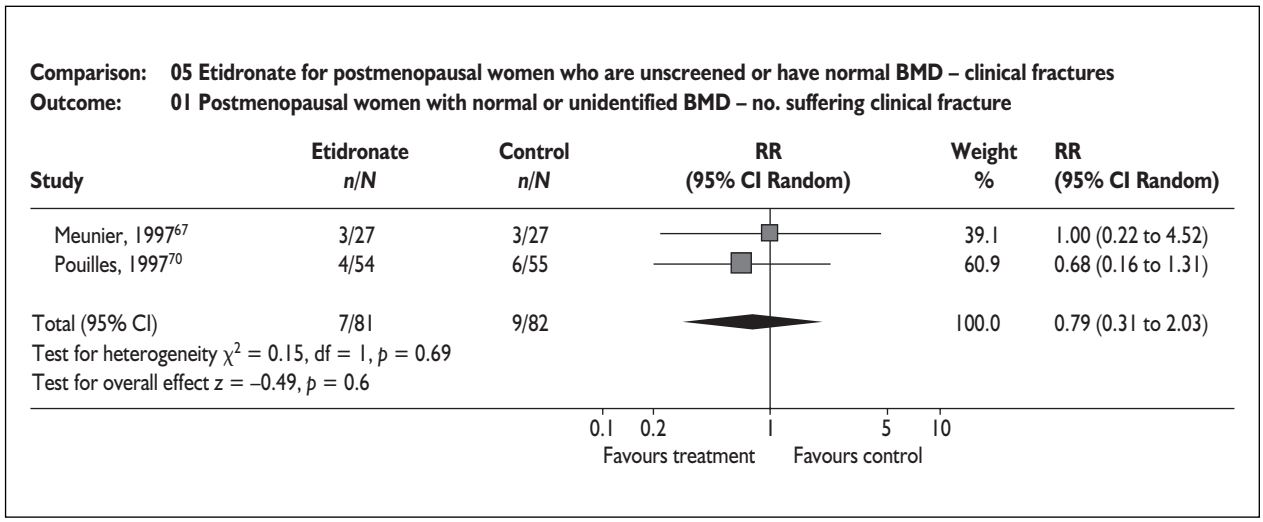

FIGURE 15 *Etidronate: clinical fracture in postmenopausal women with normal BMD or unselected for low BMD*

Quantity and quality of research available: etidronate in postmenopausal women with normal BMD or unselected for low BMD

Three RCTs were identified that studied the effects of etidronate in women with normal,[67] normal to low[62] or unspecified BMD,[70] and that reported fracture outcomes. All of these studies used 400 mg etidronate for 14 days followed by 500 mg calcium for the remainder of a 13-week cycle, and all were placebo controlled. All but one study[70] stated that the placebo group received supplementary calcium (see Appendix 10, *Tables 142* and *143* for details).

A fourth study[129] compared 400 mg etidronate for 14 days followed by 1000 mg calcium for the remainder of a 12-week cycle with placebo, HRT, and etidronate plus HRT in early postmenopausal women with normal BMD. This did not report fracture data and, although a meta-analysis[130] that includes this study indicates that such data were collected, they could not be obtained for use in this review.

None of these studies provided evidence of appropriately masked randomisation or blinded outcome assessment (see Appendix 10, *Table 144*).

Assessment of effectiveness: etidronate in postmenopausal women with normal BMD or unselected for low BMD

All fractures

Two studies[67,70] reported only clinical fractures, almost all of which resulted from some degree of trauma. The pooled results of these studies indicated a relative risk of such clinical fractures of 0.79 (95% CI 0.31 to 2.03) in women in the etidronate group, compared with controls (*Figure 15*). In the third study,[62] radiographic vertebral fracture was an end-point: no such fracture was found in either treatment group.

Etidronate in postmenopausal osteoporosis or osteopenia and in postmenopausal women with normal BMD or unselected for low BMD: summary

The best evidence for the relative risk of vertebral and non-vertebral fracture in women receiving a cyclical regimen of etidronate at 400 mg per day, compared with placebo or no treatment, is summarised in *Table 23*. All results relate to women receiving 500 mg per day supplementary calcium.

There is evidence that etidronate reduces the risk of vertebral fracture only in women with severe osteoporosis. Although the pooled data also indicate a statistically significant reduction in relative risk of such fractures in women with severe osteoporosis, osteoporosis or osteopenia, it should be noted that the only study to include women with osteoporosis without fracture or osteopenia as well as those with severe osteoporosis did not achieve a statistically significant result. Thus, as there are no separate data relating to women with osteoporosis without fracture or osteopenia, it cannot be demonstrated that etidronate reduces the risk of vertebral fracture in such women. There are no data relating to the effect of etidronate on vertebral fracture in women with normal, normal to low, or unspecified BMD (*Table 23*).

TABLE 23 *Relative risk of fracture: etidronate versus controls*

Group	Vertebral fracture	All non-vertebral fracture	Hip fracture	Wrist fracture	Other non-vertebral fracture
Women with severe osteoporosis	0.43 (0.20 to 0.91)[a]	1.04 (0.64 to 1.69)[a]	0.50 (0.05 to 5.34)[a]	No data	0.67 (0.12 to 3.82)[a]
Women with severe osteoporosis, osteoporosis or osteopenia	0.40 (0.20 to 0.83)[b]	No data	No data	No data	No data
Women with osteoporosis or osteopenia	No data	No data	No data	No data	No data
Women with normal or unspecified BMD	No data	No data	No data	No data	No data

Data are shown as RR (95% CI)
[a] Based on data from Lyritis *et al.* (1997)[120] and Watts *et al.* (1990).[124]
[b] Based on data from Montessori *et al.* (1997),[121] Lyritis *et al.* (1997)[120] and Watts *et al.* (1990)[124]

Etidronate does not appear to reduce the risk of non-vertebral fracture in women with severe osteoporosis. Evidence is lacking in relation to women with osteoporosis or osteopenia (*Table 23*). The only available evidence fails to demonstrate that etidronate reduces the risk of clinical fracture in women with normal, normal to low, or unspecified BMD.

There is no direct comparative evidence that etidronate is more effective than other interventions in reducing the risk of osteoporotic fracture. Although the point estimates suggest that it is less effective than HRT in women with severe osteoporosis, and more effective than calcium in women with osteoporosis with or without fracture, in neither case is the result statistically significant.

Etidronate: side-effects
Like alendronate, etidronate has been associated with upper gastrointestinal adverse events. Some of the RCTs included in this review reported such adverse events (see Appendix 10, *Table 145*). In four studies,[62,70,119,125] more gastrointestinal adverse events occurred in the etidronate group than in the placebo group. One of these studies[119] reported that adverse events such as gastrointestinal symptoms occurred primarily during the first 4 weeks of treatment; they occurred in five women (20%) in the etidronate group and only two (8%) in a control group receiving calcium; the difference between the groups was not statistically significant (relative risk of gastrointestinal symptoms in etidronate group compared with controls 2.40, 95% CI 0.51 to 11.21). A fifth study found no statistically significant differences between the treatment and control groups in relation to adverse effects that might be associated with etidronate (abdominal pain, diarrhoea and nausea);[124,127] however, the use of phosphate as an activating agent was associated with a substantially higher reporting of diarrhoea in subjects who received it than in those receiving placebo.[124] Another study[125] indicated that nausea following etidronate administration improved with time, and was not a cause of discontinuation.

Like alendronate, etidronate has no documented extraskeletal benefits.

Etidronate: continuance and compliance
In the studies reviewed in this section, the percentage of subjects receiving alendronate who completed the protocol ranged from 93% at 2 years[67] to 61% at 3 years.[123]

Two studies[67,70] assessed compliance by pill count. Subjects were defined as compliant if they took at least 80% of etidronate or its placebo over the study period. All subjects who completed each study were compliant by this definition.

Risedronate

Quantity and quality of research available: risedronate in postmenopausal osteoporosis and osteopenia
Six RCTs[24,131–135] were identified that compared risedronate with placebo or no treatment in postmenopausal women with osteoporosis, osteopenia or specific risk factors for hip fracture,

and that reported fracture outcomes. One of these[133] was only available in abstract form. No studies were identified that reported quality of life data.

All six studies were placebo-controlled, but had two active treatment arms. In five,[24,132–135] one arm received a daily dose of 2.5 mg of risedronate, and the other a dose of 5 mg (the dose currently licensed in the UK for the prevention and treatment of postmenopausal osteoporosis). One of these studies[134] only presented fracture data from the pooled risedronate arms. In the sixth study,[131] one arm received a 2.5-mg daily dose while the other received 2.5 mg per day for 2 weeks followed by placebo for 10 weeks of a 12-week cycle. In three of the studies that used a 2.5-mg dose,[24,132,135] the 2.5-mg arm was either wholly or partially discontinued after 1 year by a protocol amendment on the basis of evidence that a 5-mg dose produced a more consistent effect in increasing BMD while having a safety profile similar to that of a 2.5-mg dose.[135]

In all six studies, all subjects received 1 g per day elemental calcium (see Appendix 10, *Tables 146* and *147*).

Only one study[132] was reported to have met all the quality criteria (see Appendix 10, *Table 148*).

Three studies were carried out in women with severe osteoporosis,[131,132,135] one in women with osteoporosis or osteopenia[24] and one in women with osteopenia.[133] The remaining study was carried out in women with osteoporosis or specific risk factors for hip fracture.[134] This study was designed specifically to study the effect of risedronate on the risk of hip fracture in elderly women with osteoporosis or other risk factors for hip fracture; all non-vertebral osteoporotic fractures (defined as fractures of the wrist, leg, humerus, hip, pelvis or clavicle) formed a secondary end-point. This study recruited two groups of women: women aged 70–79 years with osteoporosis, and women aged 80 years or older with at least one non-skeletal risk factor for hip fracture or with osteoporosis (see Appendix 10, *Table 147*, for details). Each of the two enrolment groups was randomly assigned to treatment. The proportion of younger and older women with various risk factors was said to be balanced among the treatment groups. Only 16% of the older stratum was recruited on the basis of low femoral neck BMD; 58% were recruited solely on the basis of clinical risk factors such as a recent fall-related injury. There was evidence of at least one vertebral fracture at baseline in 39% of the younger stratum.[134]

Assessment of effectiveness: risedronate in postmenopausal osteoporosis and osteopenia

Vertebral fracture

Four studies provided data relating to vertebral fracture (*Table 24*). The two studies that used a 5-mg dose in women with severe osteoporosis[132,135] both provided information on vertebral fracture; both used a 15% vertebral fracture definition. Pooling of the data relating to subjects in these two studies indicated a relative risk of vertebral fracture of 0.63 (95% CI 0.51 to 0.78) compared with placebo (*Figure 16*). A third study in women with severe osteoporosis used different vertebral fracture thresholds in the two centres;[131] thus, a valid global vertebral fracture analysis could not be performed. Moreover, the number of women in each centre who suffered vertebral fractures was not presented.

The relative risk of vertebral fracture in women with osteoporosis or osteopenia receiving 5 mg of risedronate[24] was 0.53 (95% CI 0.24 to 1.17).

Thus, risedronate at a dose of 5 mg per day appears to reduce the risk of vertebral fracture in women with severe osteoporosis, but has not been demonstrated to reduce the risk of vertebral fracture in women with osteoporosis without fracture or with osteopenia.

Non-vertebral fracture

All six studies collected data relating to non-vertebral fracture (*Table 25*). However, one study, in postmenopausal women with osteopenia,[133] stated only that non-vertebral fractures were few in number and comparable between treatment groups. In another study,[131] in women with severe osteoporosis, more women in the group receiving cyclical risedronate suffered non-vertebral fractures, while equal numbers of women in the groups receiving either continuous risedronate or placebo suffered such fractures (RR, cyclical risedronate versus placebo, 2.25, 95% CI 0.75 to 6.77). This study only used a 2.5-mg dose of risedronate, and was underpowered to study fracture outcomes.

The pooled data from the two studies that used 5 mg of risedronate in women with severe osteoporosis[132,135] yielded a relative risk of non-vertebral fracture of 0.67 (95% CI 0.50 to 0.90) (*Figure 17*). In the McClung (2001) study,[134] women in the younger, osteoporotic, stratum who received risedronate had a relative risk of non-

TABLE 24 *Risedronate in postmenopausal osteoporosis or osteopenia: vertebral fracture data*

Study	Risedronate dose	Fracture definition	No. of women in each group suffering vertebral fracture
Clemmesen, 1997[131]	2.5 mg daily or cyclically	15% or 25% (different fracture definitions used by the Danish and Belgian centres)	Gives number of vertebral fracture identified at each centre, but not number of women suffering those fractures. States that there was a tendency towards a lower incidence and rate of new vertebral fractures in the group taking daily continuous risedronate, but this was not statistically significant
Fogelman, 2000[24]	2.5 and 5 mg per day	Any vertebral height ratio below 3 SD of the mean for the study population	Risedronate 2.5 mg: 8/60 Risedronate 5 mg: 8/112 Placebo: 17/125 RR, 5 mg vs placebo, 0.53 (95% CI 0.24 to 1.17)
Harris, 1999[132]	2.5 and 5 mg per day	15% + semi-quantitative method	Risedronate 5 mg: 61/696 Placebo: 93/678 RR 0.64 (95% CI 0.47 to 0.87)
McClung, 1998[133]	2.5 and 5 mg per day	NA	NA
McClung, 2001[134]	2.5 and 5 mg per day	NA	NA
Reginster, 2000[135]	2.5 and 5 mg per day	15% + semi-quantitative method	Risedronate 5 mg: 53/344 Placebo: 89/346 RR 0.60 (95% CI 0.44 to 0.81)

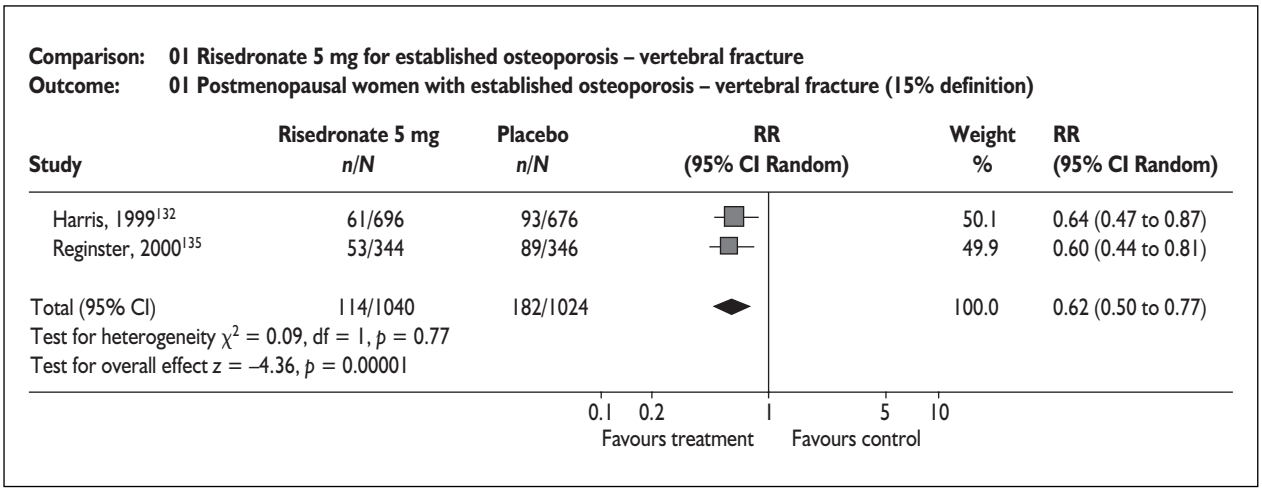

FIGURE 16 *Risedronate: vertebral fracture in severe postmenopausal osteoporosis*

vertebral fracture of 0.8 (95% CI 0.7 to 1.0; authors' calculation).

The only study that provided non-vertebral fracture data in women with osteoporosis or osteopenia who received 5 mg of risedronate[24] did not produce a statistically significant result (RR 0.55, 95% CI 0.22 to 1.34).

Thus, risedronate at a dose of 5 mg per day appears to reduce the risk of non-vertebral fracture in women with severe osteoporosis, but has not been demonstrated to reduce the risk of non-vertebral fracture in women with osteoporosis without fracture or with osteopenia.

Hip fracture

Three studies reported hip fracture data (*Table 26*).

Pooling data from the Reginster study[135] with data from the Harris study[132] yielded a relative risk of hip/pelvis fracture of 0.77 (95% CI 0.46 to 1.27) in

TABLE 25 *Risedronate in postmenopausal osteoporosis or osteopenia: non-vertebral fracture data*

Study	Risedronate dose	No. of women in each group suffering non-vertebral fracture
Clemmesen, 1997[131]	2.5 mg daily or cyclically	Continuous risedronate: 4/44 Cyclical risedronate: 9/44 Placebo: 4/44 RR, continuous risedronate vs placebo, 1.00 (95% CI 0.27 to 3.75)
Fogelman, 2000[24]	2.5 and 5 mg per day	Risedronate 2.5 mg: 4/184 Risedronate 5 mg: 7/177 Placebo: 13/180 RR, 5 mg vs placebo, 0.55 (95% CI 0.22 to 1.34)
Harris, 1999[132]	2.5 and 5 mg per day	Risedronate 5 mg: 33/812 Placebo: 52/815 RR 0.64 (95% CI 0.42 to 0.97)
McClung, 1998[133]	2.5 and 5 mg per day	Non-vertebral fractures were said to be few in number and comparable between groups. More specific data were not available
McClung, 2001[134]	2.5 and 5 mg per day	Risedronate: 583/6197 Placebo: 351/3134[43] RR 0.84 (95% CI 0.74 to 0.95)
Reginster, 2000[135]	2.5 and 5 mg per day	Risedronate 5 mg: 36/406 Placebo: 51/406 RR 0.71 (95% CI 0.47 to 1.06)

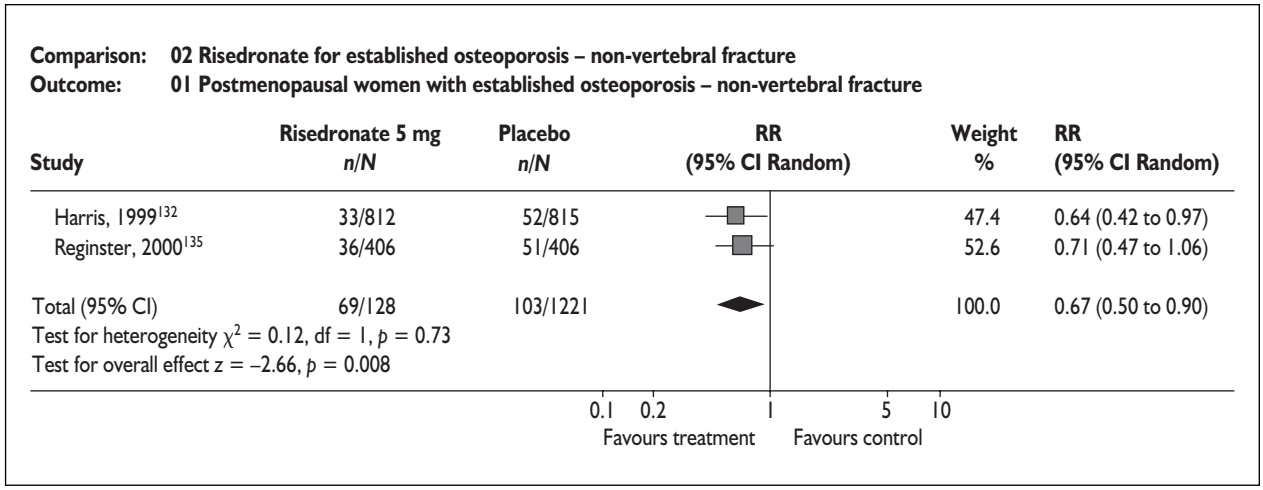

FIGURE 17 *Risedronate: non-vertebral fracture in severe postmenopausal osteoporosis*

women with severe osteoporosis who received a 5-mg dose of risedronate compared with placebo. The McClung study[134] did not provide usable data separately in relation to women receiving 2.5- and 5-mg doses of risedronate. However, according to the authors' calculations, the higher dose did not appear to confer increased protection on women in the younger, osteoporotic, stratum: the risk of hip fracture relative to placebo was calculated to be 0.5 (95% CI 0.3 to 0.9) in women receiving 2.5 mg, and 0.7 (95% CI 0.4 to 1.1) in those receiving 5 mg. Therefore, data relating to women with severe osteoporosis in the younger, osteoporotic, stratum of the study, regardless of risedronate dose, were pooled with data relating to women with severe osteoporosis receiving a 5-mg dose from the Harris and Reginster studies, yielding a relative risk of hip fracture of 0.60 (95% CI 0.42 to 0.88) in women with severe osteoporosis (*Figure 18*).

Pooling data from all women in the younger, osteoporotic, stratum of the McClung study with data relating to women in the Harris and Reginster studies who received a 5-mg dose

TABLE 26 *Risedronate in postmenopausal osteoporosis or osteopenia: hip fracture data*

Study	Risedronate dose	No. of women in each group suffering hip fracture
Harris, 1999[132]	2.5 and 5 mg per day	Risedronate 5 mg: 12/812 Placebo: 15/815 RR 0.80 (95% CI 0.38 to 1.70)
McClung, 2001[134]	2.5 and 5 mg per day	Risedronate: 137/6197 Placebo: 95/3134 RR 0.73 (95% CI 0.56 to 0.94) Younger, osteoporotic, group: Risedronate: 55/3624 Placebo: 46/1821 RR 0.60 (95% CI 0.41 to 0.89) Older group: Risedronate: 82/2573 Placebo: 49/1313 RR 0.85 (95% CI 0.60 to 1.21) Separate figures were not presented for the 2.5- and 5-mg groups, but the authors calculated a risk of hip fracture relative to placebo of 0.5 (95% CI 0.3 to 0.9) in women in the younger stratum receiving 2.5 mg, and of 0.7 (95% CI 0.4 to 1.1) in those receiving 5 mg
Reginster, 2000[135]	2.5 and 5 mg per day	Risedronate 5 mg: 14/406 Placebo: 19/406 RR 0.74 (95% CI 0.37 to 1.45)

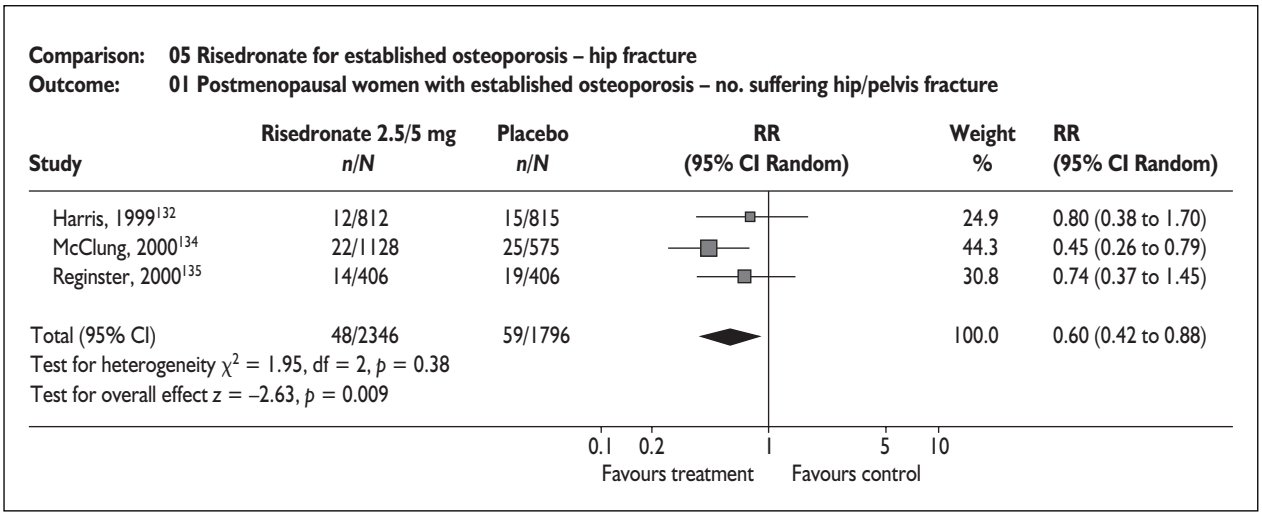

FIGURE 18 *Risedronate: hip fracture in severe postmenopausal osteoporosis*

indicated a protective effect of risedronate against hip fracture in women with severe osteoporosis or osteoporosis (RR 0.66, 95% CI 0.48 to 0.89) (*Figure 19*).

Thus, although risedronate at a dose of 5 mg per day appears to reduce the risk of hip fracture in women with severe osteoporosis or osteoporosis, there is no evidence to suggest that it does so in postmenopausal women with osteopenia, and it cannot be demonstrated that it offers protection solely in women with osteoporosis without fracture. Subgroup analysis in the McClung study[134] indicated that, in the younger, osteoporotic, stratum, risedronate was effective in preventing hip fracture in women with severe osteoporosis (RR relative to placebo 0.45, 95% CI 0.26 to 0.79), but did not demonstrate that it did so in those without baseline fractures (RR 0.6, 95% CI 0.3 to 1.2). Similarly, risedronate was not demonstrated to be effective in women in the elderly stratum, who were not necessarily osteoporotic; their risk of

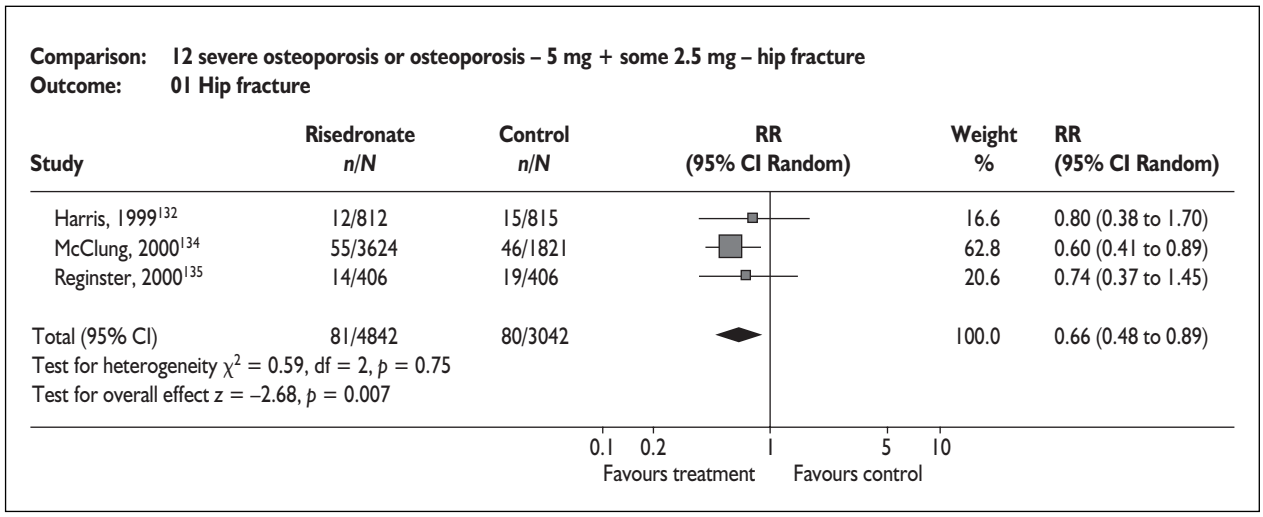

FIGURE 19 *Risedronate: hip fracture in severe postmenopausal osteoporosis or osteoporosis*

TABLE 27 *Risedronate in postmenopausal osteoporosis or osteopenia: wrist fracture data*

Study	Risedronate dose	No. of women in each group suffering wrist fracture
Harris, 1999[132]	2.5 and 5 mg per day	Risedronate 5 mg: 14/812 Placebo: 22/815 RR 0.64 (95% CI 0.33 to 1.24)
Reginster, 2000[135]	2.5 and 5 mg per day	Risedronate 5 mg: 15/406 Placebo: 21/406 RR 0.71 (95% CI 0.37 to 1.37)

hip fracture relative to placebo was 0.85 (95% CI 0.60 to 1.21).[134]

Wrist fracture

Only two studies provided wrist fracture data (*Table 27*). Pooling data from the Reginster study[135] with data from the Harris study[132] yielded a relative risk of wrist fracture of 0.68 (95% CI 0.43 to 1.08) in women with severe osteoporosis who received a 5-mg dose of risedronate compared with placebo (*Figure 20*). Pooled data from the same studies (again using unpublished data from the Reginster study[135]) indicated that a 5-mg dose of risedronate was associated with a relative risk of fracture of the humerus of 0.46 (95% CI 0.73 to 0.93).

Thus, risedronate at a dose of 5 mg per day appears to reduce the risk of vertebral and non-vertebral fracture in women with severe osteoporosis. It also appears to reduce the risk of hip fracture in women with severe osteoporosis or osteoporosis. However, it has not been demonstrated to reduce the risk of vertebral fracture or non-vertebral fracture in women with osteoporosis without fracture or with osteopenia.

Quantity and quality of research available: risedronate in postmenopausal women with normal BMD

One study[68] was identified that compared cyclic and continuous risedronate, at a dose of 5 mg per day, with placebo in early postmenopausal women with normal BMD, and that reported fracture data (for details, see Appendix 10, *Tables 149* and *150*). Randomisation was stratified by calcium intake (<400, 400–650 and 650–1500 mg per day) and calcium supplements were not provided. Mean calcium intake was approximately 1 g per day. This was originally designed as a 1-year study. At the end of that year, participants were given three options: to leave the study; to complete a second year without therapy; or to continue on treatment for a further year, with a further year without therapy thereafter. As blinding of treatment allocation was maintained throughout the study, and as the options offered resembled the continuance and compliance decisions made by subjects during the

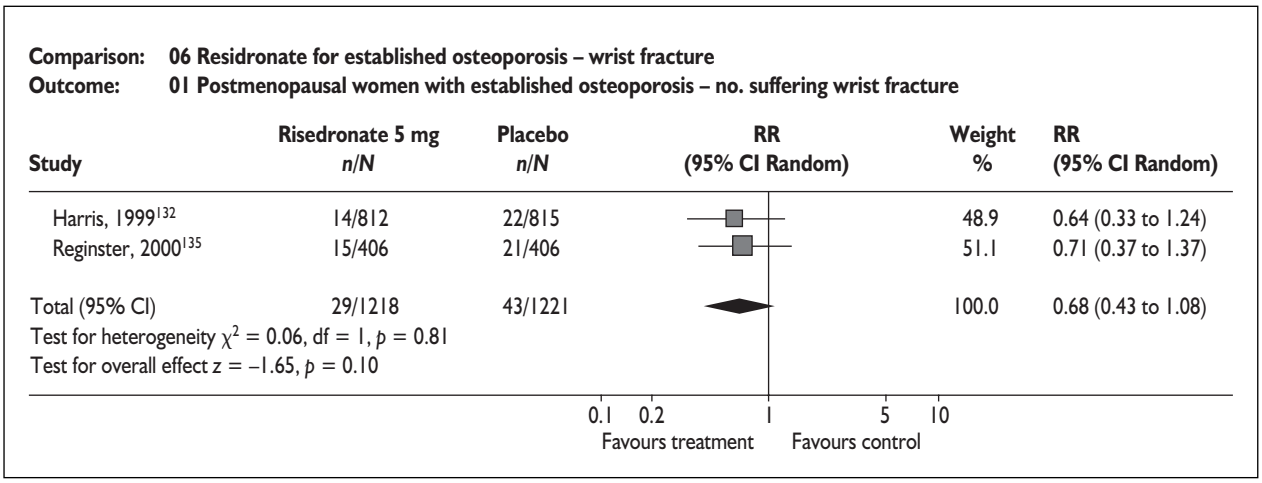

FIGURE 20 *Risedronate: wrist fracture in severe postmenopausal osteoporosis*

course of any study, results relating to the entire study period have been used here.

This study did not provide evidence of appropriately masked randomisation or specify that outcome assessment was blinded (see Appendix 10, *Table 151*).

Assessment of effectiveness: risedronate in postmenopausal women with normal BMD
Vertebral fracture
Two women, one in the cyclic risedronate group and one in the continuous risedronate group, had vertebral fractures during the follow-up period. The relative risk of vertebral fracture could not be calculated because the appropriate denominators were not known.

Non-vertebral fracture
Six subjects (three in the cyclic risedronate group and three in the placebo group) had non-vertebral fractures as a result of accidental traumatic events. The relative risk of non-vertebral fracture, in women receiving continuous risedronate compared with placebo, was 0.14 (95% CI 0.01 to 2.60); however, none of the fractures appeared osteoporotic in nature.

Risedronate in postmenopausal osteoporosis or osteopenia, and in postmenopausal women with normal BMD: summary
The best evidence for the relative risk of vertebral and non-vertebral fracture in women taking risedronate at the licensed dose, compared with placebo, is summarised in *Table 28*. All results, except those for early postmenopausal women with normal BMD, relate to women receiving supplementary calcium.

Thus, risedronate, at a dose of 5 mg per day, has been shown to have a protective effect in relation to vertebral and non-vertebral fracture in women with severe osteoporosis, and in a combined group of women with severe osteoporosis, osteoporosis or osteopenia. However, it has not been demonstrated to be effective in women with osteopenia or with osteoporosis without fracture, or in early postmenopausal women with normal BMD (*Table 28*).

Risedronate: adverse effects
All of the studies of risedronate found that the overall distribution of adverse events, and of adverse upper gastrointestinal events, was comparable in the intervention and placebo groups (see Appendix 10, *Table 152*).

As for alendronate and etidronate, risedronate has no documented extraskeletal benefits.

A weekly dose of 35 mg has been demonstrated to be as safe as a daily dose of 5 mg, and as effective in relation to BMD and vertebral fracture outcomes.[136]

Risedronate: continuance and compliance
Continuance in women taking a 5-mg dose of risedronate ranged from 46%[68] to 78%[24] at 2 years and from 51%[134] to 62%[135] at 3 years.

Only one study[135] specifically talked about compliance in terms of both the number of subjects

TABLE 28 *Relative risk of fracture: risedronate (5 mg per day) versus placebo*

Group	Vertebral fracture	All non-vertebral fracture	Hip/pelvis fracture	Wrist fracture	Other non-vertebral fracture
Women with severe osteoporosis	0.63 (0.51 to 0.78)[a]	0.67 (0.50 to 0.90)[a]	0.60 (0.42 to 0.88)[b i]	0.68 (0.43 to 1.08)[a]	No data
Women with severe osteoporosis or osteoporosis	No data	0.8 (0.7 to 1.0)[c i] (author's calculation)	0.66 (0.48 to 0.89)[d i]	No data	No data
Women with severe osteoporosis, osteoporosis or osteopenia	0.62 (0.50 to 0.76)[e]	0.66 (0.50 to 0.87)[e]	No data	No data	No data
Women with osteoporosis	No data	No data	0.58 (0.27 to 1.24)[f i]	No data	No data
Women with osteoporosis or osteopenia	0.53 (0.24 to 1.17)[g]	0.55 (0.22 to 1.34)[g]	No data	No data	No data
Early postmenopausal women with normal BMD	No data	0.14 (0.01 to 2.60)[h]	No data	No data	No data

Data are shown as RR (95% CI)
[a] Based on data from Harris *et al*. (1999)[132] and Reginster *et al*. (2000).[135]
[b] Based on data from Harris *et al*. (1999),[132] Reginster *et al*. (2000)[135] and McClung (2001, younger osteoporotic cohort, women with severe osteoporosis only).[134]
[c] Based on data from McClung (2001, younger osteoporotic cohort, all women).[134]
[d] Based on data from Harris *et al*. (1999),[132] Reginster *et al*. (2000)[135] and McClung (2001, younger osteoporotic cohort, all women.[134]
[e] Based on data from Fogelman *et al*. (2000),[24] Harris *et al*. (1999)[132] and Reginster *et al*. (2000).[135]
[f] Based on data from McClung (2001, younger osteoporotic cohort, women without baseline fracture only).[134]
[g] Based on data from Fogelman *et al*. (2000).[24]
[h] Based on data from Mortensen *et al*. (1998).[68]
[i] Includes pooled 2.5- and 5-mg data relating to McClung (2001).[134]

who continued to take the medication and the proportion of medication that they had taken. This found that, overall, 86% of subjects took at least 80% of their medication. However, as noted above, only 62% of subjects in the 5-mg arm completed the protocol.

Raloxifene

Quantity and quality of research available: raloxifene in postmenopausal osteoporosis or osteopenia

Two studies[137,138] were identified that used raloxifene in women with postmenopausal osteoporosis or osteopenia. Both compared raloxifene with placebo. In both studies, subjects in both the intervention and control groups received comparable doses of calcium and vitamin D (for details, see Appendix 10, *Tables 153* and *154*). Neither study reported on quality of life outcomes associated with raloxifene treatment, as opposed to those related to vertebral fracture.

One study[137] was carried out in women with severe osteoporosis; the other [the Multiple Outcomes of Raloxifene Evaluation (MORE) study][138] was carried out in women with osteoporosis, only 37% of whom had vertebral fracture at entry (see Appendix 10, *Table 153*). The trials varied in terms of their duration and the doses of calcium and vitamin D used (see Appendix 10, *Table 153*).

As reported, one study[137] appeared to have potential for bias in relation to randomisation and blinding; the methodological quality of the other study[138] appeared to be high, with very limited potential for the introduction of bias (see Appendix 10, *Table 155*).

The MORE study was extended for a fourth year to assess further multiple outcomes including fractures and outcomes relating to breast cancer, cardiovascular disease and uterine safety. In this fourth year, participants were allowed to take other

TABLE 29 *Raloxifene in postmenopausal osteoporosis: vertebral fracture data*

Study	Raloxifene dose	Fracture definition	No. of women in each group suffering vertebral fracture
Lufkin, 1998[137]	60 and 120 mg	15%	Raloxifene 60 mg: 21/43 Raloxifene 120 mg: 20/45 Placebo: 18/45 RR, 60 mg vs placebo, 1.22 (95% CI 0.76 to 1.96) RR, 120 mg vs placebo, 0.71 (95% CI 0.48 to 1.06)
MORE study[138]	60 and 120 mg	20%	Raloxifene 60 mg: 148/2259 Raloxifene 120 mg: 124/2277 Placebo: 231/2292 RR, 60 mg vs placebo, 0.65 (95% CI 0.53 to 0.79) RR, 120 mg vs placebo, 0.54 (95% CI 0.44 to 0.67)

bone-active agents in addition to the study medication. As a higher proportion of women in the placebo than in the treatment groups reported the use of such agents,[139] the 4-year fracture data have not been used in this review.

Assessment of effectiveness: raloxifene in postmenopausal osteoporosis or osteopenia

Both of the identified studies used raloxifene at a dose of 60 mg per day (the dose currently licensed in the UK for the treatment of postmenopausal osteoporosis) and also at 120 mg per day.

Vertebral fracture

Both studies presented separate vertebral fracture data relating to the 60- and 120-mg dose (*Table 29*).

The smaller of the two studies[137] did not produce statistically significant results relating to vertebral fracture using a 15% fracture definition (*Table 29*). The authors therefore reanalysed their results using a fracture definition of at least 30%; they then found a dose-dependent reduction, with a relative risk of fracture of 0.64 (95% CI 0.30 to 1.40) in the 60-mg group and 0.31 (95% CI 0.11 to 0.87) in the 120-mg group. The larger MORE study[138] found raloxifene to have a protective effect against vertebral fracture in women with osteoporosis with or without fracture.

Because the two studies used different fracture definitions, it did not seem appropriate to combine their results by meta-analysis. Instead, it seemed more appropriate to utilise the results from the MORE study, as this was a larger, better quality. This study found the relative risk of incident vertebral fracture in women with severe osteoporosis or osteoporosis at 3 years, compared with placebo, to be 0.65 (95% CI 0.53 to 0.79) in women receiving a 60-mg daily dose of raloxifene, and 0.54 (95% CI 0.44 to 0.67) in those receiving a 120-mg dose.

Subjects in the MORE study were divided into two study groups: women with a *T*-score below –2.5 but no vertebral fracture, and women who either had low BMD with either one or more moderate or severe or two or more mild vertebral fractures, or had at least two moderate fractures regardless of BMD. Each group was then randomised to receive either placebo or one of two doses of raloxifene.[138] Separate analysis of data relating to the two groups indicates a relative risk of vertebral fracture of 0.53 (95% CI 0.35 to 0.79) in women with osteoporosis without fracture who received 60 mg and of 0.62 (95% CI 0.43 to 0.91) in women who received 120 mg. In women with severe osteoporosis, the relative risk of vertebral fracture was 0.69 (95% CI 0.56 to 0.86) in women receiving 60 mg and 0.51 (95% CI 0.40 to 0.65) in women receiving 120 mg.

Data from the MORE study indicated that raloxifene reduced the risk of vertebral fracture similarly in smokers and non-smokers.[140]

The company submission for raloxifene contains subgroup analysis relating to participants without vertebral fractures at study entry. This claims that pooled data relating to the two doses of raloxifene from the MORE study show a similar reduction in relative risk of new vertebral fracture at 3 years in such women whether they had osteoporosis (RR versus placebo 0.31, 95% CI 0.06 to 0.71) or osteopenia (RR versus placebo 0.53, 95% CI 0.32 to 0.88) at study entry; the numbers of women in each group suffering such fractures were not specified.[39] However, as reported,[138] the entry criteria for the MORE study would appear to

TABLE 30 *Raloxifene in postmenopausal osteoporosis: non-vertebral fracture data*

Study	Raloxifene dose	No. of women in each group suffering non-vertebral fracture
Lufkin, 1998[137]	60 and 120 mg	The authors only provided the numbers of non-vertebral fractures in each group, not the number of women suffering such fractures; they stated that there was no significant difference between the groups in terms of non-vertebral fracture
MORE study[138]	60 and 120 mg	Data at 36 months: Pooled raloxifene groups: 437/4536 Placebo: 240/2292 RR 0.92 (95% CI 0.79 to 1.07)

TABLE 31 *Raloxifene in postmenopausal osteoporosis: hip fracture data*

Study	Raloxifene dose	No. of women in each group suffering hip fracture
Lufkin, 1998[137]	60 and 120 mg	Raloxifene 60 mg: 0/48 Raloxifene 120 mg: 1/47 Placebo: 0/48 RR, 120mg vs placebo, 3.06 (95% CI 0.13 to 73.34)
MORE study[138]	60 and 120 mg	Data at 36 months: Pooled raloxifene groups: 40/4536 Placebo: 18/2292 RR 1.12 (95% CI 0.65 to 1.95)

TABLE 32 *Raloxifene in postmenopausal osteoporosis: wrist fracture data*

Study	Raloxifene dose	No. of women in each group suffering non-vertebral fracture
MORE study[138]	60 and 120 mg	Data at 36 months: Pooled raloxifene groups: 151/4536 Placebo: 86/2292 RR 0.89 (95% CI 0.68 to 1.15)

exclude women without vertebral fracture who would be defined by their BMD as having osteopenia rather than osteoporosis.

Non-vertebral, hip or wrist fracture

One study[137] only presented usable data on hip fracture; additional data could not be obtained. The other study[138] only presented pooled non-vertebral fracture data from both raloxifene groups.

Neither study demonstrated that raloxifene produced a significant reduction in the risk of non-vertebral, hip or wrist fracture (*Tables 30–32*). However, women were required to discontinue participation in the MORE study if their BMD had decreased by at least 7% in the lumbar spine or 10% in the femoral neck at one year, or by at least 11% and 14%, respectively, at 2 years, or if at any time during the study they had experienced more than two incident vertebral fractures. As more women left the placebo group than the intervention groups for this reason, this may have decreased the study's ability to detect a statistically significant result in relation to non-vertebral fractures.[138] Nonetheless, the size of the study was such that its failure to demonstrate that raloxifene has a significant effect on the risk of non-vertebral fracture suggests that it in fact has no such effect.

Quantity and quality of research available: raloxifene in postmenopausal women with normal to low BMD

No RCTs were identified from the literature search that studied the use of raloxifene in postmenopausal women with normal to low BMD

TABLE 33 *Relative risk of fracture: raloxifene 60 mg versus placebo*

Group	Vertebral fracture	All non-vertebral fracture	Hip/pelvis fracture	Wrist fracture	Other non-vertebral fracture
Women with severe osteoporosis	0.69 (0.56 to 0.86)[a]	No data	No data	No data	No data
Women with severe osteoporosis or osteoporosis	0.65 (0.53 to 0.79)[a]	0.92 (0.79 to 1.07)[a c]	1.12 (0.65 to 1.95)[a c]	0.89 (0.68 to 1.15)[a c]	No data
Women with severe osteoporosis, osteoporosis or osteopenia	No data	No data	No data	No data	No data
Women with osteoporosis	0.53 (0.35 to 0.79)[a]	No data	No data	No data	No data
Women with osteopenia	0.53 (0.32 to 0.88)[b c]	No data	No data	No data	No data

Data are shown as RR (95% CI).
[a] Based on data from the MORE study.[138]
[b] Figures from pharmaceutical company submission.
[c] Pooled data from groups receiving 60- and 120-mg doses.

and that published fracture data. However, the company submission[39] indicated that three studies had been undertaken in younger postmenopausal women with normal to low BMD. Two of these studies (studies GGGF and GGGG) were undertaken in non-hysterectomised women, and the third (study GGGH) in hysterectomised women (for details see Appendix 10, *Tables 156–158*). Interim data from study GGGF have been published,[56] as have pooled data from studies GGGF and GGGG;[63] neither paper published fracture data. Study GGGH remains unpublished. These studies all used doses of 60 and 150 mg per day; two (GGGF and GGGG) also used a 30-mg dose. One study (GGGH) also included an oestrogen arm.

Two additional RCTs[47,92] were identified that reported data relating to the impact of raloxifene on quality of life in healthy postmenopausal women without menopausal symptoms that required therapy. One of these studies[92] compared raloxifene both with oestrogen and with placebo, and the other[47] with continuous combined HRT (for details, see Appendix 10, *Tables 156–158*). Both studies measured quality of life using the Women's Health Questionnaire.

Although the quality of the studies reviewed in this section was generally good (see Appendix 10, *Table 158*), the available evidence did not demonstrate that randomisation was undertaken in such a way as to prevent bias.

Assessment of effectiveness: raloxifene in postmenopausal women with normal to low BMD
Vertebral fracture
Fractures were a secondary end-point of all three prevention studies. [*Commercial-in-confidence information removed*.]

Non-vertebral fracture
No non-vertebral fracture data were reported from any study.

Quality of life
In one quality of life study,[92] the only significant changes in quality of life associated with raloxifene were deterioration in menstrual symptom scores in the 150-mg group ($p < 0.05$) and improvement in mean anxiety/fears scores in the 60-mg group. The other study that reported quality of life outcomes[47] found that women taking raloxifene reported a significant improvement in sleep problems from baseline. Statistically significant between-group differences in relation to depressed mood and menstrual symptoms favoured raloxifene, whereas those relating to memory/concentration, vasomotor symptoms and sexual behaviour favoured HRT. Significantly fewer women taking raloxifene said that their treatment worried them (10% versus 20% taking HRT, $p < 0.01$); this may reflect the increased occurrence of adverse events (specifically breast pain and vaginal bleeding) in the HRT group. Women taking raloxifene reported significantly greater treatment satisfaction than those taking HRT ($p = 0.004$).

Raloxifene in postmenopausal osteoporosis or osteopenia, and in postmenopausal women with normal to low BMD: summary

The best available evidence suggests that, at the licensed dose of 60 mg per day, raloxifene reduces the risk of vertebral fracture both in women with severe osteoporosis and in women with osteoporosis without fracture (*Table 33*). Figures included in the company submission suggest that it also reduces the risk of fracture in women with osteopenia although, as indicated above, such women do not seem to meet the study inclusion criteria. However, there is no evidence that raloxifene reduces the risk of vertebral fracture in early postmenopausal women with normal or low BMD or of non-vertebral fractures in any women.

Raloxifene: associated effects

Raloxifene has a number of potential consequences derived from its oestrogen agonist and antagonist effects. Some of these associated effects are adverse, and some potentially beneficial. The most serious adverse effect is the risk of venous thromboembolism, which is increased approximately three-fold.[138,141] This level of risk was seen in the MORE study (see Appendix 10, *Table 159*).

Pooled data from studies GGGF and GGGG indicated that a significantly higher proportion of women receiving 60 mg raloxifene suffered hot flushes compared with those receiving placebo (25% versus 18%, $p = 0.04$).[63] However, these hot flushes were generally mild, and did not cause women to withdraw from the trials. These figures are comparable with those obtained by meta-analysis of data from five placebo-controlled studies; this also found a significantly higher incidence of hot flushes in women treated with raloxifene than in those receiving placebo (24.6% versus 18.3%, $p < 0.05$).[142]

In another study reviewed here,[137] arthralgia and dizziness were significantly more common in women treated with raloxifene than in those treated with placebo, although these were not found in the larger MORE study (see Appendix 10, *Table 159*). Leg cramps have also been found to be significantly more common in women receiving raloxifene (5.5% versus 1.9%, $p < 0.05$),[142] as have an influenza-like syndrome, endometrial cavity fluid, peripheral oedema and worsening of diabetes.[143]

Data from the MORE study indicate that raloxifene may offer protection against breast cancer, at least in the short term: at 4 years, the relative risk of all types of breast cancer was 0.38 (95% CI 0.24 to 0.58) in the raloxifene group compared with placebo, and the relative risk of invasive breast cancer was 0.28 (95% CI 0.17 to 0.46).[143]

The impact of raloxifene on cardiovascular disease is not clear: it lowers fibrinogen levels[144] and total and low-density lipoprotein cholesterol[56,137,144,145] without reducing high-density lipoprotein cholesterol,[56,144] but there are as yet no available data to suggest that it reduces cardiovascular events.[146]

Raloxifene is not significantly different to placebo in terms of the incidence of vaginal bleeding or of changes in endometrial thickness.[142]

Raloxifene: continuance and compliance

In the studies reviewed in this section, the percentage of subjects receiving 60 mg raloxifene who completed the protocol ranged from over 90% in a 1-year study[137] to 78% at 3 years.[138]

In the MORE study, 92% of subjects were said to take more than 80% of the study medication; there was no difference between groups in compliance.[138] Another study found that 95% of women on raloxifene reported that they were taking their double-blinded medication regularly, compared with 86% of those on HRT ($p < 0.01$); however, pill counts did not indicate a significant difference between the groups in this respect.[47] In the USA, a retrospective search of a pharmacy prescription database[147] found that 56% of women who were members of the Kaiser Foundation Health Plan, a large health maintenancy organisation, who had been prescribed raloxifene, had discontinued treatment by 24 months.

Teriparatide [recombinant human parathyroid hormone (1–34)]

Quantity and quality of research available: teriparatide in postmenopausal osteoporosis or osteopenia

Three RCTs[94,148–151] were identified that compared teriparatide with another of the interventions or comparators reviewed in this report in women with postmenopausal osteoporosis or osteopenia, and that reported fracture outcomes (for details, see Appendix 10, *Tables 160* and *161*). A fourth study,[152] which compared teriparatide plus HRT with HRT alone, was excluded because it was not truly randomised. It had originally been intended to recruit 40 women to this trial but, after 11 women had been recruited and randomised, the new owners of the

TABLE 34 *Teriparatide in postmenopausal osteoporosis or osteopenia: vertebral fracture data*

Study	Teriparatide dose	Fracture definition	No. of women in each group suffering vertebral fracture
Cosman, 2001[148]	25 μg (400 IU) per day	15% and 20%	Using the 20% definition, no vertebral fractures occurred in the teriparatide/HRT group, compared with seven in the HRT-only group ($p < 0.02$). The number of women in the HRT-only group who suffered such fractures was not stated
Neer, 2001[151]	20 or 40 μg per day	20%	Teriparatide 20 μg: 22/444 Teriparatide 40 μg: 19/434 Placebo: 64/448 RR, 20 μg vs placebo, 0.35 (95% CI 0.22 to 0.55) RR, 40 μg vs placebo, 0.31 (95% CI 0.19 to 0.50)

company that supplied the teriparatide would only supply it to those women who had already been randomised at that time. A further eight women had at that point consented to participate: five refused randomisation and the remaining three who consented to randomisation could not be offered teriparatide because of the company's withdrawal; they therefore agreed to take part in the control arm of the trial. As a result, the trial cannot be described as truly randomised.

No studies were identified that reported the impact of teriparatide on quality of life. A study,[150] available only in abstract form, which assessed the impact of incident vertebral and non-vertebral fractures on quality of life in a subset of participants in a larger, unspecified, RCT was not relevant in this context.

Only one of the identified studies[94] compared teriparatide with another active intervention: this compared a dose of 40 μg per day (twice the US licensed dose) with a 10 mg per day dose of alendronate in women with osteoporosis. The choice of teriparatide dose pre-dated the conclusion of the large fracture prevention trial[151] whose findings in relation to the balance of skeletal benefits and adverse events determined the US licensed dose. This study only provided data on non-vertebral fracture. Of the remaining studies, both compared teriparatide with placebo, one in women with severe osteoporosis,[151] and the other in women with severe osteoporosis or osteoporosis who had been on HRT for at least 2 years.[148]

In one study, subjects were given a multivitamin including 400 IU per day vitamin D, and nutritional advice to maintain total calcium intakes of 1500 mg per day.[148] In another, all subjects were given 1000 mg calcium and 400–1200 IU vitamin D per day.[151] The third study, which was only available in abstract form, did not comment on subjects' calcium and vitamin D intakes.

The reported quality of the identified studies was fair (see Appendix 10, *Table 162*), although in two studies[94,151] it was not clear that randomisation was not open to bias.

Assessment of effectiveness of teriparatide in postmenopausal osteoporosis or osteopenia

Comparisons with active treatment

The study that compared women taking 40 μg per day teriparatide (twice the US licensed dose) with those taking 10 mg per day alendronate did not report vertebral fracture data. However, back pain was reported significantly less frequently by women in the teriparatide group (6%) than by those in the alendronate group (19%, $p = 0.012$). Mean height did not change from baseline in either group.[94]

This study found no significant difference in terms of non-vertebral fracture between women taking teriparatide and those taking alendronate (relative risk of fracture 0.30, 95% CI 0.09 to 1.05).[94]

Comparisons with placebo

Vertebral fracture

Only one of the placebo-controlled studies provided data on the number of women in each group who suffered incident vertebral fractures (*Table 34*). In this study,[151] the relative risk of such fracture, in women receiving the US licensed dose of teriparatide (20 μg per day) compared with placebo, was 0.35 (95% CI 0.22 to 0.55); the relative risk in women receiving 40 μg per day was 0.31 (95% CI 0.19 to 0.50). In the other study,[148] significantly fewer vertebral fractures occurred in

TABLE 35 *Teriparatide in postmenopausal osteoporosis or osteopenia: non-vertebral fracture data*

Study	Teriparatide dose	No. of women in each group suffering non-vertebral fracture
Neer, 2001[151]	20 or 40 μg per day	Teriparatide 20 μg: 34/541 Teriparatide 40 μg: 32/552 Placebo: 53/544 RR, 20 μg vs placebo, 0.65 (95% CI 0.43 to 0.98) RR, 40 μg vs placebo, 0.60 (95% CI 0.39 to 0.91)

TABLE 36 *Relative risk of fracture: teriparatide 20 μg per day versus placebo*

Group	Vertebral fracture	All non-vertebral fracture	Hip fracture	Wrist fracture	Humerus fracture
Women with severe osteoporosis	0.35 (0.22 to 0.55)[a]	0.65 (0.43 to 0.98)[a]	0.50 (0.09 to 2.73)[a]	0.54 (0.22 to 1.35)[a]	0.80 (0.22 to 2.98)[a]
Women with osteoporosis or osteopenia	No data	No data	No data	No data	No data

Data are shown as RR (95% CI).
[a] Based on data from Neer *et al*. (2001).[151]

the teriparatide group than in the placebo group; however, the number of women suffering such fractures was not stated.

Non-vertebral fracture

Only one placebo-controlled study reported non-vertebral fracture data[151] (*Table 35*): it found that the risk of non-vertebral fracture was significantly reduced in women receiving teriparatide, at either 20 or 40 μg per day, compared with placebo (*Table 35*). However, it was not large enough to demonstrate a significant reduction in fracture of the hip (RR 0.50, 95% CI 0.09 to 2.73), wrist (RR 0.54, 95% CI 0.22 to 1.35) or humerus (RR 0.80, 95% CI 0.22 to 2.98) in women receiving a 20-μg daily dose of teriparatide.

Quantity and quality of research available: teriparatide in postmenopausal women not selected for low BMD

No studies were identified that used teriparatide in postmenopausal women not selected for low BMD.

Teriparatide in postmenopausal osteoporosis: summary

The available evidence indicates that teriparatide reduces the risk of vertebral and non-vertebral fracture relative to placebo in women with severe osteoporosis (*Table 36*). However, it has not been demonstrated by direct comparison to be superior to alendronate in this respect, nor has its efficacy been demonstrated in women with osteoporosis without fracture or osteopenia.

Teriparatide: side-effects

The studies reviewed in this report mention a number of side-effects that appear to be associated with teriparatide. In one study,[151] women in the treatment group were significantly more likely than those in the placebo group to report nausea and headache; however, another study[148] specified that there were no reports of nausea. One study[151] reported that a large proportion of subjects had mild discomfort at the injection sites (for details, see Appendix 10, *Table 163*).

A systematic review of PTH for the treatment of osteoporosis suggests that it was associated with hypercalcaemia in a small proportion of patients. This occurred early in treatment, and may have been dose dependent. There was no published evidence that PTH use increased the risk of cancer.[153]

Teriparatide: continuance and compliance

Two studies[94,148] stated how many women in the treatment arm completed the protocol. In a study in which treatment lasted a median of 14 months,[94] 70% of women receiving 40 μg per day teriparatide completed the protocol compared with 78% of those receiving 10 mg per day alendronate. In a 3-year study, 78% of those receiving 25 μg per day teriparatide completed

the protocol, compared with 100% of the placebo arm.[148]

Two studies[94,151] commented on compliance with the teriparatide regimen. One[94] stated that median compliance with treatment, assessed by pill counts of oral medication and measurement of volume of injectable medication returned at each study visit, was 67% in women receiving teriparatide group compared with 71% in those receiving alendronate. In the other study,[148] average compliance with injections was assessed, on the basis of medications returned at each yearly visit, to range between 79 and 83%; the rates did not differ significantly between the two teriparatide groups and the placebo group.

Description of comparator treatments

Calcium

Calcium supplements are usually only required where dietary calcium intake is deficient. The UK Reference Nutrient Intake (RNI) for calcium, in people aged 19 and over, is 700 mg per day; in 1998, the Department of Health felt that the evidence was insufficient to recommend a higher intake for older women.[1] However, older people may require a higher calcium intake because of impaired absorption.

A calcium intake double the RNI has been recommended in patients with osteoporosis and, if the actual dietary intake is less than the RNI, it has been suggested that a daily supplement of as much as 40 mmol (approximately 1.6 g) is appropriate.[41]

Many formulations containing calcium are available.

Vitamin D

The term 'vitamin D' is broadly applied to a range of compounds, including ergocalciferol (calciferol, vitamin D_2) and cholecalciferol (vitamin D_3), as well as the vitamin D derivatives dihydrotachysterol, alfacalcidol (1-hydroxycholecalciferol) and calcitriol (1,25-dihydroxycholecalciferol). Only vitamin D_2 and vitamin D_3 are discussed in this section; vitamin D derivatives will be discussed in the section on calcitriol, below.

Vitamin D has a direct effect on bone strength by aiding the absorption of calcium and promoting bone mineralisation. It also appears to have an independent effect on the risk of osteoporotic fracture by reducing postural sway. Thus, recent research has shown that, in postmenopausal women with osteoporosis, vitamin D deficiency is associated with increased body sway and an elevated risk of falls and related fractures.[154]

Vitamin D deficiency is not uncommon in elderly people living alone. It can be prevented by taking a daily oral supplement of 20 μg (800 units) of vitamin D_2 (double the RNI for people aged 65 years and over). No plain tablet of this strength is available, but calcium and vitamin D_2 tablets can be given, even if the calcium is unnecessary.[41]

Vitamin D_2 is contraindicated in patients with:

- hypercalcaemia
- metastatic calcification.[41]

Calcitriol

Calcitriol [1,25-dihydroxycholecalciferol; $1,25(OH)_2D_3$] is the most physiologically active metabolite of vitamin D,[155] and the only one that is licensed in the UK for the treatment of postmenopausal osteoporosis. The licensed dose for severe osteoporosis is 250 ng (0.25 μg) twice daily.[41]

Calcitriol is contraindicated in patients with:

- hypercalcaemia
- metastatic calcification.[41]

Plasma calcium and creatinine should be monitored in women taking calcitriol.[41]

Calcitriol has a shorter duration of action than vitamins D_2 and D_3, and therefore problems associated with hypercalcaemia due to excessive dosage are shorter lasting and easier to treat.[41]

Calcitriol is marketed by Roche as Rocaltrol®. Rocaltrol is available in 250- and 500-ng capsules, at a net price, for 20 capsules, of £4.12 and £7.36, respectively.[41]

HRT

The term HRT refers to the use of female sex steroid hormones (oestrogen with or without progestogen) in perimenopausal and postmenopausal women for non-contraceptive purposes. As the main purpose of HRT is oestrogen supplementation, women without a uterus may be given unopposed oestrogen. However, to reduce the risk of cancer of the endometrium, women with an intact uterus should also be given progestogen. In women who have

suffered from endometriosis, endometrial foci may remain despite hysterectomy, and the addition of a progestogen is therefore also recommended for these women.[41] Progestogen may be given either sequentially (for the last 10–14 days of each 28-day oestrogen treatment cycle) or continuously alongside oestrogen (usually combined in one preparation).[41]

HRT is licensed for the prophylaxis of postmenopausal osteoporosis. For this purpose, small doses of oestrogen may be given for several years starting in the perimenopausal period. They are usually given orally or transdermally, although subdermal administration is also possible. In particular, it is currently recommended that women who undergo natural or surgical menopause before the age of 45 years should be given HRT for 5–10 years. It is currently felt that, in menopausal women with a uterus, the risks of taking HRT for longer than 5 years may outweigh the benefits, but long-term HRT may be considered if several risk factors for osteoporosis are present.[41]

HRT is contraindicated in:

- pregnant or breast-feeding women
- women with oestrogen-dependent cancer
- women with active thrombophlebitis, thromboembolic disorders or a history of recurrent venous thromboembolism (unless already on anticoagulant treatment)
- women with liver disease
- women with Dubin–Johnson and Rotor syndromes
- women with undiagnosed vaginal bleeding.[41]

In women with predisposing factors to DVT and pulmonary embolism (such as a personal or family history of DVT or pulmonary embolism, severe varicose veins, obesity, surgery, trauma or prolonged bed rest), the need for HRT should be reviewed as in some cases the risks of treatment may exceed the benefits. Travel may also increase the risk of DVT.[41]

Several HRT preparations are available. The 'natural' oestrogens include CEEs and the plant derivatives estradiol, estrone and estriol; the latter are identical in structure to human oestrogens[156] and are considered to have a more appropriate profile for HRT than synthetic oestrogens (ethinyloestradiol and mestranol).[41] In the USA, CEEs are most commonly used; the dose is 0.625–1.25 mg per day. In the UK, oestradiol is most frequently used; the oral dose is 1–2 mg per day and the transdermal dose 50 μg per day.[41] Transdermal oestrogen is less likely to cause headache and nausea than oral oestrogen.[157]

More than 95% of women who take sequential HRT will have monthly withdrawal bleeding, while more than 75% of women who receive continuous combined preparations will have some bleeding during the first year, and approximately 10–15% will continue to have some bleeding after 12 months. Endometrial biopsy is recommended in women on cyclic progestin whose bleeding begins before day 6 of the cycle or is unusually heavy and prolonged, and in women on continuous therapy whose bleeding continues for more than 6 months. As a result, more than 10% of women receiving HRT may require endometrial biopsy each year. As women who have recently experienced menopause are at higher risk of excessive, unpredictable bleeding while receiving continuous therapy,[157] continuous preparations are not recommended for use in the perimenopause or within 12 months of the last menstrual period.[41]

Results: comparator treatments

For each of the relevant interventions, the studies that compare the intervention with other active interventions are discussed before those that compare the intervention with placebo. Studies in which both the intervention and control groups receive other interventions (calcium, vitamin D or HRT) in comparable doses are treated as comparisons with placebo/no treatment.

Calcium

Quantity and quality of research available: calcium in postmenopausal osteoporosis or osteopenia

Four RCTs[61,158–160] were identified that met the inclusion criteria and that compared the effects of calcium, with or without vitamin D, with those of another intervention or comparator reviewed in this report, and that reported fracture outcomes. Only one of these studies was a comparison with active treatment (calcitriol).[160] The remainder[61,158,159] were comparisons with placebo or no treatment. All four studies used doses of 1–1.2 g per day of calcium, comparable with the licensed dose of 1–1.5 g per day (for details of study design, see Appendix 10, *Tables 164* and *165*). No study was found that reported quality of life outcomes in women with postmenopausal osteoporosis or osteopenia who were taking calcium.

TABLE 37 *Calcium in postmenopausal osteoporosis or osteopenia: vertebral fracture data*

Study	Calcium dose	Fracture definition	No. of women in each group suffering vertebral fracture
Hansson, 1987[61]	1 g per day	Not given	One vertebral fracture occurred in the calcium group and one in the control group; the relative risk of fracture cannot be calculated as the denominators are not clear
Orimo, 1987[158]	1 g per day	20%	There were 108 new vertebral fractures in the calcium group and 79 in the control group. No data were available relating to the number of women suffering these fractures
Recker, 1996[159]	1.2 g per day	20%	Calcium: 15/53 Placebo: 21/41 RR 0.55 (95% CI 0.33 to 0.93)
Tilyard, 1992[160]	1 g per day	15%	Year 1: Calcium: 17/253 Calcitriol: 14/262 RR 1.26 (95% CI 0.63 to 2.50) Year 2: Calcium: 30/240 Calcitriol: 14/236 RR 2.11 (95% CI 1.15 to 3.87) Year 3: Calcium: 44/219 Calcitriol: 12/213 RR 3.57 (95% CI 1.94 to 6.56)

All four studies reported results relating to women with severe osteoporosis. One study,[159] which reported the spine antifracture efficacy of calcium in elderly women with low self-chosen calcium intakes, with and without pre-existing vertebral fractures, did not select participants on the basis of low BMD. However, this study was designed to evaluate vertebral fracture in two groups: women with, and those without, prevalent vertebral fractures on entry. For logistical reasons, it was necessary to randomise subjects to treatment without reference to their prevalent fracture status, but when they were broken down into fracture and non-fracture groups for analysis the subgroups were found to be similar in age and customary calcium intake. The results relating to women with prevalent fractures are therefore reported here, and those relating to women without prevalent fractures are reported in a later section.

As reported, the methodological quality of most of these studies was not high (see Appendix 10, *Table 166*). In particular, most failed to demonstrate that the method of randomisation did not allow bias. One study[61] also failed to give sufficient information regarding the baseline comparability of the treatment group, while in another[158] the efficacy of calcium may have been underestimated because of the significant difference between the calcium and control groups in terms of number of baseline fractures.

Assessment of effectiveness of calcium in postmenopausal osteoporosis or osteopenia

Comparison with active treatment

In the second and third years of the study that compared 1 g per day calcium with 0.25 μg per day calcitriol,[160] a significantly greater number of women in the calcium group suffered incident vertebral fractures when compared with the calcitriol group. However, this effect was evident only after 2 years of treatment (*Table 37*), and the total 3-year figures are not presented. Moreover, subgroup analysis indicated that no significant treatment effect was seen in women with six or more vertebral fractures at baseline,[160] or in those aged 64 years or younger.[161]

Over the 3-year period, 11 women in the calcitriol group suffered non-vertebral fractures, compared with 22 in the calcium group (RR 0.49, 95% CI 0.24 to 0.99).[160]

Comparisons with placebo or no treatment

Vertebral fracture

These studies are diverse in their findings. In one

TABLE 38 *Calcium in postmenopausal women not selected for low BMD: comparisons with active treatment*

Study	Comparator	Type of fracture	No. of subjects suffering fracture		RR of fracture (95% CI): calcium vs comparator
			Calcium	Comparator	
Komulainen, 1998[162]	Calcium + vitamin D_3	Non-vertebral	15/116	11/116	1.36 (0.65 to 2.84)
		Hip	2/116	1/116	2.00 (0.18 to 21.75)
Komulainen, 1998[162]	HRT	Non-vertebral	15/116	6/116	2.50 (1.01 to 6.22)
		Hip	2/116	0/116	5.00 (0.24 to 103.03)
Komulainen, 1998[162]	HRT, calcium, vitamin D_3	Non-vertebral	15/116	7/116	2.14 (0.91 to 5.06)
		Hip	2/116	0/116	5.00 (0.24 to 103.03)

small study,[61] the number of vertebral fractures was the same in the calcium and untreated groups. A second study found more incident fractures in the calcium group than in the control group, but did not indicate how many women suffered such fractures;[158] without this information, the relative risk of fracture cannot be calculated and it is impossible to exclude the possibility that, although there were more fractures in the calcium group, a smaller proportion of women in that group may have suffered such fractures than in the control group. In addition, in this study, as noted above, disparity between the groups at baseline may have disadvantaged the calcium group. The third study[159] found that calcium reduced the risk of incident vertebral fracture in women with low self-chosen calcium intakes (RR versus placebo 0.55, 95% CI 0.33 to 0.93) (*Table 37*).

Non-vertebral fracture

None of the non-comparative studies provided data relating to non-vertebral fracture.

Quantity and quality of research available: calcium in postmenopausal women not selected for low BMD

Four RCTs[73,74,159,162] were identified that studied the use of calcium in postmenopausal women with normal or unspecified BMD, and that provided fracture data. One of these studies was carried out in non-osteoporotic early postmenopausal women,[162] and another in healthy postmenopausal women with normal BMD and no prevalent fractures.[74] Another study[159] has been mentioned earlier: it reported the spine antifracture efficacy of calcium in elderly women with low self-chosen calcium intakes who were not selected on the basis of low BMD. The results relating to women without prevalent fractures at entry are reported in this section. The fourth study[73] was carried out in women without symptomatic vertebral fractures, who again were not selected on the basis of low BMD. Women were originally recruited for 2 years, but 86 of the 122 women who completed that original 2-year study agreed to continue in the study for a further 2 years, still blinded to their treatment allocation and BMD results.[163] Both the 2-year and the 4-year results are therefore reported here.

One study[162] compared calcium alone with calcium plus vitamin D_3, HRT, and HRT plus calcium and vitamin D_3. The remaining three studies were placebo controlled (for further details, see Appendix 10, *Tables 167* and *168*).

In terms of reporting quality, none of these studies provided evidence of adequate concealment of randomisation, and two failed to provide evidence of blinded outcome assessment (see Appendix 10, *Table 169*).

Assessment of effectiveness: calcium in postmenopausal women not selected for low BMD

Comparisons with active treatment

The study that compared calcium with other interventions[162] only provided data relating to non-vertebral fractures. Although the point estimates suggest that calcium alone was less effective in preventing non-vertebral fracture than any of the comparators, the study was underpowered in relation to fracture outcomes and, in all but one comparison (calcium versus HRT for the prevention of all non-vertebral fractures), the confidence intervals cross unity (*Table 38*).

TABLE 39 *Calcium in postmenopausal women not selected for low BMD: vertebral fracture data*

Study	Calcium dose	Fracture definition	No. of women in each group suffering vertebral fracture
Recker, 1996[159]	1.2 g per day	20%	Calcium: 12/42 Placebo: 13/61 RR 1.34 (95% CI 0.68 to 2.64)
Reid, 1993[73]	1 g per day	20%	4-year data (symptomatic fracture only): Calcium: 0/38 Placebo: 1/40 RR 0.35 (95% CI 0.01 to 8.35)
Riggs, 1998[74]	1.6 g per day	15%	There were eight incident vertebral fractures in the calcium group and nine in the placebo group. Data were not available relating to the number of women suffering these fractures

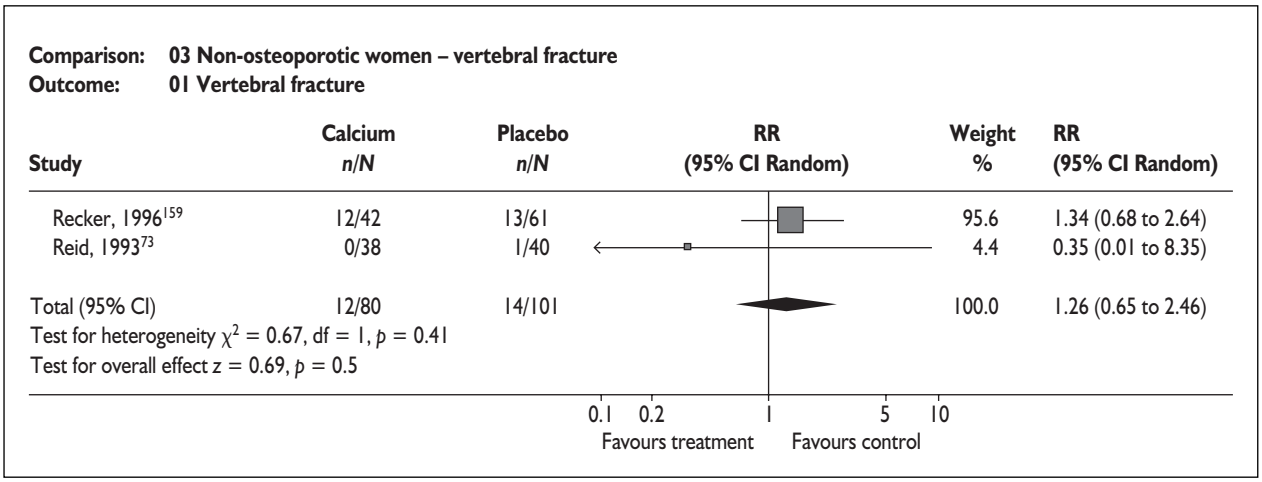

FIGURE 21 *Calcium: vertebral fracture in postmenopausal women not selected for low BMD*

Comparisons with placebo

Vertebral fracture

All three placebo-controlled studies provided vertebral fracture data (*Table 39*). None demonstrated that calcium reduced the risk of vertebral fracture relative to placebo. Meta-analysis of the data from the Recker[159] and Reid[73] studies did not demonstrate a statistically significant difference in the risk of vertebral fracture between women receiving calcium and those receiving placebo (RR 1.26, 95% CI 0.65 to 2.46) (*Figure 21*).

Non-vertebral fracture

Two of the placebo-controlled studies provided data on non-vertebral fracture. These data are also inconclusive (*Table 40*). Data from the Reid study[163] suggested that calcium might be protective against non-vertebral fracture, but the relative risk could not be calculated (*Table 40*). The other study[74] showed no difference in terms of non-vertebral fracture between the calcium and control groups.

Calcium in postmenopausal osteoporosis or osteopenia, and in postmenopausal women not selected for low BMD: summary

As may be seen, there is less evidence than might be desired relating to the efficacy of calcium alone either in women with postmenopausal osteoporosis or in those not selected for low BMD. Most of the studies are too small to demonstrate statistical significance relative to fracture outcomes. However, direct comparison suggests that calcium is less effective than calcitriol in reducing the risk of vertebral and non-vertebral fracture in women with severe osteoporosis.

The evidence suggests that calcium supplementation may be beneficial in women with low dietary calcium intakes, but has little effect in those with adequate or high dietary calcium

TABLE 40 *Calcium in postmenopausal women not selected for low BMD: non-vertebral fracture data*

Study	Calcium dose	No. of women in each group suffering non-vertebral fracture
Recker, 1996[159]	1.2 g per day	No data
Reid, 1993[73]	1 g per day	At 4 years, there were two symptomatic fractures in 2/38 subjects in the treatment group and nine symptomatic fractures (including one vertebral fracture) in 7/40 subjects in the placebo group. As it was not clear whether six or seven women in the placebo group suffered non-vertebral fracture, the RR could not be calculated
Riggs, 1998[74]	1.6 g per day	There were 11 incident non-vertebral fractures in the calcium group and 12 in the placebo group. Data on the number of women suffering these fractures were not available

TABLE 41 *Relative risk of fracture: calcium versus placebo*

Group	Vertebral fracture	All non-vertebral fracture	Hip fracture	Wrist fracture	Other non-vertebral fracture
Women with severe osteoporosis	0.55 (0.33 to 0.93)[a c]	No data	No data	No data	No data
Women with severe osteoporosis or osteoporosis	No data	No data	No data	No data	No data
Women with osteopenia	No data	No data	No data	No data	No data
Postmenopausal women with normal or low BMD	1.26 (0.65 to 2.46)[b c]	No data	No data	No data	No data

[a] Based on data from Recker *et al*. (1996, fracture arm).[159]
[b] Based on data from Recker *et al*. (1996, non-fracture arm)[159] and Reid *et al*. (1993).[73]
[c] May not apply to women with adequate dietary calcium intakes.

intakes. However, there is no evidence that calcium supplementation is beneficial even in those with low dietary calcium intakes, unless they are already severely osteoporotic (*Table 41*).

Calcium: side-effects

Calcium is in some cases associated with gastrointestinal problems. In two of the studies reviewed here,[74,159] the incidence of gastrointestinal problems (abdominal cramping, constipation, bloating and diarrhoea) was higher in the calcium group than in the control group. In a further two studies[73,160] which did not comment on the overall distribution of gastrointestinal problems in the study populations, some withdrawals from the calcium arm were attributed to gastrointestinal symptoms (for details, see *Appendix 10*, *Table 170*).

Calcium supplementation can cause hypercalcaemia and hypercalciuria, conditions that may lead to the deposition of excess calcium in the kidneys. The risk of symptomatic nephrolithiasis has been shown to increase slightly in women taking calcium supplements, although it decreases in women with a higher dietary calcium intake.[164] Although one subject withdrew from one of the studies reviewed here as a result of renal stones that were considered to be potentially related to calcium supplementation,[73] and one woman in another study suffered hypercalciuria;[74] in the latter study both hypercalciuria and renal stones were also observed in the placebo group.

Calcium: continuance and compliance

Few studies provided specific information relating to continuance in subjects receiving calcium. However, in one study[61] 88% of the calcium arm continued on treatment at 3 years, and in another[74] 74% remained on treatment at 4 years. One study[159] noted that, in women with low self-reported calcium intakes, median compliance with calcium supplementation, expressed as the percentage of pills prescribed that were not returned on a subsequent visit, was 64%.

TABLE 42 *Calcium plus vitamin D in postmenopausal women not selected for low BMD: comparisons with active treatment*

Study	Comparator	Type of fracture	No. of subjects suffering fracture		RR of fracture (95% CI): calcium + Vitamin D vs comparator
			Calcium + vitamin D_3	Comparator	
Komulainen, 1998[162]	Calcium	Non-vertebral	11/116	15/116	0.73 (0.35 to 1.53)
		Hip	1/116	2/116	0.50 (0.05 to 5.44)
Komulainen, 1998[162]	HRT	Non-vertebral	11/116	6/116	1.83 (0.70 to 4.79)
		Hip	1/116	0/116	3.00 (0.12 to 72.89)
Komulainen, 1998[162]	HRT, calcium, vitamin D_3	Non-vertebral	11/116	7/116	1.57 (0.63 to 3.91)
		Hip	1/116	0/116	3.00 (0.12 to 72.89)

Calcium plus vitamin D

Quantity and quality of research available: calcium plus vitamin D in women with postmenopausal osteoporosis or osteopenia

No RCTs were identified that compared calcium plus vitamin D with those of another intervention or comparator reviewed in this report in women with osteoporosis and osteopenia, and that reported fracture outcomes.

Quantity and quality of research available: calcium plus vitamin D in postmenopausal women not selected for low BMD

Four RCTs[51,162,165,166] were identified that compared calcium plus vitamin D_3 (cholecalciferol) with another intervention or comparator reviewed in this report in women who had not been selected for low BMD, and that reported fracture outcomes. Two of these studies[51,162] were carried out in healthy women in their forties, fifties and sixties, and the other two[165,166] in ambulatory elderly women living in nursing homes or apartment homes for the elderly. The mean age of the populations of the latter two studies was more than 20 years older than the mean age of the women who took part in the Baeksgaard study,[51] and more than 30 years older than the mean age of those who took part in the Komulainen study[162] (see Appendix 10, *Tables 171* and *172*).

One study[162] compared calcium plus vitamin D_3 with calcium alone, HRT, and HRT plus calcium and vitamin D_3. The remaining three studies were placebo controlled. In one study,[51] the two active treatment arms received calcium and vitamin D in equal quantities, but one also received a multivitamin supplement. In another study,[166] the two active treatment arms again received calcium and vitamin D in equal quantities, but one received it as a fixed formulation and the other as separate components.

As reported, the quality of all of the studies appeared to be poor: in particular, none provided evidence of appropriately masked randomisation or of blinded outcome assessment (for details, see Appendix 10, *Table 173*).

Assessment of effectiveness: calcium plus vitamin D in postmenopausal women not selected for low BMD

Comparisons with active treatment

In the study that compared calcium plus vitamin D with other active treatments, the point estimates suggest that calcium plus vitamin D_3 may be more effective than calcium alone in preventing non-vertebral fracture; however, the confidence intervals for this, and all other comparisons, cross unity (*Table 42*).

Comparisons with placebo or no treatment

Vertebral fracture

Only one study[51] provided data relating to vertebral fracture: in this study, two women, one in the calcium plus vitamin D_3 group and one in the calcium, vitamin D_3 plus multivitamin group, suffered radiologically verified vertebral fractures (RR of fracture, pooled calcium plus vitamin D_3 groups versus placebo, 2.39, 95% CI 0.12 to 49.07).

Non-vertebral fracture

Two of the placebo-controlled studies[165,166] provided data relating to non-vertebral fracture. These studies were both carried out in elderly women, and had incident hip fractures as their primary outcome measure. The larger of these two studies[165] found a statistically significant reduction

TABLE 43 *Calcium plus vitamin D in elderly postmenopausal women not selected for low BMD: non-vertebral fracture data*

Study	Calcium dose	Vitamin D dose	No. of women in each group suffering non-vertebral fracture
Chapuy, 1994[165]	1.2 g per day	800 IU per day	Calcium + vitamin D: 255/1176 Placebo: 308/1127 RR 0.79 (95% CI 0.69 to 0.92)
Chapuy, 2002[166]	1.2 g per day	800 IU per day	Provides information relating to hip fracture and non-hip non-vertebral fracture, but not relating to the total number of women suffering non-vertebral fracture

TABLE 44 *Calcium plus vitamin D in elderly postmenopausal women not selected for low BMD: hip fracture data*

Study	Calcium dose	Vitamin D dose	Number of women in each group suffering hip fracture
Chapuy, 1994[165]	1.2 g per day	800 IU per day	Calcium + vitamin D: 137/1176 Placebo: 178/1127 RR 0.74 (95% CI 0.60 to 0.91)
Chapuy, 2002[166]	1.2 g per day	800 IU per day	Calcium + vitamin D: 27/393 Placebo: 21/190 RR 0.62 (95% CI 0.36 to 1.07)

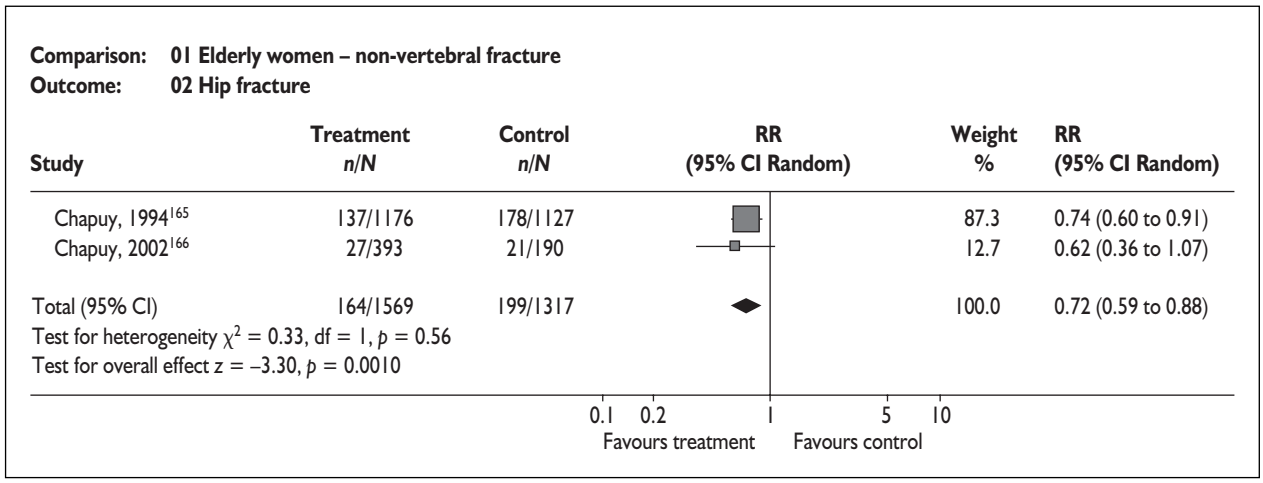

FIGURE 22 *Calcium plus vitamin D: hip fracture in elderly postmenopausal women not selected for low BMD*

in the risk of all non-vertebral fractures in women given calcium plus vitamin D_3 (*Table 43*).

Hip fracture

The same two studies[165,166] provided information relating to hip fracture. The larger of the two studies[165] found a statistically significant reduction in the risk of hip fracture in women given calcium plus vitamin D_3 (*Table 44*). Pooled data from the two studies indicate a relative risk of hip fracture of 0.72 (95% CI 0.59 to 0.88) in elderly women receiving calcium plus vitamin D_3 compared with those receiving placebo (*Figure 22*). However, in both studies, the subjects' baseline dietary calcium intake was said to be low (mean intake below 600 mg per day), and in one study[166] mean baseline dietary vitamin D_3 levels were also said to be very low (40.8 IU per day). Comparable results would therefore not necessarily be achieved in women with adequate dietary calcium and vitamin D_3 intakes.

Non-hip non-vertebral fracture

One study[166] indicated that comparable numbers of women in each group suffered non-hip, non-vertebral fractures. The data were expressed only

TABLE 45 *Relative risk of fracture: calcium plus vitamin D versus placebo*

Group	Vertebral fracture	All non-vertebral fracture	Hip fracture	Wrist fracture	Other non-vertebral fracture
Women with severe osteoporosis	No data	No data	No data	No data	No data
Women with severe osteoporosis or osteoporosis	No data	No data	No data	No data	No data
Women with osteopenia	No data	No data	No data	No data	No data
Women unselected for low BMD	2.95 (0.21 to 71.21)[a,d]	0.79 (0.69 to 0.92)[b,e]	0.72 (0.59 to 0.88)[c,e]	No data	No data

Data are shown as RR (95% CI).
[a] Based on data from Baeksgaard *et al*. (1998).[51]
[b] Based on data from Chapuy *et al*. (1994).[165]
[c] Based on data from Chapuy *et al*. (1994)[165] and Chapuy *et al*. (2002).[166]
[d] Probably symptomatic fracture only.
[e] May not apply to women with adequate dietary calcium and vitamin D_3 intakes.

as percentages of women in each group suffering such fractures: 17.8% of women in the pooled treatment groups and 17.9% of those in the placebo group experienced at least one such fracture.

Calcium plus vitamin D in postmenopausal osteoporosis or osteopenia, and in postmenopausal women not selected for low BMD: summary

No evidence was found relating to the antifracture efficacy of calcium plus vitamin D_3 in postmenopausal women known to have osteoporosis or osteopenia.

Calcium plus vitamin D_3 has not been demonstrated to protect against vertebral fracture in healthy women in their late fifties and sixties (*Table 45*). It has been shown to offer protection against non-vertebral and hip fracture in elderly women with low dietary calcium and vitamin D intakes many of whom would, because of their age, probably be suffering from osteoporosis or osteopenia, but there is no evidence that it is beneficial to women with adequate dietary calcium and vitamin D intakes.

Calcium plus vitamin D: side-effects

The potential toxicity of calcium alone has been discussed above. Excess consumption of vitamin D also leads to hypercalcaemia, which may in turn lead to kidney failure as the excess calcium is deposited in the blood vessels. However, there is no evidence of adverse effects with serum 25-hydroxyvitamin D concentrations as high as 140 nmol l^{-1}, which would require a total vitamin supply of 10,000 IU per day[167] (over 12 times the dose recommended for osteoporosis prevention). Although, in one of the studies reviewed here, three women receiving vitamin D_3 developed hypercalcaemia, this resulted in one case from recent myeloma, and in the other cases from hyperparathyroidism.[166] None of the studies suggested that the combined calcium/vitamin D_3 therapy was responsible for any adverse effects in the study participants (for details, see Appendix 10, *Table 174*).

Calcium plus vitamin D: continuance and compliance

Only two studies[165,166] specifically commented on continuance in women receiving calcium plus vitamin D_3. In one of these,[166] 73% of those who received a combined formulation and 71% of those who received the two components separately completed the 2-year study protocol. In this study, because of the age of the participants, most withdrawals were due to death. In the other study, which was carried out in a similarly elderly population, only 54% in the treatment and placebo arms completed 18 months of the 3-year study.[165]

Only one study[166] commented specifically on compliance with medication. This was high, with a mean compliance of more than 95% in each group, because, to ensure compliance, the study medication was taken in the presence of a nurse.

TABLE 46 *Calcitriol in postmenopausal osteoporosis or osteopenia: comparisons with active treatment*

Study	Comparator	Type of fracture	No. of subjects suffering fracture		RR of fracture (95% CI): Calcitriol vs comparator
			Calcitriol	Comparator	
Arthur, 1990[169]	Vitamin D_2	Vertebral	0/4	0/6	Not calculable
		Non-vertebral	0/4	0/4	Not calculable
Falch, 1987[170]	Vitamin D_3	Vertebral	10/32	6/30	1.56 (0.65 to 3.77)
		Non-vertebral	Not stated. There was said to be no significant difference between the two different treatment groups		Not calculable
Tilyard, 1992[160]	Calcium	Vertebral:			
		1st study year	14/262	17/253	0.80 (0.40 to 1.58)
		2nd study year	14/236	30/240	0.47 (0.26 to 0.87)
		3rd study year	12/213	44/219	0.28 (0.15 to 0.52)
					Combined data for the 3-year study period were not available
		Non-vertebral	11/314	22/308	0.49 (0.24 to 0.99)
Caniggia, 1984[53]	Oestradiol valerate	Vertebral	0/5	1/5	0.33 (0.02 to 6.65)
Caniggia, 1984[53]	Calcitriol + oestradiol valerate	Vertebral	0/5	1/7	0.44 (0.02 to 9.11)

Calcitriol

Quantity and quality of research available: calcitriol in postmenopausal osteoporosis or osteopenia

Although three vitamin D derivatives (alfacalcidol, calcitriol and dihydrotachysterol) have been studied in postmenopausal osteoporosis or osteopenia, only calcitriol [$1,25(OH)_2D_3$] is licensed for this purpose in the UK, and therefore only studies using this intervention will be reviewed here. The licensed dose for severe osteoporosis is 250 ng (0.25 μg) twice daily.

Eight RCTs[53,87,160,168–172] were identified that compared calcitriol with another intervention or comparator reviewed in this report, and that reported fracture outcomes. Four of these studies[53,160,169,170,172] compared calcitriol with another active intervention: vitamin D_2,[169] vitamin D_3,[170] calcium[160] and HRT[53] (for details see Appendix 10, *Table 175*). Five studies compared calcitriol with placebo[53,87,171,172] or no treatment.[168]

Seven studies were carried out in women with severe osteoporosis.[53,87,160,168,170–172] The remaining study[169] was carried out in women with osteopenia, osteoporosis or severe osteoporosis; 40% had vertebral compression fractures at study entry (see Appendix 10, *Table 176*).

The dose of calcitriol used in these studies ranged from 0.25 to 1 μg per day (for details, see Appendix 10, *Table 175*), comparable to the licensed dose of 0.5 μg per day in a divided dose.

With one exception,[160] all the studies were small or extremely small. Many failed to report adequately concealed randomisation, and some did not state that the outcome assessors were blinded to treatment allocation (for details, see Appendix 10, *Table 177*).

Assessment of effectiveness: calcitriol in postmenopausal osteoporosis or osteopenia

Comparisons with active interventions

Only one study that compared calcitriol with another active treatment[160] was large enough to yield statistically significant results. This study indicated that, after the first year of treatment, calcitriol was more effective than calcium in reducing the risk of vertebral fracture; it also appeared to reduce the risk of non-vertebral fracture (*Table 46*).

TABLE 47 *Calcitriol in severe postmenopausal osteoporosis: vertebral fracture data*

Study	Calcitriol dose	Fracture definition	No. of women in each group suffering vertebral fracture
Aloia, 1988[168]	0.5–2.0 μg per day taken in a divided dose twice a day (mean dose 0.8 μg per day)	Not stated	Calcitriol: 3/12 Placebo: 5/15 RR 0.75 (95% CI 0.22 to 2.52)
Caniggia, 1984[53]	0.5 μg per day	Not stated	Calcitriol: 0/5 Placebo: 2/5 RR 0.20 (95% CI 0.01 to 3.35)
Gallagher, 1989[87]	0.5–1.0 μg per day taken in a divided dose twice a day	15%	There were 15 fractures in the calcitriol group and 32 in the placebo group. Data on the number of women suffering fractures were not published and, as the original data are no longer available,[a] it was not possible to calculate the RR of fracture
Gallagher, 1990[171]	0.5–2.0 μg per day	15%	Calcitriol: 8 Placebo: 9 As the denominator was not clear, and the original data are no longer available,[a] it was not possible to calculate the RR of fracture
Ott, 1989[172]	0.5–2.0 μg per day (mean dose 0.53 μg per day)[b]	15%	Calcitriol: 9/35 Placebo: 6/37 RR 1.59 (95% CI 0.63 to 3.99)

[a] Gallagher GC (personal communication).
[b] Ott SM (personal communication).

Comparisons with placebo or no treatment

Vertebral fracture

Individually, none of the studies that compared calcitriol with placebo or no treatment demonstrated that it offered protection against vertebral fracture (*Table 47*). When the results of those studies that provided data in usable form were pooled, they yielded a relative risk of vertebral fracture of 1.02 (95% CI 0.44 to 2.32) in women receiving calcitriol compared with controls, again suggesting that calcitriol conferred no antifracture benefit in severe postmenopausal osteoporosis (*Figure 23*). However, it should be noted that all of the studies included in the meta-analysis were very small, so that even when pooled there were fewer than 60 subjects in each arm. Moreover, none of the relevant studies stated that they used a 20% fracture definition. The result therefore cannot be regarded as secure, especially when compared with evidence that calcitriol is more effective than calcium in reducing the risk of vertebral fracture.

Non-vertebral fracture

Only one study[172] presented data relating to non-vertebral fracture. This failed to demonstrate any benefit from calcitriol treatment: five out of 43 women in the calcitriol group and two out of 43 women in the placebo group suffered non-vertebral fracture, a relative risk of non-vertebral fracture of 2.50 (95% CI 0.51 to 12.19) in women receiving calcitriol compared with placebo.

Quantity and quality of research available: calcitriol in postmenopausal women not selected for low BMD

One RCT[58] was identified that studied calcitriol in elderly women with normal femoral neck BMD for their age (*Z*-scores +2.0 to –2.0), and that reported fracture outcomes. Calcitriol alone was compared with HRT alone, combination calcitriol and HRT therapy, and placebo (for details, see Appendix 10, *Tables 178–180*). At baseline, 28% of participants had a spinal *T*-score below –2.5, and a further 27% between –1.5 and –2.4; however, as not all participants had osteoporosis or osteopenia, this study is discussed here rather than in the two sections immediately above.

As reported, this study appeared to be of reasonable quality; however, it failed to provide evidence of adequately concealed randomisation (see Appendix 10, *Table 180*).

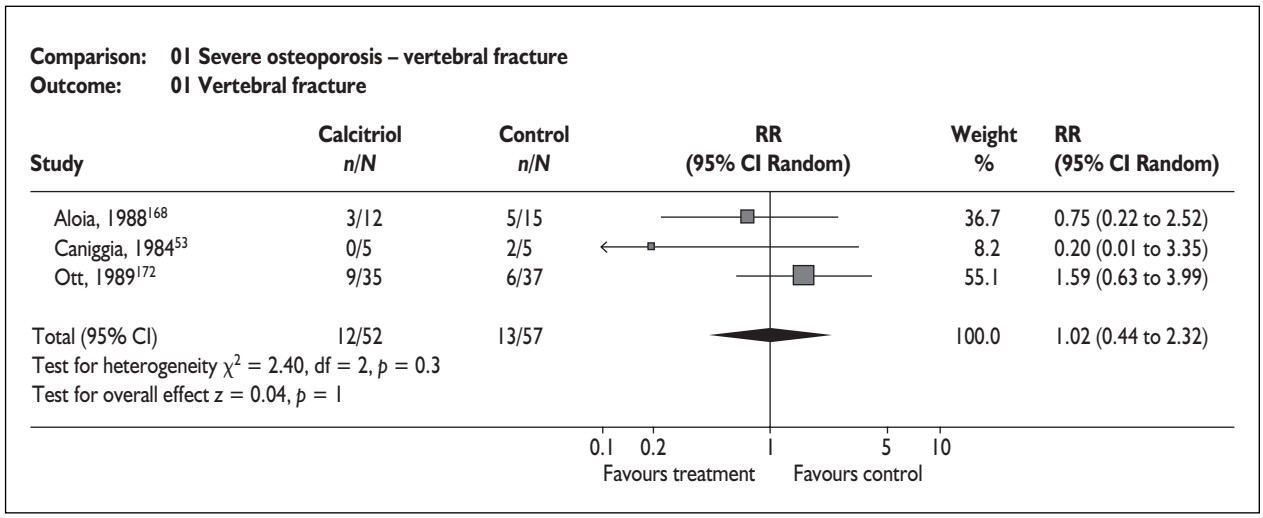

FIGURE 23 *Calcitriol: vertebral fracture in severe postmenopausal osteoporosis*

TABLE 48 *Relative risk of fracture: calcitriol versus placebo*

Group	Vertebral fracture	All non-vertebral fracture	Hip fracture	Wrist fracture	Other non-vertebral fracture
Women with severe osteoporosis	1.02 (0.44 to 2.32)[a]	2.50 (0.51 to 12.19)[b]	No data	No data	No data
Women with severe osteoporosis or osteoporosis	No data	No data	No data	No data	No data
Women with osteopenia	No data	No data	No data	No data	No data
Elderly women not selected for low BMD	4.44 (0.50 to 39.03)[c]	0.46 (0.17 to 1.27)[c]	No data	No data	No data

Data are shown as RR (95% CI).
[a] Based on data from Aloia *et al*. (1988),[168] Caniggia *et al*. (1984)[53] and Ott and Chesnut (1989).[172]
[b] Based on data from Ott and Chesnut (1989).[172]
[c] Based on data from Gallagher *et al*. (2001).[58]

Assessment of effectiveness: calcitriol in postmenopausal women not selected for low BMD

Vertebral fracture

In the one relevant trial,[58] which used a 20% fracture definition, calcitriol was not demonstrated to be more effective than placebo in reducing the risk of vertebral fracture (RR 4.44, 95% CI 0.50 to 39.03). There was no statistically significant difference between calcitriol and either HRT alone or HRT plus calcitriol (RR of vertebral fracture in women receiving calcitriol alone 1.98, 95% CI 0.37 to 10.57, and 1.84, 95% CI 0.36 to 10.36, respectively), or in women receiving combination therapy with calcitriol and HRT compared with placebo (RR 2.29, 95% CI 0.21 to 24.82).

Non-vertebral fracture

Again, there was no statistically significant difference between calcitriol and either HRT alone or HRT plus calcitriol in relation to non-vertebral fracture: five out of 101 women in the calcitriol group, 12 out of 101 in the HRT group, eight out of 102 in the combined treatment group and 12 out of 112 in the placebo group experienced at least one non-vertebral fracture (Gallagher JC: personal communication), giving a relative risk of fracture in the calcitriol group of 0.46 (95% CI 0.17 to 1.27) relative to placebo, 0.42 (95% CI 0.15 to 1.14) relative to HRT and 0.63 (95% CI 0.21 to 1.86) relative to combined treatment. Combined therapy was not demonstrated to reduce the risk of fracture relative to placebo (RR 0.73, 95% CI 0.31 to 1.72).

Calcitriol in postmenopausal osteoporosis and osteopenia, and in postmenopausal women not selected for low BMD: summary

Although calcitriol has been shown to reduce the risk of vertebral and non-vertebral fracture relative to calcium in women with severe osteoporosis, there is no evidence that it reduces the risk of either vertebral or non-vertebral fracture relative to placebo or no treatment either in women with severe osteoporosis or in elderly women not selected for low BMD (*Table 48*). However, as the studies involved are all very small, it seems plausible that an adequately powered trial might demonstrate antifracture benefit.

Calcitriol: side-effects

Although calcitriol can cause hypercalcaemia, at the recommended dosages this is generally mild and responds to reductions in dosage.[155] Several of the studies reviewed in this report stated that calcitriol was associated with hypercalciuria or hypercalcaemia in all or most of the intervention group[168,169,171,172] (for details, see Appendix 10, *Table 181*). In most cases this was not sufficiently serious to lead to withdrawal, but in one study[160] two withdrawals from the calcitriol group were due to persistently elevated serum calcium. In another study,[170] it was necessary to halve the initial calcitriol dose of 0.50 μg per day in 28% of the calcitriol group because total serum calcium exceeded 2.65 mmol l^{-1}. Investigators in one study felt that hypercalciuria could have been avoided by parenteral calcitriol administration.[168]

Because calcitriol has a narrow therapeutic window, its use must be adequately supervised, with periodic monitoring of serum calcium and creatinine levels, to avoid renal toxicity.[155]

In one study,[160] 4% of women withdrew from the calcitriol arm because of gastrointestinal symptoms.

Calcitriol: continuance and compliance

In the studies reviewed in this section, the percentage of subjects receiving calcitriol who completed the protocol ranged from 71%[168] to 91%[172] at 2 years and 83% at 3 years.[58] No study reported compliance in terms of the proportion of medication taken by study completers.

HRT

Quantity and quality of research available: HRT in postmenopausal osteoporosis and osteopenia

Ten RCTs[50,52,53,65,72,118,122,125,173,174] were identified that compared HRT with another intervention or comparator reviewed in this report, and that reported fracture outcomes. One of these studies[52] compared HRT with alendronate, either alone or plus HRT. Three studies[118,122,125] compared HRT with etidronate alone, and one[125] also with HRT plus etidronate. A fifth study[53] compared HRT with calcitriol, either alone or with HRT. Six studies compared HRT with placebo,[50,52,53,72,173,174] and four[65,118,122,125] with no treatment (for details, see Appendix 10, *Table 182*).

Five studies were carried out in women with severe osteoporosis,[53,65,118,125,173] three in women with severe osteoporosis, osteoporosis or osteopenia,[50,122,174] and two in women with osteoporosis or osteopenia[52,72] (for details, see Appendix 10, *Table 183*).

In two studies,[72,174] some or all participants received a dose of oestrogen lower than that currently recommended for the treatment of osteoporosis.

In the majority of studies, some or all subjects received supplementary calcium. Some studies gave all participants supplementary calcium at a dose of 500 mg per day[52] or 1000[50,122,125] mg per day. Others evaluated participants' dietary intakes, and supplied calcium supplements to bring their total daily intake up to either 1000 mg[72] or 1500 mg.[65] In another study,[174] women whose daily calcium intake did not reach 1200–1500 mg were given a supplementary 500 mg per day, while in a fourth study[173] women whose calcium intake was estimated to be less than 800 mg per day were instructed to maintain a diet providing that amount. Only two studies[53,118] did not state that the subjects received supplementary calcium.

In one study,[125] all subjects were also given 400 U per day vitamin D_2.

As reported, few of the studies provided evidence of appropriately masked randomisation or of blinded outcome assessment. In five studies,[53,65,118,122,174] inadequate information was provided to ensure confidence in the comparability of the groups at study entry (see Appendix 10, *Table 184*).

Assessment of effectiveness of HRT in postmenopausal osteoporosis and osteopenia

Comparisons with active interventions

None of the direct comparisons between HRT and other active interventions demonstrated a statistically significant difference in terms of fracture prevention (*Table 49*).

TABLE 49 *HRT in postmenopausal osteoporosis or osteopenia: comparisons with active treatment*

Study	Comparator	Type of fracture	No. of subjects suffering fracture		RR of fracture (95% CI): HRT vs comparator
			HRT	Comparator	
Arthur, 1990[169]	Vitamin D_2	Vertebral	0/4	0/6	Not calculable
		Non-vertebral	0/4	0/4	Not calculable
Bone, 2000[52]	Alendronate (10 mg per day)	All clinical fractures	10/143	5/92	1.29 (0.45 to 3.64)
Bone, 2000[52]	Alendronate (10 mg per day) plus CEE (0.625 mg per day)	All clinical fractures	10/143	8/140	1.22 (0.50 to 3.01)
Ishida, 2001[118]	Etidronate	Vertebral + non-vertebral	10%	3%	Not calculable
Pacifici, 1988[122]	Etidronate	Vertebral	Incidence said to be 'almost identical' in both groups. Total vertebral height loss was significantly lower in the hormone-treated group (7.5 ± 4.4%) than in the etidronate group (13.6 ± 10.6%) ($p < 0.05$)		Not calculable
Wimalawansa, 1998[125]	Etidronate	Vertebral	Only gives numbers of fractures; these were too few for the differences between the groups to be statistically significant		Not calculable
		Non-vertebral	Only gives numbers of fractures; these were too few for the differences between the groups to be statistically significant		Not calculable
Wimalawansa, 1998[125]	Etidronate + HRT	Vertebral	Only gives numbers of fractures; these were too few for the differences between the groups to be statistically significant		Not calculable
		Non-vertebral	Only gives numbers of fractures; these were too few for the differences between the groups to be statistically significant		Not calculable
Caniggia, 1984[53]	Calcitriol	Vertebral	1/5	0/5	3.00 (0.15 to 59.89)
Caniggia, 1984[53]	Calcitriol + oestradiol valerate	Vertebral	1/5	1/7	1.40 (0.11 to 17.45)

Comparisons with placebo or no treatment

Vertebral fracture

Although the majority of studies that compared HRT with placebo or no treatment reported vertebral fracture outcomes, only two[50,173] did so in a form that permitted the analysis of relative risks (*Table 50*). Both studies used transdermal oestradiol, in one case[173] at a higher dose than is currently licensed in the UK for the treatment of osteoporosis. In both cases, the confidence intervals cross unity. Ideally, the results of the two studies should not be pooled, as they use different fracture definitions. However, if pooled, they still fail to achieve statistical significance: the relative risk of vertebral fracture, in women with severe osteoporosis, osteoporosis or osteopenia receiving HRT, is 0.71 (95% CI 0.24 to 2.12) compared with placebo (*Figure 24*).

TABLE 50 *HRT in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: vertebral fracture data*

Study	HRT dose	Fracture definition	No. of women in each group suffering vertebral fracture
Alexandersen, 1999[50]	Combined continuous HRT (transdermal 17β-estradiol 50 μg per day + oral NETA 1 mg per day)	20%	HRT: 1/17 Placebo: 0/19 RR 3.33 (95% CI 0.14 to 76.76)
Bone, 2000[52]	CEE 0.625 mg per day	NA	Pooled clinical fracture data only reported; most of these fractures were said to be non-vertebral
Caniggia, 1984[53]	Oestradiol valerate 2 mg per day	Not given	There was one vertebral fracture in the HRT group and two in the placebo group. The number of women suffering fractures was not stated
Ishida, 2001[118]	Conjugated oestrogen 0.625 mg per day + medroxyprogesterone 2.5 mg per day	Not given	Only gives data relating to combined vertebral and non-vertebral fractures. Fracture incidence was said to be 10% in the untreated group and 0% in the HRT group
Lindsay, 1990[65]	CEE 0.625 mg per day plus, for women with an intact uterus, cyclic MPA (5 or 10 mg per day for 12–14 days per calendar month)	Not given	No data
Lufkin, 1992[173]	Transdermal estradiol 0.1 mg per day for days 1–21, plus oral MPA 10 mg per day for days 11–21, of a 28-day cycle	15%	HRT: 7/34 Placebo: 12/34 RR 0.58 (95% CI 0.26 to 1.30)
Pacifici, 1988[122]	Conjugated oestrogens 0.625 mg per day orally for 25 days per month, plus MPA 10 mg per day orally from days 15–25 each month	Compression fractures 15%, wedging and biconcave fractures 20%	Incidence said to be 'almost identical' in both groups. Total vertebral height loss was significantly lower in the hormone-treated group (7.5 $\pm$ 4.4%) than in the placebo group (20.8 $\pm$ 20.2%) ($p < 0.05$)
Recker, 1999[72]	CEE (0.3 mg per day) plus medroxyprogesterone (2.5 mg per day)	Method of Davies *et al.*[175]	There were three incident fractures in the HRT group and four in the placebo group; the number of women suffering those fractures was not stated
Wimalawansa, 1998[125]	Premarin 0.625 mg per day + norgestrel 150 μg for 12 days per month	20%	There were two incident fractures in subjects taking HRT alone and five in the control group; the number of women suffering those fractures was not stated
Zarcone, 1997[174]	CEE (0.15, 0.3 or 0.625 mg per day) plus progestogen (unspecified dose)	Not given	10% of women taking 0.15 or 0.3 mg oestrogen daily, and 3.3% of those taking 0.625 mg, suffered incident vertebral fractures, compared with 16.7% of women in the placebo group

NETA, norethisterone acetate; MPA, medroxy progesterone acetate.

Non-vertebral fracture

The majority of studies that compared HRT with placebo or no treatment reported non-vertebral fracture outcomes, but again few did so in a form that permitted the analysis of relative risks. In all those for which relative risks could be calculated, the confidence intervals crossed unity (*Table 51*). However, in one of these studies,[72] some or all participants received a dose of oestrogen lower than that currently recommended for the treatment of osteoporosis.

Pooling of results from those studies that provided usable data yielded a relative risk of non-vertebral

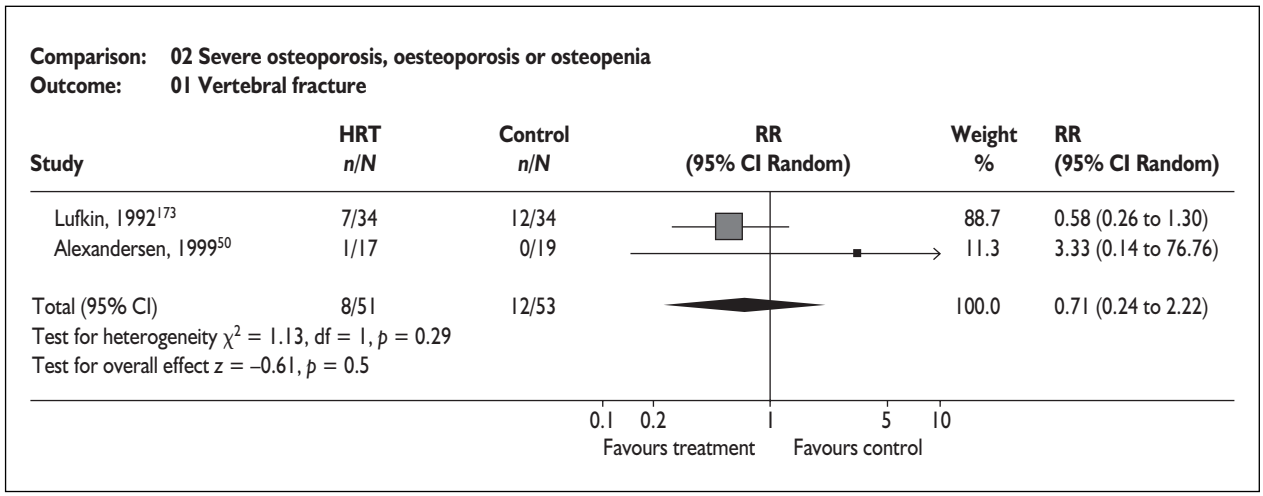

FIGURE 24 *HRT: vertebral fracture in severe postmenopausal osteoporosis, osteoporosis or osteopenia*

TABLE 51 *HRT in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment: non-vertebral fracture data*

Study	Dose	No. of women in each group suffering non-vertebral fracture
Alexandersen, 1999[50]	Combined continuous HRT (transdermal 17β-estradiol 50 μg per day + oral NETA 1 mg per day)	HRT: 1/26 Placebo: 3/24 RR 0.31 (95% CI 0.03 to 2.76) The fractures were mainly of clear traumatic origin
Bone, 2000[52]	CEE 0.625 mg per day	Clinical fractures (mainly non-vertebral, generally resulting from trauma): HRT: 10/143 Placebo: 4/50 RR 0.87 (95% CI 0.29 to 2.66)
Ishida, 2001[118]	Conjugated oestrogen 0.625 mg per day + medroxyprogesterone 2.5 mg per day	Only gives data relating to combined vertebral and non-vertebral fractures. Fracture incidence in the untreated group was said to be 10%, and 0% in the HRT group
Lindsay, 1990[65]	CEE 0.625 mg per day plus, for women with an intact uterus, cyclic MPA (5 or 10 mg per day for 12–14 days per calendar month)	HRT: 1/25 Control: 2/25[a] RR 0.50 (95% CI 0.05 to 5.17)
Recker, 1999[72]	CEE (0.3 mg per day) plus medroxyprogesterone (2.5 mg per day)	HRT: 7/64 Placebo: 6/64[a] RR 1.17 (95% CI 0.41 to 3.28)
Wimalawansa, 1998[125]	Premarin 0.625 mg per day + norgestrel 150 μg for 12 days per month	HRT: 1/18 Control: 1/18 RR 1.00 (95% CI 0.07 to 14.79)
Zarcone, 1997[174]	CEE (0.15, 0.3 or 0.625 mg per day) plus progestogen (unspecified dose)	Brief reference is made to treatment being associated with 'a notable reduction' in fractured neck of femur, but no figures are given

[a] Data from Torgerson and Bell-Syer (2001).[176]

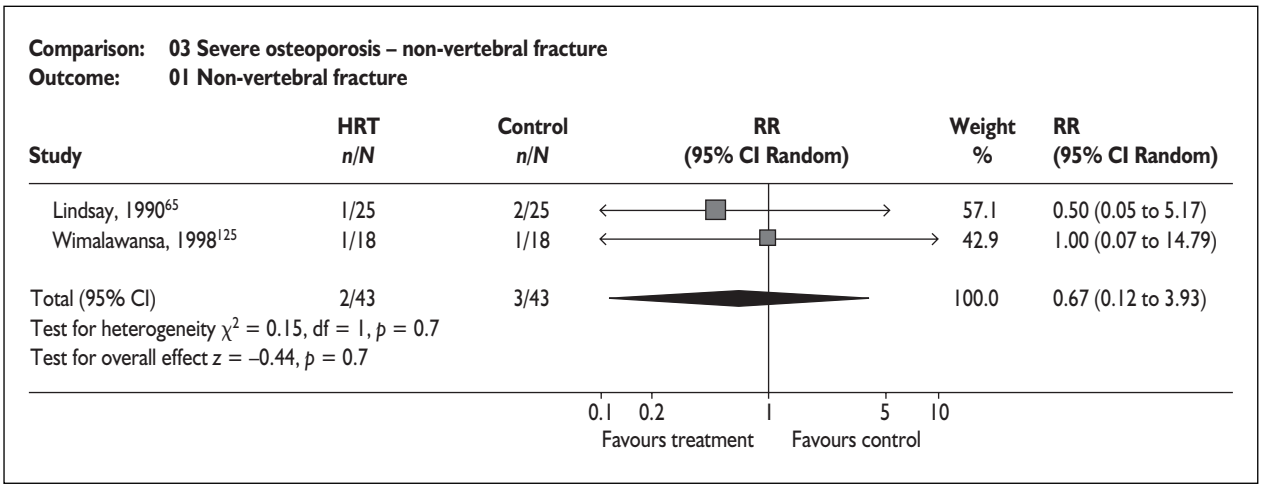

FIGURE 25 *HRT: non-vertebral fracture in severe postmenopausal osteoporosis*

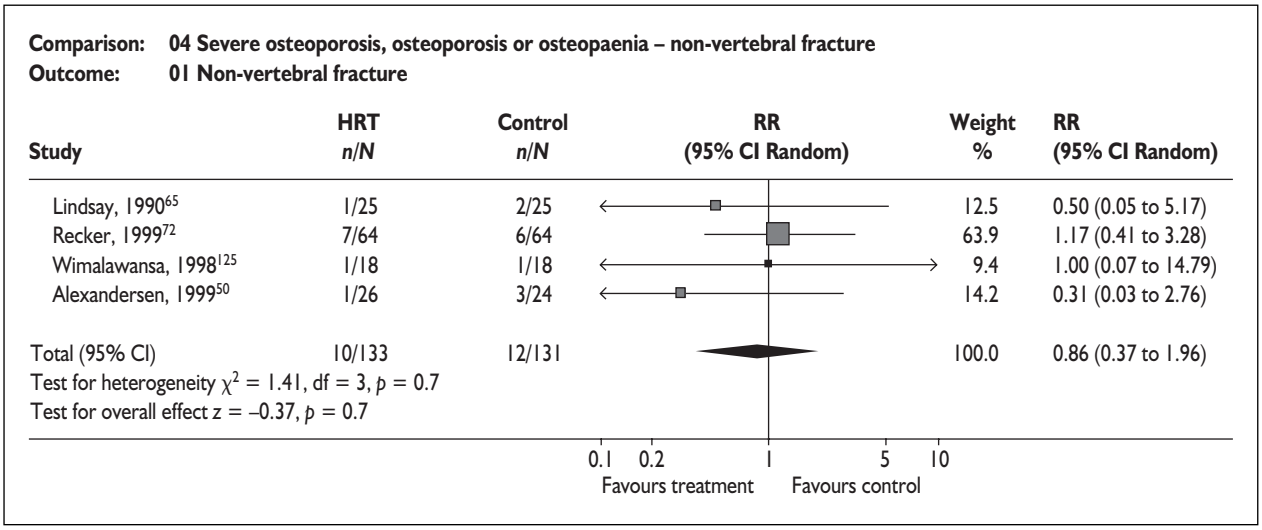

FIGURE 26 *HRT: non-vertebral fracture in severe postmenopausal osteoporosis, osteoporosis or osteopenia*

fracture associated with HRT of 0.67 (95% CI 0.12 to 3.93) in women with severe osteoporosis (*Figure 25*) and of 0.86 (95% CI 0.37 to 1.96) in women with severe osteoporosis, osteoporosis or osteopenia, compared with controls (*Figure 26*). Thus, HRT has not been demonstrated to reduce the risk of non-vertebral fracture in women with low BMD.

Quantity and quality of research available: HRT in postmenopausal women not selected for low BMD

Nineteen RCTs[49,55,57–59,64,69,71,75,84,85,88–91,162,177–180] were identified that studied the use of HRT in women with normal or undifferentiated BMD, and that reported fracture outcomes.

A twentieth study[129] compared 2.5 g per day percutaneous 17β-E_2, plus 200 mg per day oral micronised progesterone for 12 days a month, with placebo, etidronate and HRT plus etidronate in early postmenopausal women with normal BMD. This did not report fracture data, and although a meta-analysis[130] that included this study indicated that such data were collected, they could not be obtained for use in this review.

Two additional RCTs[47,92] were identified that reported data relating to quality of life in healthy postmenopausal women who did not have menopausal symptoms that required therapy. One of these studies[92] compared oestrogen with both raloxifene and placebo; the other[47] compared continuous combined HRT with raloxifene (for details, see Appendix 10, *Tables 185* and *186*). Both studies measured quality of life using the Women's Health Questionnaire. The Heart and Estrogen/Progestin Replacement Study (HERS)

also reported quality of life outcomes as measured by the Duke Activity Status Index, the RAND energy/fatigue scale and Mental Health Inventory, and the Burnam depression screening scale.[181]

Four of the fracture studies compared HRT with other interventions. The EPIC study[71] compared HRT with various doses of alendronate. Another study compared HRT with calcium, vitamin D_3 and calcium, and HRT plus vitamin D_3,[162] a third with calcitriol and with HRT plus calcitriol,[58] and a fourth with exercise and with HRT plus exercise.[85] A fifth study[88] compared unopposed oestrogen with oestrogen plus medroxyprogesterone. Fifteen studies compared HRT with placebo[49,55,57–59,64,69,71,75,85,88,89,91,177,178,180] and another two with no treatment.[90,179]

Three studies[69,89,90] were carried out in postmenopausal women with health problems: one in women with mild primary hyperparathyroidism,[69] another in women with Alzheimer's disease,[89] and the third in women recruited from patients at a hospital for chronic diseases, who were less physically active than the general population.[90]

The majority of studies used oestrogen in current licensed doses. However, one of the older studies[90] used an oestrogen dose considerably higher than is currently considered appropriate. This was deliberately chosen to make the results as clear as possible; it was not known at that time that many of the complications of oestrogen therapy were dose related.[90] Another early study[49] used a synthetic oestrogen (mestranol) not currently recommended for use in the prevention of postmenopausal osteoporosis.

Several studies that reported fracture data had primary end-points related to CHD rather than to osteoporosis.[88,91,178,180] The use of data from such studies, and indeed of any studies that recruit women without known osteoporosis, in meta-analyses of treatments for osteoporosis has been criticised on the grounds that some interventions appear to reduce the risk of vertebral fracture only in women with osteoporosis.[182] However, this is an argument only for analysing the data relating to women without known osteoporosis or osteopenia separately from the data relating to osteoporotic women, as is done here. It is important to examine the effects of the various interventions for osteoporosis on postmenopausal women who are unselected for low BMD or osteoporotic fracture, especially when, as is the case with HRT, those interventions may be recommended to postmenopausal women on the basis of a package of alleged benefits, including the prevention of osteoporosis.

As reported, the quality of the studies of HRT for the prevention of osteoporosis was varied (see Appendix 10, *Table 187*). Many failed to demonstrate the use of a method of randomisation that would prevent the introduction of bias, and some did not state that the outcome assessors were blinded to treatment allocation. However, the largest studies[178,180] were of high quality.

Assessment of effectiveness of HRT in postmenopausal women not selected for low BMD

Comparisons with active treatment

Fracture data from the studies that compare HRT with another active intervention are summarised in *Table 52*. In relation to the EPIC study, oestrogen is compared only with the 5-mg dose of alendronate that is licensed for the prevention of postmenopausal osteoporosis. As may be seen, the confidence intervals cross unity in all cases except for one: HRT appears to reduce the risk of non-vertebral fracture relative to calcium (RR 0.40, 95% CI 0.16 to 0.99).

Comparisons with placebo or no treatment

Vertebral fracture

Only seven studies that compared HRT with placebo or no treatment provided vertebral fracture data: the results of these studies are summarised in *Table 53*. Only the largest of these studies[180] produced a statistically significant result, indicating that HRT reduces the risk of vertebral fracture relative to placebo in postmenopausal women not selected for low BMD (RR 0.65, 95% CI 0.44 to 0.97).

Data from those studies that reported radiographic vertebral fractures and those which only reported clinical fractures have been meta-analysed separately. Only two studies[58,179] provided data on radiographic fracture in a form that could be used to calculate a relative risk; although the mean age of participants in one study[58] was over 20 years older than in the other,[179] they produced similar point estimates, both indicating a higher risk of fracture in the HRT group (*Table 52*), but in both cases the confidence intervals cross unity, and continue to do so even when the data are pooled (RR of radiographic fracture in women receiving opposed or unopposed oestrogens compared with controls 2.05; 95% CI 0.71 to 5.97) (*Figure 27*).
Meta-analysis of the results of those studies that

TABLE 52 *HRT in postmenopausal women not selected for low BMD: comparisons with active treatment*

Study	Comparator	Type of fracture	No. of subjects suffering fracture		RR of fracture (95% CI): HRT vs comparator
			HRT	Comparator	
EPIC study[a]	Alendronate 5 mg[b]	Clinical vertebral	0/110	3/333	0.43 (0.02 to 8.26)
		All non-vertebral	6/110	23/333	0.79 (0.33 to 1.89)
		Hip	0/110	0/333	Not calculable
		Wrist	0/110	2/333	0.60 (0.03 to 12.44)
		Other non-vertebral	5/110	22/333	0.69 (0.27 to 1.77)
Komulainen, 1998[162]	Calcium	Non-vertebral	6/116	15/116	0.40 (0.16 to 0.99)
		Hip	0/116	2/116	0.20 (0.01 to 4.12)
Komulainen, 1998[162]	Calcium + vitamin D_3	Non-vertebral	6/116	11/116	0.55 (0.21 to 1.43)
		Hip	0/116	1/116	0.33 (0.01 to 8.10)
Komulainen, 1998[162]	HRT + vitamin D_3	Non-vertebral	6/116	7/116	0.86 (0.30 to 2.47)
		Hip	0/116	0/116	Not calculable
Gallagher, 2001[c]	Calcitriol	Vertebral	2/100	4/101	0.51 (0.09 to 2.70)
		Non-vertebral	12/101	5/101	2.40 (0.88 to 6.56)
Gallagher, 2001[c]	HRT + calcitriol	Vertebral	2/100	2/98	0.98 (0.14 to 6.82)
		Non-vertebral	12/101	8/102	1.51 (0.65 to 3.55)
Cheng, 2000[d]	Exercise	Vertebral and non-vertebral	0	0	Not calculable
Cheng, 2000[d]	HRT + exercise	Vertebral and non-vertebral	0	0	Not calculable

[a] Data from Hosking DJ (personal communication).
[b] For comparability with HRT, the 4-year results are reported here.
[c] Data from Gallagher JC (personal communication).
[d] Data from Cheng S (personal communication).

report only clinical fractures[71,178,180] suggests a reduction in relative risk in women receiving oestrogen of 0.66 (95% CI 0.47 to 0.93) (*Figure 28*).

Meta-analysis of the results for all studies that provide usable data relating to vertebral fracture, whether clinical or radiographic, did not seem appropriate, given the disparity in the results of the separate analyses.

Non-vertebral fracture
Eighteen studies presented data relating to non-vertebral fractures (*Table 54*).

It did not seem appropriate to pool the data from all of the studies that provided usable data. One study[89] was undertaken in a population (elderly women with Alzheimer's disease) so different from the others that its inclusion did not seem appropriate for that reason. A second study[49] used a synthetic oestrogen no longer recommended for the prevention of postmenopausal osteoporosis. A third[90] used a dose of oestrogen four times higher than is now considered appropriate for HRT; in addition, it is not clear whether it reported only non-vertebral fractures or all clinical fractures. These three studies were therefore excluded from the meta-analysis. Pooling of all the remaining data indicated a relative risk of non-vertebral fracture of 0.86 (95% CI 0.72 to 1.02) in women taking HRT relative to controls; as can be seen, the confidence intervals cross unity (*Figure 29*).

Hip fracture
Five studies provided data relating to hip fracture (*Table 55*).

The pooled data relating to hip fracture (RR 0.74, 95% CI 0.53 to 1.03) failed to achieve statistical significance (*Figure 30*).

Wrist fracture
Four studies provided data relating to wrist fracture (*Table 56*).

TABLE 53 *HRT in postmenopausal women not selected for low BMD: comparisons with placebo or no treatment: vertebral fracture data*

Study	HRT dose	Fracture definition	No. of women in each group suffering vertebral fracture
Cauley, 2001[178]	CEE 0.625 mg per day plus MPA 2.5 mg per day	Clinical only	Clinical fracture only: HRT: 13/1380 Placebo: 19/1383 RR 0.69 (95% CI 0.34 to 1.38)
Cheng, 2000[85]	Combined estradionoretisteron acetate	Not stated	No woman in any group suffered vertebral fracture[a]
EPIC study[71]	Open-label oestrogen–progestin (in USA, 0.625 mg per day CEE + 5 mg per day MPA; in Europe, 2 mg per day 17β-estradiol for 22 days, 1 mg per day NETA on days 13–22 and 1 mg per day estradiol on days 23–28)	Clinical only	Clinical vertebral fractures at 4 years (the point at which the HRT arm discontinued treatment): HRT: 0/110 Placebo: 3/502[b] RR 0.35 (95% CI 0.02 to 6.14)
Gallagher, 2001[58]	HRT (CEE 0.625 mg per day plus, in non-hysterectomised women, MPA 2.5 mg per day)	20%	HRT: 2/100 Placebo: 1/112 RR 2.24 (95% CI 0.21 to 24.33)
Mosekilde, 2000[179]	Oral sequential HRT (estradiol 1 mg per day days 1–6, 2 mg per day days 7–28, plus norethisteron 1 mg per day on days 19–28) or, for hysterectomised women, estradiol 2 mg per day continuously (alternative formulations available for women suffering side-effects)	20%	HRT: 8/502 Control: 4/504 RR 2.01 (95% CI 0.61 to 6.63)
Orr-Walker, 2000[69]	Continuous combined HRT (CEE 0.625 mg per day plus, for unhysterectomised women, MPA)	20%	There were no vertebral fractures in either group
WHI, trial[180]	CEE (0.625 mg per day) plus MPA (2.5 mg per day)	Clinical only	HRT: 41/8506 Placebo: 60/8102 RR 0.65 (95% CI 0.44 to 0.97)

[a] Cheng S (personal communication).
[b] Hosking DJ (personal communication).

The pooled data relating to wrist fracture (RR 0.95, 95% CI 0.58 to 1.53) again failed to achieve statistical significance (*Figure 31*).

Other non-vertebral fractures

The pooled data relating to hip fracture non-hip, non-wrist non-vertebral fractures (RR 0.67, 95% CI 0.32 to 1.43) also failed to achieve statistical significance (*Figure 32*). However, although the Women's Health Initiative WHI trial[180] did not demonstrate that HRT offered protection against hip fracture, it indicated that it offered protection against non-hip, non-vertebral fractures (RR versus placebo 0.79, 95% CI 0.71 to 0.87).

Quality of life

Only three studies reported quality of life data. HERS found that HRT was associated with improved mental health and a reduction in depressive symptoms relative to placebo only in those women who reported hot flushes at study entry. Women without flushing at study entry who were assigned to HRT had greater declines in physical function and energy scores than those receiving placebo. Thus, HRT appeared to improve quality of life only for women with menopausal symptoms.[181]

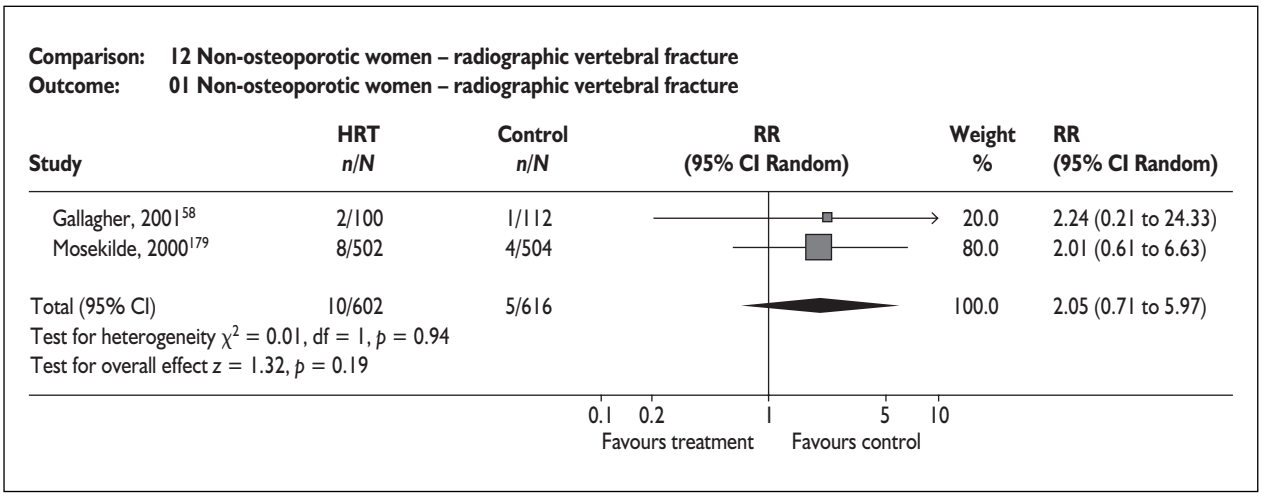

FIGURE 27 *HRT: radiographic vertebral fracture in postmenopausal women not selected for low BMD*

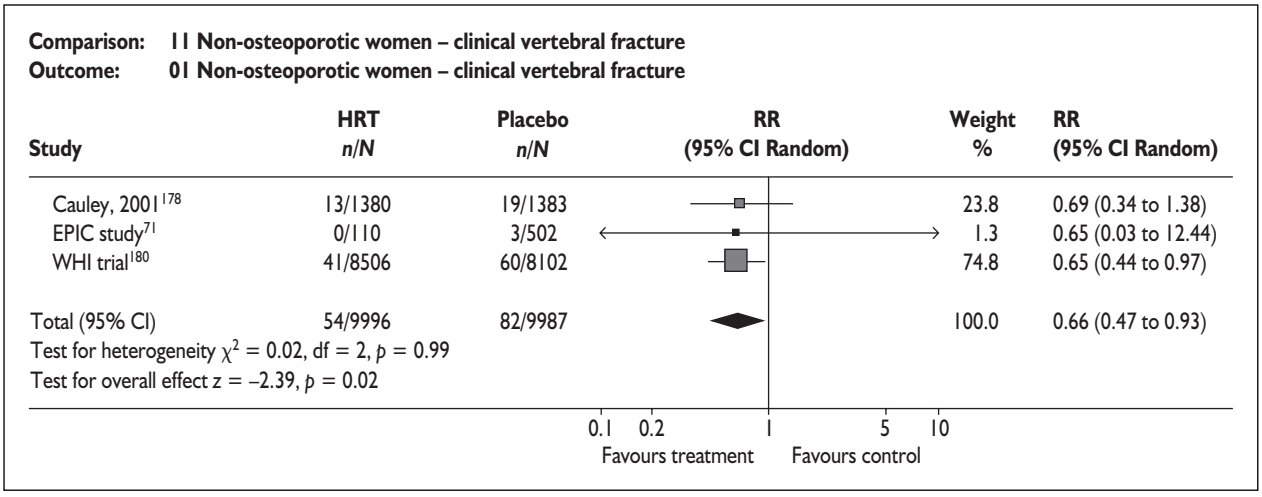

FIGURE 28 *HRT: clinical vertebral fracture in postmenopausal women not selected for low BMD*

TABLE 54 *HRT in postmenopausal women not selected for low BMD: comparisons with placebo or no treatment: non-vertebral fracture data*

Study	Dose	No. of women in each group suffering non-vertebral fracture
Aitken, 1973[49]	Mestranol 40 μg per day	HRT: 0/68 Placebo: 2/66 RR vs placebo 0.19 (95% CI 0.01 to 3.97)
Bjarnason, 2000[177]	17β-Estradiol (1 or 2 mg per day) sequentially combined with gestodene (25 or 50 μg on days 17–28 of a 28-day cycle) in the following combinations: 1/25, 2/25, 2/50 17β-Estradiol (1 mg per day) continuously combined with gestodene (25 μg per day)	HRT: 4/112 Control: 1/41[a] RR 1.46 (95% CI 0.17 to 12.72)
Cauley, 2001[178]	CEE 0.625 mg per day plus MPA 2.5 mg per day	HRT: 130/1380 Placebo: 138/1383[a] RR 0.94 (95% CI 0.75 to 1.19)

continued

TABLE 54 *HRT in postmenopausal women not selected for low BMD: comparisons with placebo or no treatment: non-vertebral fracture data (cont'd)*

Study	Dose	No. of women in each group suffering non-vertebral fracture
Cheng, 2000[85]	Combined estradionoretisteron acetate	According to Torgerson,[176] 1/40 women in the HRT group and 1/40 in the control group suffered non-vertebral fracture. However, according to Cheng (personal communication) no women suffered fracture
Delmas, 2000[55]	17β-Estradiol (1 mg per day) plus NETA (0.25 or 0.5 mg per day)	HRT: 1/90 Control: 2/45[a] RR 0.25 (95% CI 0.02 to 2.68)
Eiken, 1997[57]	Continuous HRT (2 mg per day estradiol + 1 mg per day NETA); sequential HRT (2 mg per day estradiol for 12 days, followed by 2 mg per day estradiol plus 1 mg per day NETA for 10 days, followed by 1 mg per day estradiol for 6 days)	Continuous HRT: 1/50 Sequential HRT: 0/50 Placebo/untreated: 6/51 RR, pooled HRT group vs placebo, 0.09 (95% CI 0.01 to 0.69)
EPIC study[71]	Open-label oestrogen–progestin (in USA, 0.625 mg per day CEE + 5 mg per day MPA; in Europe, 2 mg per day 17β-estradiol for 22 days, 1 mg per day NETA on days 13–22 and 1 mg per day estradiol on days 23–28)	Data at 4 years: HRT: 6/110 Placebo: 33/502[b] RR 0.83 (95% CI 0.36 to 1.93)
Gallagher, 2001[58]	HRT (CEE 0.625 mg per day plus, in non-hysterectomised women, MPA 2.5 mg per day)	HRT: 12/101 Placebo: 12/112[c] RR 1.11 (95% CI 0.52 to 2.36)
Genant, 1997[59]	CEE 0.3, 0.625 or 1.25 mg per day	Pooled oestrogen groups: 3/303 Control: 2/102[a] RR 0.50 (95% CI 0.09 to 2.98)
Herrington, 2000[88]	Unopposed CEE (0.625 mg per day); CEE (0.625 mg per day) plus MPA (2.5 mg per day)	HRT: 7/100 Placebo: 16/105[d] RR 0.46 (95% CI 0.20 to 1.07)
Lees, 2001[64]	Cyclical estradiol-17β (1 or 2 mg) (days 1–28) and dydrogesterone (5, 10 or 20 mg) (days 15–28) in the following combinations: 1/5, 1/10, 2/10, 2/20	Oestrogen 1 mg: 5/231 Oestrogen 2 mg: 5/231 Placebo: 3/118 RR, pooled oestrogen group vs placebo, 0.85 (95% CI 0.24 to 3.04)
Mosekilde, 2000[179]	Oral sequential HRT (estradiol 1 mg per days 1-6, 2 mg per day days 7–28, plus norethisteron 1 mg per day on days 19–28) or, for hysterectomised women, estradiol 2 mg per day continuously (alternative formulations available for women suffering side-effects)	HRT: 29/502 Control: 41/504[e] RR 0.71 (95% CI 0.45 to 1.12)
Mulnard, 2000[89]	CEE (0.625 and 1.25 mg per day)	Pooled HRT groups: 1/81 Placebo: 0/39[a] RR 1.46 (95% CI 0.06 to 35.13)
Nachtigall, 1979[90]	Conjugated oestrogen (2.5 mg per day) plus cyclic MPA (10 mg per day for 7 days per month)	HRT: 0/84 Control: 6/84 RR 0.08 (95% CI 0.00 to 1.34)
Orr-Walker, 2000[69]	Continuous combined HRT (CEE 0.625 mg per day plus, for unhysterectomised women, MPA)	HRT: 2/21 Placebo: 1/21 RR 5.00 (95% CI 0.25 to 98.28)

continued

TABLE 54 *HRT in postmenopausal women not selected for low BMD: comparisons with placebo or no treatment: non-vertebral fracture data (cont'd)*

Study	Dose	No. of women in each group suffering non-vertebral fracture
PEPI trial[91]	CEE (0.625 mg per day) CEE (0.625 mg per day) plus MPA (10 mg per day for 12 days per month) CEE (0.625 mg per day) plus MPA (2.5 mg per day) CEE (0.625 mg per day) plus micronised progesterone (200 mg per day for 12 days per month)	HRT: 21/701 Placebo: 6/174[a] RR 0.87 (95% CI 0.36 to 2.12)
Weiss, 1999[75]	Transdermal estradiol (0.025, 0.05, 0.06 and 0.10 mg per day)	There were no spontaneous fractures. Traumatic fractures were as follows: 0.025 mg: 1/32 0.05 mg: 0/31 0.06 mg: 1/32 0.10 mg: 1/35 Placebo: 1/46 RR, pooled treatment groups vs placebo, 1.06 (95% CI 0.11 to 9.95)
WHI trial[180]	CEE (0.625 mg per day) plus MPA (2.5 mg per day)	Does not report total numbers of women suffering non-vertebral fractures

[a] Data from Torgerson and Bell-Syer (2001).[176]
[b] Hosking DJ (personal communication).
[c] Gallagher JC (personal communication).
[d] Saylor G (personal communication).
[e] Vestegaard P (personal communication).

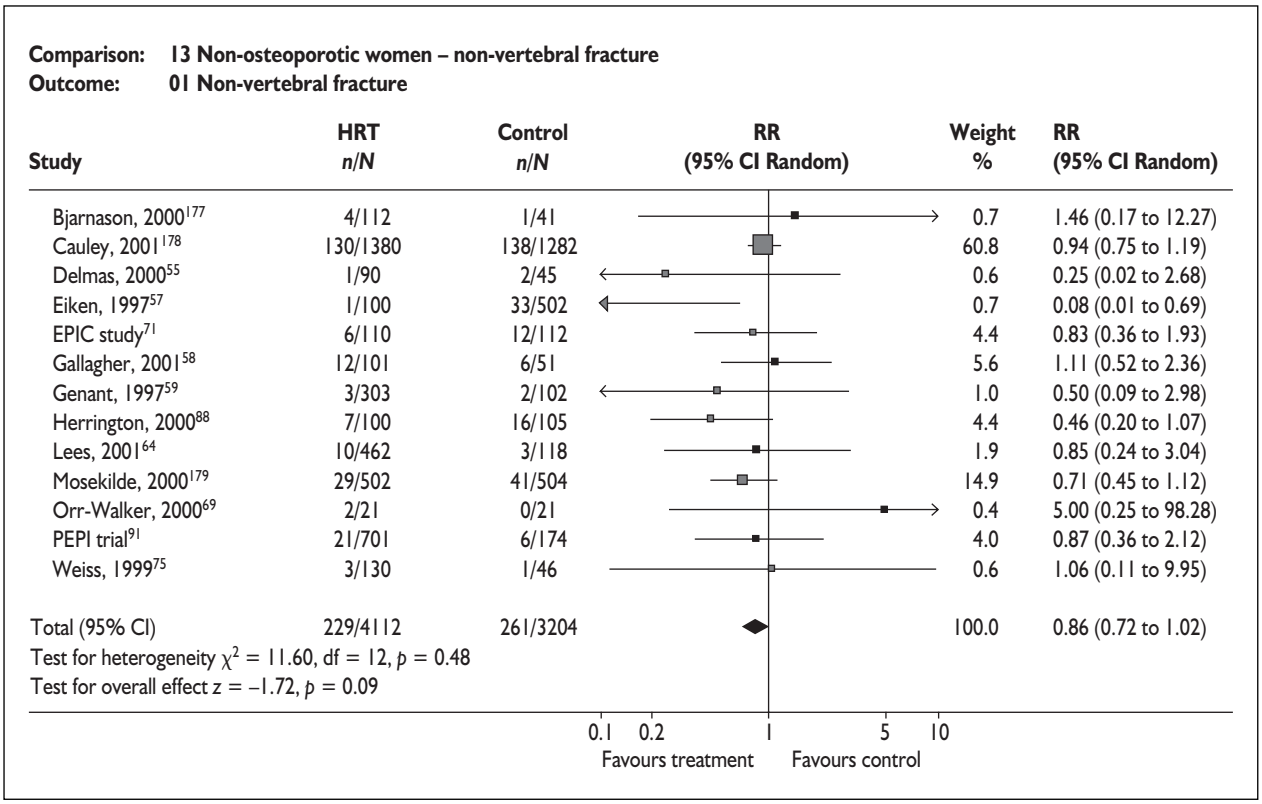

FIGURE 29 *HRT: non-vertebral fracture in postmenopausal women not selected for low BMD*

TABLE 55 *HRT in postmenopausal women not selected for low BMD: comparisons with placebo or no treatment: hip fracture data*

Study	Dose	No. of women in each group suffering hip fracture
Cauley, 2001[178]	CEE 0.625 mg per day plus MPA 2.5 mg per day	HRT: 14/1380 Placebo: 13/1383[a] RR 1.08 (95% CI 0.51 to 2.29)
EPIC study[71]	Open-label oestrogen–progestin (in USA, 0.625 mg per day CEE + 5 mg per day MPA; in Europe, 2 mg per day 17β-estradiol for 22 days, 1 mg per day NETA on days 13–22 and 1 mg per day estradiol on days 23–28)	Data at 4 years: HRT: 0/110 Placebo: 1/502[b] RR 1.51 (95% CI 0.06 to 36.84)
Herrington, 2000[88]	Unopposed CEE (0.625 mg per day); CEE (0.625 mg per day) plus MPA (2.5 mg per day)	HRT: 1/100 Placebo: 1/105[c] RR 1.05 (95% CI 0.07 to 16.56)
Lees, 2001[64]	Cyclical 17β-estradiol (1 or 2 mg) (days 1–28) and dydrogesterone (5, 10 or 20 mg) (days 15–28) in the following combinations: 1/5, 1/10, 2/10, 2/20	Oestrogen 1 mg: 0/231 Oestrogen 2 mg: 0/231 Placebo: 1/118 RR, pooled oestrogen group vs placebo, 0.09 (95% CI 0.00 to 2.09)
WHI trial[180]	CEE (0.625 mg per day) plus MPA (2.5 mg per day)	HRT: 44/8506 Placebo: 62/8102 RR 0.68 (95% CI 0.46 to 0.99)

[a] Data from Torgerson and Bell-Syer (2001).[176]
[b] Hosking DJ (personal communication).
[c] Saylor G (personal communication).

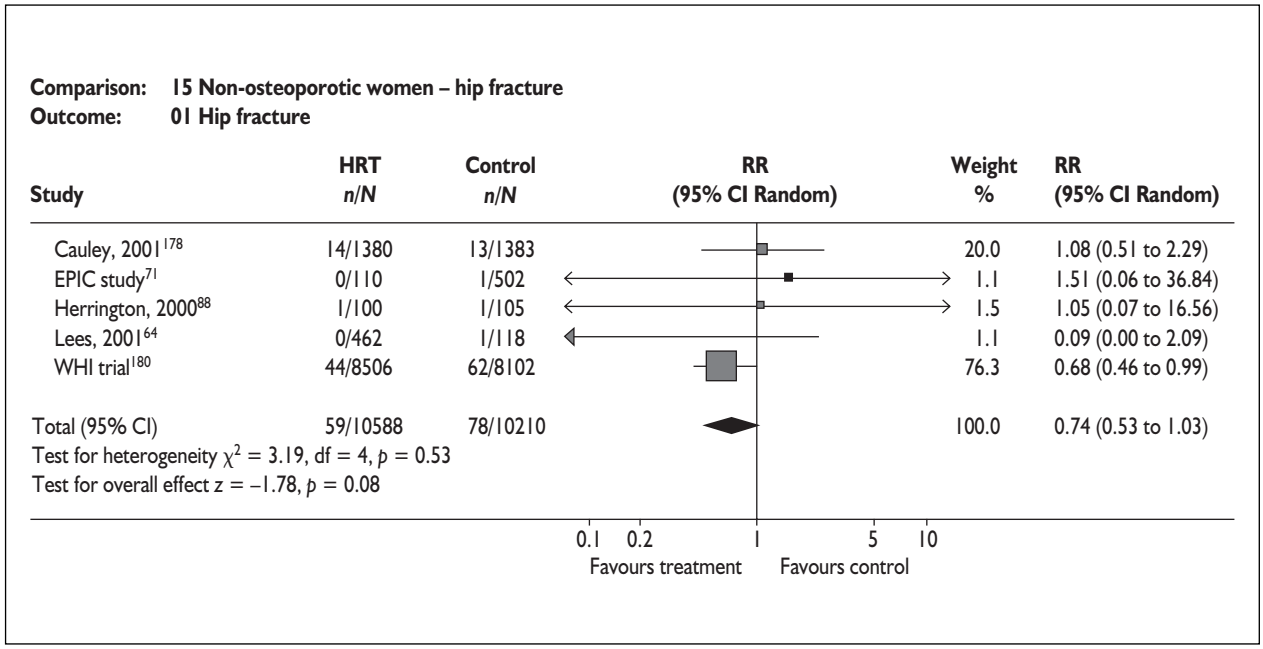

FIGURE 30 *HRT: hip fracture in postmenopausal women not selected for low BMD*

TABLE 56 *HRT in postmenopausal women not selected for low BMD: comparisons with placebo or no treatment: wrist fracture data*

Study	Dose	No. of women in each group suffering wrist fracture
Cauley, 2001[178]	CEE 0.625 mg per day plus MPA 2.5 mg per day	HRT: 29/1380 Placebo: 29/1383[a] RR 1.00, 95% CI 0.60 to 1.67
EPIC study[71]	Open-label oestrogen–progestin (in USA, 0.625 mg per day CEE + 5 mg per day MPA; in Europe, 2 mg per day 17β-estradiol for 22 days, 1 mg per day NETA on days 13–22 and 1 mg per day estradiol on days 23–28)	Data at 4 years: HRT: 0/110 Placebo: 5/502[b] RR 0.41, 95% CI 0.02 to 7.40
Herrington, 2000[88]	Unopposed CEE (0.625 mg per day); CEE (0.625 mg per day) plus MPA (2.5 mg per day)	HRT: 1/100 Placebo: 3/105[c] RR 0.35, 95% CI 0.04 to 3.31
Lees, 2001[64]	Cyclical estradiol-17β (1 or 2 mg) (days 1–28) and dydrogesterone (5, 10 or 20 mg) (days 15–28) in the following combinations: 1/5, 1/10, 2/10, 2/20	Oestrogen 1 mg: 2/231 Oestrogen 2 mg: 1/231 Placebo: 0/118 RR, pooled oestrogen group vs placebo, 1.80 (95% CI 0.09 to 34.59)

[a] Data from Torgerson and Bell-Syer (2001).[176]
[b] Hosking DJ (personal communication).
[c] Saylor G (personal communication).

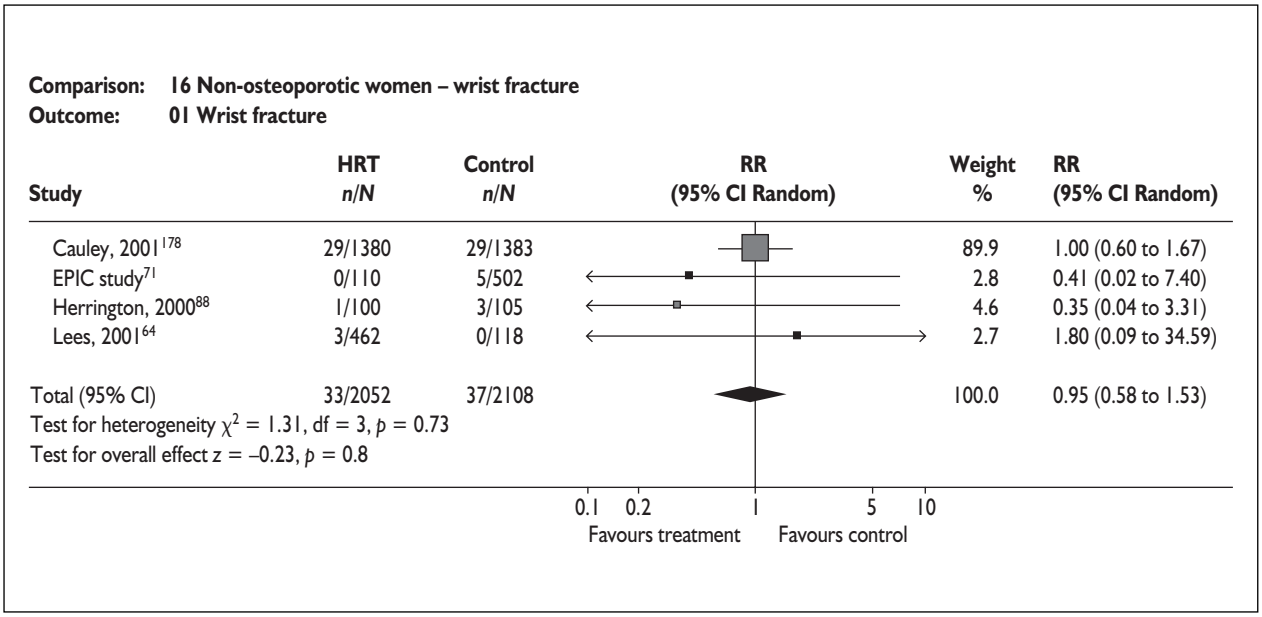

FIGURE 31 *HRT: wrist fracture in postmenopausal women not selected for low BMD*

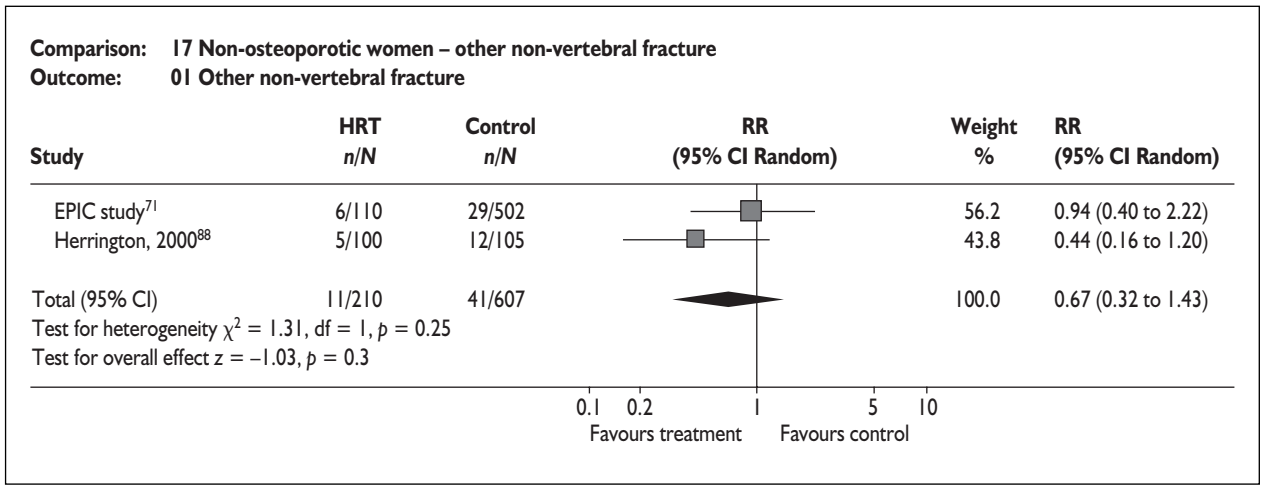

FIGURE 32 *HRT: non-hip, non-wrist fracture in postmenopausal women not selected for low BMD*

One quality of life study[92] found that oestrogen was associated with significant improvements from baseline in the mean scores for sleep problems and vasomotor symptoms, but significant deterioration in the menstrual symptom scores ($p < 0.05$ in each case). The other quality of life study[47] found that women taking HRT reported significant improvements in memory/concentration, vasomotor symptoms and sexual behaviour compared with those taking raloxifene, but significant worsening in mood and menstrual symptoms. Significantly more women taking HRT said that their treatment worried them (20% versus 10%, $p < 0.01$), perhaps reflecting the increased occurrence of adverse events (specifically breast pain and vaginal bleeding) in the HRT group. Women taking HRT reported significantly lower treatment satisfaction than those taking raloxifene ($p = 0.004$).

HRT in postmenopausal osteoporosis and osteopenia, and in postmenopausal women not selected for low BMD: summary

As may be seen from *Table 57*, the evidence base relating to the use of HRT for the prevention and treatment of postmenopausal osteoporosis is deficient in many areas; where it is not deficient, it generally fails to demonstrate any clear benefit. For comparability with other interventions, *Table 57* reports the relative risk of morphometric vertebral fracture in women not selected for low BMD; this figure suggests that HRT offers no protection against such fractures. However, meta-analysis of the data from those studies that only report clinical vertebral fractures[71,85,178,180] indicates that HRT has a protective effect in relation to such fractures in postmenopausal women not selected for low BMD (RR in women receiving HRT of 0.65, 95% CI 0.46 to 0.92). This discrepancy is curious and not easily explained: as noted earlier, the Fracture Intervention Trial indicated that, in the same population, alendronate caused very similar reductions in the risk of radiographic and clinical fractures. In the absence of evidence that HRT has a different effect on radiographic and clinical fractures, the evidence relating to clinical fractures should probably be preferred, as it is based on larger studies.

The largest study of HRT[180] found that it was associated with a statistically significant reduction in both hip and non-hip non-vertebral fractures in women not selected for low BMD (RR in women receiving HRT of 0.68, 95% CI 0.46 to 1.03, and RR 0.79, 95% CI 0.71 to 0.87, respectively); the total number of women suffering any non-vertebral fracture was not stated.

Thus, it seems possible that HRT may offer protection against both vertebral and non-vertebral fracture in postmenopausal women not selected for low BMD. However, it should be noted that the WHI trial on which this evidence of benefit largely depends was stopped early because, in women taking oestrogen plus progesterone, the evidence for harm from the increased risk of breast cancer, CHD, stroke and pulmonary embolism outweighed the evidence of benefit from the reduction in fracture risk and possible benefit from the reduction in the risk of colon cancer. The balance of risks in hysterectomised women receiving unopposed oestrogen was not clear, and thus that component of the trial is still ongoing.[180]

HRT: associated effects

HRT impacts on health in a number of ways, both detrimental and beneficial. The pooled results of

TABLE 57 *Relative risk of fracture: HRT versus placebo or no treatment*

Group	Vertebral fracture	All non-vertebral fracture	Hip fracture	Wrist fracture	Other non-vertebral fracture
Women with severe osteoporosis	0.58 (0.26 to 1.30)[a]	0.67 (0.12 to 3.93)[b]	No data	No data	No data
Women with severe osteoporosis, osteoporosis or osteopenia	0.71 (0.24 to 2.12)[c]	0.86 (0.37 to 1.96)[d]	No data	No data	No data
Women with osteoporosis or osteopenia	No data	1.17 (0.41 to 3.28)[e]	No data	No data	No data
Women with osteopenia	No data	No data	No data	No data	No data
Women not selected for low BMD	2.05 (0.71 to 5.97)[f]	0.86 (0.72 to 1.02)[g]	0.87 (0.63 to 1.20)[h]	0.95 (0.58 to 1.53)[h]	0.67 (0.32 to 1.43)[i]

Data are shown as RR (95% CI).
[a] Based on data from Lufkin *et al*. (1992).[173]
[b] Based on data from Lindsay and Tohme (1990)[65] and Wimalawansa (1998).[125]
[c] Based on data from Alexandersen *et al*. (1999)[50] and Lufkin *et al*. (1992).[173]
[d] Based on data from Alexandersen *et al*. (1999),[50] Lindsay and Tohme (1990),[65] Recker *et al.* (1999)[72] and Wimalawansa (1998).[125]
[e] Based on data from Recker *et al*. (1999).[72]
[f] Based on data from Gallagher *et al*. (2001)[58] and Mosekilde *et al*. (2000).[179]
[g] Based on data from Bjarnason *et al*. (2000),[177] Cauley *et al*. (2001),[179] Delmas *et al*. (2000),[55] EPIC study (1999),[71] Eitken *et al*. (1997),[57] Gallagher *et al*. (2001),[58] Genant *et al*. (1997),[59] Herrington *et al*. (2000),[88] Lees and Stevenson (2001),[64] Mosekilde *et al*. (2000),[179] Orr-Walker *et al*. (2000),[69] PEPI trial (1996)[91] and Weiss *et al*. (1999).[75]
[h] Based on data from Cauley *et al*. (2001),[178] EPIC study (1999),[71] Herrington *et al*. (2000),[88] Lees and Stevenson (2001)[64] and WHI trial (2002).[180]
[i] Based on data from the EPIC study (1999)[71] and Herrington *et al*. (2000).[88]

four major RCTs indicate that, relative to placebo, HRT increases the risk of breast cancer (RR 1.27, 95% CI 1.02 to 1.56), stroke (RR 1.27, 95% CI 1.06 to 1.51) and pulmonary embolism (RR 2.16, 95% CI 1.47 to 3.18).[29] It also appears to increase the risk of gallbladder disease.[183] In addition, in unhysterectomised women, oestrogen unopposed by progestogen increases the risk of endometrial cancer.[184,185]

In terms of benefits, pooled RCT data indicate that HRT offers protection against colorectal cancer (RR 0.64, 95% CI 0.45 to 0.92).[29] It also reduces the frequency and severity of hot flushes and night sweats.[186] Thus, of the studies reviewed here, the PEPI study found that, at 1 and 3 years, women in each active treatment group had significantly lower vasomotor symptom levels than those in the placebo group.[187] A large cross-sectional study[188] also found that, after adjusting for relevant variables, current unopposed oestrogen use was associated with a decreased risk in elderly women of reporting six or more depressive symptoms [odds ratio 0.6, 95% CI 0.4 to 0.9]; however, this effect disappeared with the addition of a progestin (odds ratio 0.8, 95% CI 0.5 to 1.4).

Despite the evidence from the WHI study that HRT has a detrimental effect in relation to CHD, meta-analysis of the results of four major RCTs, including the WHI study, has not demonstrated that it has a significant effect on either CHD (RR 1.11, 95% CI 0.96 to 1.30) or endometrial cancer (RR 0.76, 95% CI 0.45 to 1.31).[29] Existing trials are too small to provide information relating to other important, but rarer, conditions such as ovarian cancer.[29] HRT may possibly offer protection against Alzheimer's disease;[189,190] but it does not appear to slow its progress or improve cognitive or functional outcomes in women with the disease.[89]

HRT is also associated with side-effects that reduce the quality of life, such as vaginal bleeding, breast tenderness, headaches, weight gain, mood change

and nausea. These were reported by women taking oestrogen in a number of the studies reviewed in this report, and in some studies were specified as reasons for withdrawal (see Appendix 10, *Table 168* for details). Some of these side-effects, such as vaginal bleeding, may be attributed to the progestogen rather than the oestrogen component of HRT. Thus, a large study reported that breast discomfort was significantly more common in women receiving combination treatment than in those receiving either placebo or unopposed oestrogens.[187]

HRT: continuance and compliance

Continuance is particularly problematic with HRT because of the impact of side-effects on quality of life. In the studies reviewed in this section, the percentage of subjects receiving HRT who completed the protocol ranged from 100% at 1 year[53] to 72% at 3.5 years[72] and 83% at 4 years[125] in women with low BMD, and from 70% at 2 years[55] to 24% at 3 years[177] in women not selected for low BMD. In relation to compliance, in one RCT[47] a lower proportion (86%) of women taking HRT than of women taking raloxifene (95%) reported taking their double-blinded medication regularly ($p < 0.01$), although pill counts did not indicate a significant difference between the groups in this respect. Overall, the available evidence suggests that relatively few women are likely to comply with HRT for the long periods recommended for the prevention of osteoporosis.

Initial compliance with HRT is likely to be higher in women with menopausal symptoms than in those without, and compliance cannot therefore be extrapolated from women prescribed HRT for the relief of menopausal symptoms to asymptomatic women prescribed it for osteoporosis prevention.[191] Three UK studies have specifically looked at continuance in patients prescribed HRT for osteoporosis; one found that 61% remained on treatment at 6 months,[192] while the others found that only 49%[193] and 36% remained on treatment at 1 year.[194] In one of these studies,[192] 55% of those women who were not on HRT at 6 months had never started treatment (33% of these because they viewed it as controversial and 41% because they were concerned about side-effects or breast cancer), while the most common reason given for stopping treatment was withdrawal bleeding, cited by 36% of those who had started therapy.

A retrospective search of a US pharmacy prescription database[147] found that, among members of a large health maintenance organisation (the Kaiser Foundation Health Plan), only 28% of women who had been prescribed oestrogens, for whatever reason, remained on treatment at 24 months. A Spanish RCT[195] randomised to either continuous oestrogen or transdermal oestradiol women who had requested HRT following surgical menopause caused by hysterectomy and bilateral oophorectomy for benign disease. Although a high rate of continuance might have been expected in this group, as they would not have the vaginal bleeding and other side-effects associated with progestogen use, at 5 years only 47% of the oral oestrogen group and 20% of the transdermal oestradiol group remained on treatment. Fear of cancer was a major reason for withdrawal, affecting 18–22% in each group, and 22% of the transdermal oestradiol group withdrew because of erythema in the patch application area.

Side-effects may be diminished, and compliance improved, by changing from one oral oestrogen or progestin to another, from oral to transdermal oestrogen, or from sequential to continuous combined HRT.[157] One RCT that compared sequential with continuous combined HRT[196] found that compliance was higher in the group receiving the continuous preparation (compliance after 1 year 93% versus 66%, and after 2 years 73% versus 49%). Seventeen per cent of the sequential HRT group withdrew because of the return of monthly bleeding and a further 7% because of irregular bleeding, whereas only 3% of women receiving continuous HRT withdrew because of irregular bleeding.

Exercise

Quantity and quality of research available: exercise in postmenopausal osteoporosis and osteopenia

One RCT was identified that studied the effect of exercise in women who had suffered upper limb fracture in the past 2 years, and that reported fracture outcomes.[197] This study compared brisk walking with upper limb exercises. Vertebral fracture was a secondary outcome measure. This study also measured general health-related quality of life, using the NHP, and physical activity, using the London Health and Fitness Questionnaire (for details, see Appendix 10, *Tables 189* and *190*).

In addition, two RCTs[198,199] reported quality of life outcomes in osteoporotic or osteopenic women undertaking exercise programmes. One of these[198] studied the effect of hour-long thrice-weekly exercise classes on postmenopausal women with low BMD: the classes included aerobic exercise,

exercises designed to promote flexibility, and localised anisometric exercises that concentrated on the muscles. Although this study did not report fracture outcomes, it measured participants' psychological well-being using Dupuy's General Well-Being Schedule. The other study[199] studied elderly women with severe osteoporosis, and used a home exercise programme that incorporated a tailored range of motion, strengthening and aerobic conditioning; this was to be performed for at least an hour thrice-weekly. It measured quality of life using a disease-specific osteoporosis quality of life questionnaire that assessed symptoms, emotional and physical function, activities of daily living, and leisure and social aspects. This study was available in abstract form only (for details, see Appendix 10, *Tables 189* and *190*).

The quality of these studies was varied (see Appendix 10, *Table 191*). As one study was published in abstract form only,[199] its reporting quality was poor.

Assessment of effectiveness of exercise in postmenopausal osteoporosis and osteopenia

Vertebral fracture

The brisk walking study reported vertebral fractures only in terms of the group mean total number of fractures per year; thus, the relative risk of fracture could not be calculated. However, there was said to be no significant difference between the treatment groups in terms of vertebral fracture.

Non-vertebral fracture

Clinical fracture rates were said to be similar in the two groups, despite the fact that the brisk walking group experienced significantly more falls than the control group (an excess of 15.2 falls per 100 person-years over the course of the study).

Quality of life

In the brisk walking study, the NHP scores showed only small changes over the study period, with no significant differences between the two groups. However, the brisk walking group showed a significant improvement in physical stamina compared with the control group ($p = 0.04$).[197]

In the study of exercise classes, after controlling for baseline differences between the groups, the exercise programme was found to have a positive effect on well-being ($p = 0.012$). In addition, at 12 months, the back pain reported by the treatment group was lower than that reported by the controls (2.65 versus 3.93, $p = 0.008$).[198] Interim results from the home exercise study showed a trend towards improvement in overall disease-specific quality of life in the exercise group ($p = 0.12$). This improvement was due primarily to improved symptoms ($p < 0.05$) and physical functioning ($p < 0.01$).[199]

Quantity and quality of research available: exercise in postmenopausal women not selected for low BMD

Three RCTs were identified that studied the effects of exercise in postmenopausal women not selected for low BMD, and that reported fracture outcomes.[200–202] One of these[200] studied the effects of an exercise class involving 45 minutes of weight-bearing exercise to music three times a week for three 10-week terms a year on women aged 60–73 years. Both the exercise and control group received 1000 mg supplementary calcium daily.

The second study[203] used a non-progressive exercise programme (warm-ups, stretching, balancing, arm and leg exercises with elastic bands to improve multimuscular movement patterns) which was to be carried out at home at least three times a week for at least 20 minutes in women aged 45–75 years. Subjects were followed for between 1 and 5 years. Fractures were not reported at the end of the original study, but a follow-up study carried out 10 years after the start of the original study reported both vertebral and non-vertebral fractures in the 137 of the original 222 participants who were available for follow-up and had not switched from the control to the exercise group.[201]

The third study[202] investigated whether, 8 years after the end of a 2-year RCT of home-based intensive progressive back exercise, any effect could be seen in terms of muscle strength, BMD and incidence of vertebral fractures in healthy postmenopausal white women who did not have radiographic evidence of vertebral wedging or compression at baseline. At the end of the 2-year trial, the exercise group discontinued the prescribed exercises; all subjects were free to participate in any self-selected physical activities, and were not monitored. Fifty of the original 65 women (77%) returned for evaluation 10 years from baseline, 27 out of 34 (79%) from the exercise group and 23 out of 31 (74%) from the control group. Three had moved away, three had physical impairments, eight could not return for personal reasons and one had died. Although a few subjects had received HRT during the intervening period, none had taken it for more than 4 months. (For further details of these studies, see Appendix 10, *Tables 192* and *193*).

TABLE 58 *Exercise in postmenopausal women not selected for low BMD: comparisons with no treatment: vertebral fracture data*

Study	Exercise regimen	Fracture definition	No. of women in each group suffering vertebral fracture
McMurdo, 1997[200]	45 minutes of weight-bearing exercise three times a week for 30 weeks a year	NA	–
Preisinger, 2001[201]	Home exercise for at least 20 minutes at least three times a week	20%	Exercise: 5/73 Control: 8/64 RR 0.55 (95% CI 0.19 to 1.59)
Sinaki, 2002[202]	Intensive progressive back exercise	20%	Exercise: 3/27 Control: 7/23 RR 0.37 (95% CI 0.11 to 1.25)

TABLE 59 *Exercise in postmenopausal women not selected for low BMD: comparisons with no treatment: non-vertebral fracture data*

Study	Exercise regimen	No. of women in each group suffering vertebral fracture
McMurdo, 1997[200]	45 minutes of weight-bearing exercise three times a week for 30 weeks a year	Exercise: 0/58 Control: 2/60[a] RR 0.21 (95% CI 0.01 to 4.22)
Preisinger, 2001[201]	Home exercise for at least 20 minutes at least three times a week	Exercise: 22/73 Control: 13/64 RR 1.48 (95% CI 0.82 to 2.70)
Sinaki, 2002[202]	Intensive progressive back exercise	None reported

[a] McMurdo MET (personal communication)

None of these studies reported quality of life outcomes, nor were any other relevant studies identified that reported such outcomes.

As reported, the quality of these studies was variable (see Appendix 10, *Table 194*).

Assessment of effectiveness of exercise in postmenopausal women not selected for low BMD

Vertebral fracture

None of the studies reviewed in this section demonstrated that exercise had a statistically significant protective effect in relation to vertebral fracture (*Table 58*). Because all three studies used different forms of exercise regimen, it was not appropriate to pool the results.

Non-vertebral fracture

None of the studies reviewed in this section demonstrated that exercise had a statistically significant protective effect in relation to non-vertebral fracture (*Table 59*). Again, it was not appropriate to pool the results.

Exercise: impact on health

Brisk walking has been shown to be beneficial in reducing high-density lipoproteins in previously sedentary women[204] and the risk of CHD in postmenopausal women aged between 50 and 79 years.[205] However, the trial reviewed above found that brisk walking was also associated with a significantly increased risk of falling.[197]

Exercise: continuance and compliance

The acceptability of exercise as an intervention varied between the studies. In the study of brisk walking,[197] only 165 of the 508 women who were contacted (33%) agreed to take part in the study. Of the 165, 68 (41%) dropped out, almost all in the first year. Dropouts were evenly distributed between the brisk walking group and the control group that 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%). Those women who dropped out tended to be less physically fit than the others, and thus those subjects may have

TABLE 60 *Comparison of interventions with placebo or no treatment: relative risk of morphometric vertebral fracture*

Intervention	Women with severe osteoporosis	Women with severe osteoporosis or osteoporosis	Women with osteoporosis or osteopenia	Women with normal or unspecified BMD
Alendronate	0.53 (0.41 to 0.68)	0.53 (0.42 to 0.67)	0.60 (0.46 to 0.80)	0.34 (0.04 to 3.25)
Etidronate	0.43 (0.20 to 0.91)	No data	No data	No data
Risedronate	0.63 (0.51 to 0.78)	No data	0.53 (0.24 to 1.17)	No data
Raloxifene	0.69 (0.56 to 0.86)	0.65 (0.53 to 0.79)	0.53 (0.32 to 0.88)	No data
Teriparatide	0.35 (0.22 to 0.55)	No data	No data	No data
Calcium	0.55 (0.33 to 0.93)[a]	No data	No data	1.26 (0.65 to 2.46)
Calcium + vitamin D	No data	No data	No data	2.95 (0.21 to 71.21)
Calcitriol	1.02 (0.44 to 2.32)	No data	No data	4.44 (0.50 to 39.03)
HRT	0.58 (0.26 to 1.30)	No data	No data	2.05 (0.71 to 5.97)

Data are shown as RR (95% CI).
[a] May not apply to women with adequate dietary calcium intakes.

been lost who would have benefited most from the intervention. Self-reported compliance with the walking reported by those who completed the study was good, but could not be validated. As the study took place in a relatively poor inner-city population, it may not be typical of other areas.[197]

In one of the studies that used exercise classes,[198] nine women in each group (13% of study entrants overall) were lost to follow-up; in general, these women were in worse physical and psychological health than study completers. A further 17 women dropped out of the exercise group during the course of the exercise programme, largely during the first 3 months; thus, overall, 44 of an initial 70 women in the exercise group (63%) completed the programme. The average assiduity of these 44 women was 73%. In the other study that used exercise classes,[200] 14 out of 58 (24%) dropped out from the exercise group and 12 out of 60 (20%) from the control group. In this study, the average compliance with calcium, based on tablet counts, was 97% in each group.

One of the studies of home exercise[203] defined compliance with regular exercise as exercising at least three times a week for 20 minutes for the study period of between 1 and 5 years (mean 3.0 ± 1.3 years); mean compliance was found to be 48%. At long-term follow-up (mean 7.6 ± 1.1 years), 33% of the exercise group were compliant with the regular exercise.[201] Another study of home exercise has only published interim reports, and has not presented evidence relating to continuance or compliance.[199] The study of home back exercises reported that there had been no dropouts from either group during the 2 years of the study.[202] For a summary of adverse effects, see Appendix 10, *Table 195*.

Conclusions

Impact of interventions on vertebral fracture

Data relating to the efficacy of the interventions reviewed in this report in preventing vertebral fracture are summarised in *Table 60*. As may be seen, calcium has been shown to reduce the risk of vertebral fracture in women with severe osteoporosis and low self-chosen dietary calcium intakes, and alendronate, etidronate, risedronate, raloxifene and teriparatide have all been shown to do so in women with severe osteoporosis with

TABLE 61 *Comparison of interventions with placebo or no treatment: relative risk of non-vertebral fracture*

Intervention	Women with severe osteoporosis	Women with severe osteoporosis or osteoporosis	Women with osteoporosis or osteopenia	Women with normal or unspecified BMD
Alendronate	0.81 (0.65 to 1.01)	0.81 (0.66 to 0.98)	0.74 (0.52 to 1.06)	0.88 (0.47 to 1.64)
Etidronate	1.04 (0.64 to 1.69)	No data	No data	No data
Risedronate	0.67 (0.50 to 0.90)	0.8 (0.7 to 1.0)[a] (author's calculation)	0.55 (0.22 to 1.34)	0.14 (0.01 to 2.60)
Raloxifene	No data	0.92 (0.79 to 1.07)	No data	No data
Teriparatide	0.65 (0.43 to 0.98)	No data	No data	No data
Calcium	No data	No data	No data	No data
Calcium + vitamin D	No data	No data	No data	0.79 (0.69 to 0.92)
Calcitriol	2.50 (0.51 to 12.19)	No data	No data	0.46 (0.17 to 1.27)
HRT	0.67 (0.12 to 3.93)	No data	1.17 (0.41 to 3.28)	0.86 (0.72 to 1.02)

Data are shown as RR (95% CI).
[a] Includes pooled 2.5- and 5-mg data from one study.

adequate calcium intakes (see *Table 50*). Alendronate and raloxifene have also been demonstrated to reduce the risk of vertebral fracture in women with adequate calcium or vitamin D intakes who have osteoporosis with or without fracture. Although subgroup analysis suggests that alendronate does not reduce the risk of vertebral fracture in women with osteopenia, it has been claimed by the manufacturers, on the basis of subgroup analysis of data from the MORE study, that raloxifene does reduce the risk of fracture in such women.

Only raloxifene appears to reduce the risk of vertebral fracture in postmenopausal women unselected for low BMD but, as full data have not been made public, there is some uncertainty regarding this result. There is also evidence to suggest that HRT reduces the risk of clinical vertebral fractures in such women.

Impact of interventions on non-vertebral fracture

Data relating to the efficacy of the interventions reviewed in this report in preventing non-vertebral fracture are summarised in *Table 61*. Calcium plus vitamin D has been shown to protect against non-vertebral fracture in elderly women with low dietary calcium intakes, some of whom were also deficient in vitamin D; although these women were not selected for low BMD, their age was such as to suggest that the majority could be expected to have been suffering from osteoporosis or osteopenia. Only risedronate and teriparatide have been demonstrated to reduce the risk of non-vertebral fracture in women with severe osteoporosis with adequate calcium intakes; alendronate has been shown to do so in women with osteoporosis with or without fracture and with adequate calcium or vitamin D intakes.

As hip fracture is arguably the most important non-vertebral fracture in terms of its health impact, data relating to the efficacy of the interventions reviewed in this report in preventing hip fracture are summarised in *Table 62*. Calcium plus vitamin D has been shown to protect against hip fracture in elderly women with low dietary calcium intakes, some of whom were also deficient in vitamin D; although these women were not selected for low BMD, their age was such as to suggest that the majority could be expected to have been suffering from osteoporosis or osteopenia. Only risedronate has been

TABLE 62 *Comparison of interventions with placebo or no treatment: relative risk of hip fracture*

Intervention	Women with severe osteoporosis	Women with severe osteoporosis or osteoporosis	Women with osteoporosis or osteopenia	Women with normal or unspecified BMD
Alendronate	0.49 (0.24 to 1.01)	0.46 (0.23 to 0.91)	0.68 (0.30 to 1.54)	Insufficient data
Etidronate	0.50 (0.05 to 5.34)	No data	No data	No data
Risedronate	0.60 (0.42 to 0.88)	0.66 (0.48 to 0.89)	No data	No data
Raloxifene	No data	1.12 (0.65 to 1.95)	No data	No data
Teriparatide	0.50 (0.09 to 2.73)	No data	No data	No data
Calcium	No data	No data	No data	No data
Calcium + vitamin D	No data	No data	No data	0.72 (0.59 to 0.88)[a]
Calcitriol	No data	No data	No data	No data
HRT	No data	No data	No data	0.67 (0.32 to 1.43)

Data are shown as RR (95% CI).
[a] May not apply to women with adequate dietary calcium and vitamin D_3 intakes.

demonstrated to reduce the risk of hip fracture in women with severe osteoporosis with adequate calcium intakes; alendronate and risedronate have been shown to do so in women with osteoporosis with or without fracture and with adequate calcium or vitamin D intakes.

Summary

Calcium, with or without vitamin D, has been shown to reduce the risk of both vertebral and non-vertebral fracture, including hip fracture, relative to placebo or no treatment, in women with low dietary intakes of those nutrients who either have severe osteoporosis or, because of their age, are at high risk of fracture. There is no evidence that supplementary calcium, with or without vitamin D, has an antifracture effect in women not selected for low dietary calcium intakes, and direct comparison suggests that calcitriol is more effective than calcium alone in preventing vertebral and non-vertebral fracture in such women.

Only alendronate, risedronate and teriparatide have been shown to reduce the risk of both vertebral and non-vertebral fracture, relative to placebo or no treatment, in women with severe osteoporosis or osteoporosis and with adequate calcium intakes; alendronate and risedronate have also been shown to reduce the risk of hip fracture in such women. However, none of these drugs has been demonstrated, in direct comparisons, to be significantly more effective than either each other or the other active interventions reviewed in this report. Moreover, it is undesirable to suggest, on the basis of indirect comparisons, that one intervention is more effective than another. Although in this report every effort has been made to ensure that only data from studies with comparable populations have been pooled, it is not possible to guarantee the comparability of the populations receiving the different interventions, and therefore the results of indirect comparisons are inevitably less secure than those of direct comparisons. However, with that caveat, the pooled data suggest that alendronate, risedronate and teriparatide are all associated with similar reductions in risk of vertebral and non-vertebral fracture, as the confidence intervals around the relative risks all overlap (*see Tables 60* and *61*). Thus, there is no evidence that any one of these three interventions is more effective than any other in reducing the risk of vertebral and non-vertebral fracture in women with severe osteoporosis or osteoporosis and with adequate calcium intakes. However, while it has been shown that alendronate and risedronate also reduce the risk of hip fracture in such women (see *Table 61*),

the studies of teriparatide were not sufficiently large to demonstrate an effect on hip fracture.

Raloxifene has been shown to reduce the risk of vertebral fracture in women with severe osteoporosis, osteoporosis or osteopenia, but there is no evidence that it reduces the risk of non-vertebral fracture.

Although there is also evidence from a large, high-quality study to suggest that HRT reduces the risk of both clinical vertebral fracture and non-hip, non-vertebral fractures in women not selected for low BMD, this study was stopped early in women receiving oestrogen plus progesterone because the increased risks of breast cancer, CHD, stroke and pulmonary embolism outweighed the benefits associated with the reduction in the risk of fracture, and the possible reduction in the risk of colon cancer. It does not, therefore, seem appropriate to offer long-term HRT with the primary aim of osteoporosis prevention to women who are not at high risk of fracture; in women at high risk, the balance of risks and benefits should be carefully assessed for each individual woman.

In interventions intended for long-term prevention rather than for the immediate amelioration of a health problem, the impact of those interventions on quality of life takes on a particular importance. In this context, it is important to differentiate between the quality of life impact caused by the antifracture efficacy of an intervention and any general quality of life impact that it may have independently of that antifracture efficacy. No studies were identified that measured quality of life in postmenopausal women taking four of the five interventions shown to reduce the risk of osteoporotic fracture (calcium, vitamin D, risedronate and teriparatide); one study indicated that alendronate was associated with improvements in general health-related quality of life as measured by the NHP. Some of the improvement seen in this study (e.g. in pain and physical ability) may be due to alendronate's impact on vertebral fracture.

Calcium and vitamin D are both available as oral preparations that are easy to take; calcium may be associated with mild gastrointestinal side-effects and a slightly increased risk of symptomatic renal stones. By contrast, the dosing regimen required to maximise the uptake of alendronate and risedronate, and to reduce the risk of upper gastrointestinal side-effects, is demanding of the patient, although lifestyle disruptions can be minimised by the use of the newer once-weekly formulations that appear to be therapeutically equivalent to the daily dose. Teriparatide has to be injected: although this may seem less convenient than an oral preparation, it does not have the lifestyle impact of the dosing regimen required for the bisphosphonates.

Alendronate and risedronate have both been associated with upper gastrointestinal side-effects, but there is evidence to suggest that these may not be significantly more common in women taking alendronate than in other women of similar age and health status. The side-effects of teriparatide include mild discomfort at the injection site, and possibly also nausea and headache.

Treatment with teriparatide is limited to 18 months, compared with the apparently open-ended treatment with the bisphosphonates and with calcium and vitamin D.

Chapter 4
Economic analysis

The appraisal team reviewed the existing evidence, taken to be the submission documents,[38–40,42,43] using the quality assessment checklist presented by Drummond and Jefferson.[206] These documents are contained in Appendix 11.

The model constructed by the appraisal team is presented, with results and discussion.

Methods for economic analyses

The appraisal team constructed a model to estimate the cost-effectiveness of osteoporosis interventions. The key inputs to this model are the efficacy data for each intervention in terms of the ability to reduce the incidence of hip, vertebral, wrist and proximal humerus fractures. The model calculates the number of fractures that occur and provides as output data the costs associated with osteoporotic fractures, and the quality-adjusted life-years (QALYs) accrued by a cohort of 100 osteoporotic women, with each fracture being detrimental to health. When the costs of the intervention are included, the marginal cost compared with no treatment (assumed to be a sufficient intake of calcium and vitamin D) can be calculated. When this figure is divided by the gain in QALYs a cost per QALY ratio can be calculated.

In addition to osteoporotic fractures, the conditions of breast cancer and CHD were modelled, as some interventions have been shown to affect the risk of these conditions.

This section is divided into the following subsections:

- the structure of the model, which will discuss the formulation of the appraisal model and the modelling assumptions made
- the population of the model
- the health state values assumed for each event contained within the model
- the costs associated with each event contained within the model
- the cost-effectiveness ratios calculated for each intervention.

Structure of the model

The model used to calculate cost-effectiveness ratios is an updated version of Sheffield Health Economic Model for Osteoporosis (SHEMO) that was reported in Kanis and colleagues.[207] This model deviates from approaches used previously, which were based on cohort analyses using the standard techniques of decision analysis and Markov models.[208,209]

The basic design of SHEMO is similar, in many ways, to the conventional Markov models used in the area of osteoporosis, where 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, it differs in a crucial respect to the conventional cohort Markov design since individual patients pass through the model one at a time. The model simulates for each patient whether or not an event occurred in the forthcoming year and then a mean estimate is taken of costs and QALYs for each cohort.

The full patient history is recorded and factors such as prior fractures and current residential status can be used therefore to determine the likelihood of events in the next period. Following the simulated event, the quality of life of the patient and costs incurred in that period are calculated. These values have taken into account any residual costs or quality of life impacts from previous fractures, breast cancer or CHD. The model simulates at 1-year intervals until either the patient dies or a user-defined time horizon, which was set to 10 years for the majority of the economic analyses, has been reached. This process is repeated until a selected number of 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. Examples are given in Appendix 12.

Modelling assumptions

For the purpose of this report, the transition states between which patients can move were limited to fracture states (hip, wrist, vertebral, proximal humerus and death due to hip fracture), CHD

states (non-fatal event and fatal events), breast cancer states (non-fatal breast cancer and fatal breast cancer) and death from other causes. A separate variable was used to indicate the residential status of the patient, either community or nursing home. A 'no event' state, which signifies that the patient did not have an event that would be associated with a change of state, was also included. The transition probability for the no event state was calculated as 1 minus the summation of the transition probabilities for the remaining states.

Diseases where possible links with osteoporosis treatments may exist, such as Alzheimer's disease, venous thrombolic events and cancer, were excluded from this study.

The characteristics of the population to be analysed are flexible. The age, *T*-score and prior history of the population are all user defined. For this report the focus was on those with severe osteoporosis (osteoporosis and with a documented fracture) and those with osteoporosis alone.

For the purpose of this report, selected patient groups were chosen for analysis, for example 60-year-olds suffering established osteoporosis and a *T*-score of –2.5 SD, although a user can enter whatever patient groups are desired.

The basic probabilities for moving from transition state to transition state have been taken from epidemiological data, where possible from the UK, and transformed where appropriate.

Having established the transition probabilities, the model simulates the experiences of each patient in the cohort under no treatment. Outputs are the number of life-years gained (discounted at 1.5% per annum), the number of QALYs gained (also discounted at 1.5% per annum) and the discounted costs incurred (discounted at 6% per annum).

As a patient moves into a transition state, there is an initial one-off cost incurred and an ongoing cost incurred that is assumed to last until the end of the simulation. By using such a methodology, states with high ongoing costs can be distinguished from those where the costs incurred are all in the initial year. In circumstances where a patient has already suffered the state before, it has been assumed that only the one-off costs will be incurred, with the ongoing costs from that state remaining constant. For example, if the consequences of a vertebral fracture comprised an initial cost of £600 and a recurrent cost of £300 per year, a further vertebral fracture in the same individual would cost a further £600; however, the recurrent costs would not increase from £300 per year. This may underestimate the costs involved, but few data could be found on the additional ongoing costs of second events.

When a patient moves into a transition state this affects the patient's quality of life. It has been assumed that there will be a QALY multiplier effect within the first year and a QALY multiplier that will last for the remaining years of the simulation. By using this methodology, states from which the patient will recover but not to the level prior to the event can be modelled. It is assumed that when a patient suffers a transition state for a second or more time, only the initial year reduction in quality of life will be taken into consideration. It is noted that in some cases this will underestimate the loss in QALYs, for example second hip or wrist fractures on a different side to the first, or a second vertebral fracture. However, owing to a lack of data the approach of assuming no extra residual QALY loss from a second incident was taken.

Having established a baseline 'no treatment' cost for the cohort, the incremental effects from pharmaceutical treatments have been calculated. The efficacy of each treatment is modelled by the use of relative risks in entering a transition state. It is expected that a cohort using a treatment with a relative risk 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. For each intervention the relative risks were drawn from the meta-analysis undertaken.

The effect of treatment on fracture probability was assumed to be instantaneous and to persist unchanged throughout the treatment period. A 5-year treatment period was assumed, which corresponds to the duration of exposure in RCTs, particularly those undertaken in the past 10 years. In addition to the treatment relative risk, the model incorporates fall times, which have been defined as the time from when the treatment is stopped to the time that the relative risk returns to 1 compared with no treatment. It is assumed that the relative risk returns to 1 in a linear manner during the fall time. The incorporation of fall times is important in accurately modelling those treatments that are thought to have long residual effects. The fall time was assumed to be zero for effects on breast cancer and CHD.

Each treatment option was been assigned costs additional to drug acquisition, namely GP visits, assumed to be two per annum, and BMD scans, assumed to occur in year 2 and year 5 of treatment. Lack of compliance is modelled assuming that the patient incurs 3 months of drug costs but receives no health benefits.

It was assumed that for a year in which death occurred, the QALYs gained are half those for the prior year, that costs are incurred equal to half of the ongoing annual costs, and that only one half of the drug acquisition cost is paid. The exception to this rule is when the patient is simulated to have died from breast cancer. Owing to the expected 2-year period before death, costs and QALYs are accrued for a further 2 years at the levels from the onset of the breast cancer episode.

The results from the individual patient model were converted into a meta-model using Gaussian process techniques.[210] The formulation of this model is discussed in Appendix 12.

Population of the model

Population start age

For the purposes of this report, women were analysed separately at the ages of 50, 60, 70 or 80 years.

Fracture status of the population upon entry to the model

This report focuses on two broad patient groups, those with osteoporosis and those with severe osteoporosis. By definition, the former group enters the model with no prior fracture; however, those in the latter group have suffered a previous fracture.

An estimate of the distribution of previous fractures for a group suffering from severe osteoporosis was made using the incidence of fracture depicted in *Figure 2*. For each year above age of 50 years the expected cumulative number of fractures per site was calculated. These data were then proportioned to provide the percentages shown in *Table 63*. For example, 8% of osteoporotic fractures up to the age of 50 years were hip fractures. This figure rose with age and hip fractures accounted for 21% of all osteoporotic fractures at the age of 80 years. Thus, in each cohort of 100 individual patients at 70 years of age, 11% are assumed to have had hip fractures, 19% vertebral fractures, 56% wrist fractures and 14% proximal humerus fractures.

This approach is likely to cause some bias, owing to patients with more than one prior osteoporotic fracture. For example, in an extreme case, where all 80-year-olds had one prior hip, vertebral, wrist and proximal humerus fractures, 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.

TABLE 63 *The assumed distribution of prior fractures by age*

	Age (years)			
Fracture site	**50**	**60**	**70**	**80**
Hip	8%	8%	11%	21%
Vertebra	31%	22%	19%	22%
Wrist	50%	57%	56%	43%
Proximal humerus	11%	13%	14%	14%

Initial BMD score of the population

It was assumed that the *T*-score of patients entering the model would be at the threshold of osteoporosis (–2.5 SD). Sensitivity analyses were conducted to estimate the change in cost-effectiveness ratios given a higher *T*-score.

Discount rates

The discount rate for costs was set to 6% per annum, in accordance with published guidelines. The default discount rate for QALYs was set to 1.5% per annum.[211]

Time horizon of the model

The time horizon of the model was constrained to a 10-year period, owing to the uncertainty around future medical costs and technologies that may become available, and the gap in the evidence base concerning the effect of fractures on quality of life after a period of 10 years. The presented results, however, do take into account the expected number of future QALYs lost owing to mortality within the time horizon. This methodology is explained in Appendix 13.

Calculating the basic transition probabilities for each state within the model

This section describes the default risks for women with a *T*-score of –2.5 and without prior fracture. The following section details how individual events would alter the basic transition probabilities.

Osteoporotic

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

For patients in this state, the probability is zero, with 'no event' signifying that the patient remains osteoporotic. All patients with osteoporosis will start the model in this state. Patients with severe osteoporosis will never be in this state and will be distributed across the fracture sites at the start of the model in accordance with *Table 63*.

Fracture risks
The estimated risks for women with a *T*-score of –2.5 SD and no prior fracture are shown in *Table 5*.

Death due to hip fracture
The percentages of deaths 1 year after a hip fracture that were assumed to be directly attributable to the fracture are given in *Table 7*.

First entry to nursing home after hip fracture
The percentage of women who are assumed to move from community living to a nursing home following a hip fracture is given in *Table 8*.

Sustained a non-fatal CHD event
The assumed risks of suffering a non-fatal CHD event are contained in *Table 9*.

Death due to CHD
The assumed risks of suffering a fatal CHD event are contained in *Table 9*.

Risk of contracting breast cancer
The assumed risks of contracting breast cancer are given in *Table 10*. These data have been adjusted for the association between low BMD and decreased risk of breast cancer.[32]

Death due to breast cancer
The risk of dying from breast cancer is considered on page 10. These data have been adjusted for the association between low BMD and decreased risk of breast cancer.[32]

Death due to other causes
These were computed from interim life tables and adjusted for deaths due to CHD and breast cancer. Note that excess mortality is assumed for low BMD, as reported by Browner and colleagues.[35] The data are presented in *Table 11*.

Events that impact on the transition probabilities of other events
The model has the facility to allow prior patient states to influence the transition matrix. This is needed since the risk of a secondary fracture, at any site, is higher than the risk before an initial fracture.

All fracture states
A prior fracture substantially increases the risk of subsequent fractures. The meta-analysis of Klotzbuecher and colleagues[15] was used, with some additional assumptions. The increased risks due to prior fractures are given in *Table 2*.

Review of health state values associated with osteoporosis

A review was undertaken to identify the best available utility estimates. The health state utility values (HSUVs) include osteoporosis, severe osteoporosis, hip fracture, vertebral fracture, wrist fracture, proximal humerus fracture, breast cancer and CHD. Previous economic evaluations of the prevention and treatment of osteoporosis have relied on the use of assumptions or judgements obtained from expert panels, such as the recent review undertaken by the National Osteoporosis Foundation (NOF),[212] rather than use empirical evidence to value these health states. This has been recognised as one of the main weaknesses of work in this area.[213,214] Recently, several studies have elicited health state valuations for many of these states using recognised preference-based measures of health-related quality of life, such as the EuroQol 5 Dimensions (EQ-5D) or (HUI-III), or direct preference elicitation techniques such as time trade-off (TTO) or standard gamble. The purpose of this section is to update an existing systematic review[207] to identify the best available HSUV associated with the consequences of established osteoporosis and its treatment.

Identifying the studies
The review drew on papers identified from a series of systematic searches undertaken for an HTA review of treatment for osteoporosis.[207] These include 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, breast cancer and CHD. Studies were identified through searches of electronic databases, handsearching, citation searching, reference list checking and those known to researchers involved in the HTA review (see Appendix 8). For comparison, normative HSUV data have been presented by age group for the UK.[215]

Results
The HSUVs for fractures were found to differ considerably from the assumptions used in previously published economic evaluations in this area (*Table 1*). The value used in the NOF report[212] for vertebral fractures of 0.97, for example, compares with values ranging from 0.31

TABLE 64 *HSUVs used in the model*[a]

Health state	Value	Source
Established osteoporotic	Use values associated with the type of fracture (see below)	
Hip fracture	First year: 0.83 (95% CI 0.72 to 0.96) Second and subsequent years: 0.925 (95% CI 0.81 to 1.05)	Murray *et al*., 2002[216]
Nursing home	0.4	NOF, 1998[212]
Vertebral fracture	First year: 0.83 Second and subsequent years: 0.93	Oleksik *et al*., 2000[217]
Wrist fracture in first year	First year: 0.981 (95% CI 0.978 to 0.986) Second and subsequent years: 1	Dolan *et al*., 1999[218]
Proximal humerus	First year: 0.794 Second and subsequent years: 0.973	Kanis *et al*., 2004[251]
Breast cancer	0.62 (Assumed range 0.33 to 0.84)	Hutton *et al*., 1996[219]
CHD	0.85	Assumption

[a] These values are the multipliers for the proportionate effect of a fracture on HSUVs in the first and, when possible, for subsequent years.

to 0.91. These empirical estimates were obtained using a recognised preference elicitation procedure, but there is a considerable range of values for each of the health states. This range reflects a number of differences in the derivation of the estimates including: the source of values, what is being valued, how long after the fracture the assessment was undertaken, the valuation technique and the anchor states used in the valuation task. The selection of estimates for the model involves both technical and value judgements, which are discussed in Appendix 14.

Selection of values for the model

The justification for the final selection of states used in the model is given in Appendix 14 and shown in *Table 64* with 95% confidence intervals. The values are 'multipliers' for the proportionate effect that the fracture (or CHD and breast cancer) has on an HSUV. The multiplier should be applied to the age/gender HSUVs of patients without a fracture being used in the model.

Cost data

This report uses the costs reported in Kanis and colleagues,[207] having inflated, where applicable to 2001/02 prices.[220] The costs of fatality were inadvertently omitted from the parameters that were varied, thus these have remained constant at the 1999/2000 value. This error is not expected to have significant impact on the cost-effectiveness ratios, but will slightly favour no treatment over interventions with beneficial effects on hip and breast cancer.

The costs presented were estimated following a systematic literature review. These were divided where possible, into first year costs and costs that are assumed to be paid for the remainder of a patient's lifetime. The costs were also weighted by patient age, based on data regarding the length of stay in hospital and patient age. The full methodology is presented in detail by Kanis and colleagues,[207] with the updated costs given in *Table 65*. These costs were used as the input to the cost-effectiveness model.

The cost of a GP visit was estimated at £17.50 and the cost of a BMD scan at £34.

Calculation of the cost-effectiveness of each intervention

Having formulated a statistical relationship via Gaussian process modelling techniques, an extensive analysis of the uncertainty relating to the efficacy of each intervention could be undertaken. For each treatment, 1000 values for efficacy of each type of fracture (and breast cancer for raloxifene) were selected by Monte Carlo methods, assuming log-normal distributions and assuming independence in the relationship between the selected relative risks. From these samples the

TABLE 65 *Costs of each event, by age and by initial and subsequent years*

State	Costs (£), 50 years of age		Costs (£), 60 years of age		Costs (£), 70 years of age		Costs (£), 80 years of age	
	1st year costs	Subsequent annual costs	1st year costs	Subsequent annual costs	1st year costs	Subsequent annual costs	1st year costs	Subsequent annual costs
Hip fracture	4,880	–	4,880	–	6,139	–	8,080	–
Hip fracture leading to nursing home entry	29,620	22,298	29,620	22,298	30,857	22,940	32,795	23,897
Death due to hip fracture	8,666	–	8,666	–	8,666	–	8,666	–
Vertebral fracture	451	210	451	210	510	210	550	210
Wrist fracture	340	–	340	–	340	–	554	–
Proximal humerus fracture	969	–	969	–	969	–	1,584	–
Non-fatal breast cancer	8,541	–	8,541	–	8,541	–	8,541	–
Fatal breast cancer	10,981	–[a]	10,981	–[a]	10,981	–[a]	10,981	–[a]
Non-fatal CHD	2,058	665	2,058	665	2,058	665	2,058	665
Fatal CHD	2,160	–	2, 160	–	2,160	–	2,160	–

[a] It is assumed that the subsequent annual costs specific to the patient will be incurred in the 2 years for which the patient is assumed to live before death.

TABLE 66 *Cost for each intervention per annum*

Intervention	Assumed dosage	Cost per annum (£)
Alendronate	10 mg per day	301
Risedronate	5 mg per day	284
Etidronate	400 mg per day for 14 days in a 90-day cycle	163
Raloxifene	60 mg per day	257
Teriparatide	20 μg per day	3546
Oestrogen	625 μg per day	58

Gaussian model generated 1000 cost and QALY estimates. These formed the basis for the estimated mean cost per QALY compared with no treatment and the 90% confidence intervals.

The mean cost per QALY is calculated as the mean cost difference divided by the mean QALY difference for the 1000 points sampled from the intervention efficacy and the estimated value at no treatment. Confidence intervals were calculated by ranking the 1000 cost per QALYs from most favourable to the intervention to least favourable, and cropping the data symmetrically to form the required interval.

These confidence intervals reflect genuine uncertainty around the estimate rather than random noise. As the results were generated from a statistical relationship, any differences in the mean cost per QALY and the confidence intervals between treatments are due solely to the relative risks around efficacy.

The advantage of the Gaussian process technique is that given the same starting assumptions, the results for a new drug with defined relative risks can be instantly calculated with the benefits associated with an individual patient methodology retained.

The cost-effectiveness analysis stopped after a time horizon of 10 years. In order that the loss of life due to fractures or breast cancer was taken into consideration the expected QALY of an average person from the end of the model until death was calculated. This was then multiplied by the number of hip mortalities that were expected to be saved by the intervention, or expected to be caused when the hip fracture relative risk was greater than one. This same methodology was also applied to the expected mortalities from breast cancer. (see Appendix 13 for the full methodology). A similar methodology for assessing the effect of associating mortality with vertebral fractures is also contained in Appendix 13.

Scenario analyses

The default analysis for each treatment was the efficacies taken from the meta-analysis of RCTs. Where there were wide confidence intervals that span unity, a secondary analysis was performed assuming that the intervention has no effect on that condition. Where there was a paucity of RCT data and observational data existed, these were also examined.

Costs of the interventions

The cost for each intervention is given in *Table 66*. The interventions of calcitriol and calcium were not evaluated owing to the lack of evidence showing a significant effect on fracture rates.

Results

The results section has been divided into two categories: analyses assessing patients who have suffered a previous fracture, and those patients who have not. These categories have been further subdivided. One set of analyses concentrated on women at the threshold of osteoporosis (a *T*-score of –2.5 SD). Estimating the cost-effectiveness at this threshold put a maximum limit on the cost per QALY value for women with osteoporosis. A second analysis was conducted assuming that the fracture risks are double those seen in women at the threshold of osteoporosis, which may be due to lower *T*-score values (–3.22 SD) or to non-skeletal factors, such as smoking or a history of maternal hip fracture. The cost-effectiveness ratio, in terms of cost per QALY, will be significantly better in this group for each intervention.

Calculation of cost per QALY values was undertaken at the ages of 50, 60, 70 and 80 years. However, it must be stressed that the results at the extremes of these age ranges may be questionable since within RCTs of osteoporosis interventions these patients represent a small minority. Indeed, an RCT[221] that assessed the efficacy of risedronate in women aged over 80 years, but not selected

TABLE 67 *Costs incurred and QALYs accrued from no treatment in women with previous fractures and T-scores of –2.5*

Age (years)	Cost incurred (£)	QALYs accrued
50	103,572	711.97
60	149,267	683.12
70	186,818	550.43
80	488,050	391.42

owing to prior vertebral fracture or BMD status, showed a non-significant benefit in preventing fractures. The applicability of results at 80 years of age may be questionable, in that an increasing incidence of falls may reduce the efficacy of any intervention.

The cost-effectiveness values of each intervention were calculated against an option of no treatment, with the assumption that all women had sufficient intakes of calcium and vitamin D. This value allowed an evaluation of whether the intervention is worth purchasing compared to the no treatment option, given various cost per QALY thresholds.

For those interventions that may be deemed cost-effective, further analyses were conducted to rank the order of cost-effectiveness at the specified cost per QALY threshold by calculating the incremental cost-effectiveness ratio (ICER) between pairs of drugs.

Illustrative analyses were performed assuming a cost per QALY threshold of £30,000; the results presented may change were different threshold values used.

Estimated cost-effectiveness ratios for each intervention in women with severe osteoporosis and with a *T*-score of –2.5

No treatment (intake of calcium and vitamin D assumed adequate)

A measure of the cost-effectiveness of an intervention is to compare it with a no treatment option, which for osteoporosis is assumed to be calcium and vitamin D supplements. To calculate this cost-effectiveness ratio the estimated costs and QALYs associated with a no treatment option must be calculated. These are presented in *Table 67*. As expected, the costs incurred increase with age owing to the increase in fracture incidence. Conversely, the QALYs accrued decline as a consequence of the increased fractures, increased mortality rates and the lower utility assumed per annum as a woman ages.[215] All the results presented are summated for a cohort of 100 women.

For each intervention the costs incurred and the QALYs accrued are estimated, based on Monte Carlo sampling for the efficacy distribution. The marginal costs incurred and QALYs accrued are then calculated by subtracting those associated with no treatment. Dividing the marginal cost by the marginal QALY gives the expected cost per QALY ratio. A 95% confidence interval was estimated from the Monte Carlo analyses. The primary efficacy data were taken from RCTs; however, where there is ambiguity over from which population the efficacy data should be taken, or where the confidence interval for the relative risk is very wide and spans unity, the results from a number of different scenarios are given.

The treatment duration for all interventions bar teriparatide was assumed to be 5 years, with an associated fall time of 5 years. For teriparatide, the treatment duration was assumed to be 18 months, followed by 42 months of full efficacy and a fall time of 1 year.

Where an intervention is estimated to be cost-saving and produces an increase in QALYs, the intervention is said to be dominating compared with no treatment. Where the costs accrued are greater, but there has been a reduction in QALYs, the intervention is said to be dominated compared with no treatment.

Alendronate

The efficacy data for alendronate were seen to be comparable in women with severe osteoporosis alone and in women with severe osteoporosis and osteoporosis combined. The efficacy data from the combined group of severe osteoporosis and osteoporosis were used (*Table 68*) since the point values are similar and the confidence intervals are narrower owing to the larger number of patients analysed.

The reduced cost per QALY at 70 and 80 years is to be expected for interventions that reduce hip and vertebral fractures, which have the greatest incidents at these ages. The cost per QALY at 60 years is greater than that at 50 years of age, owing to the lower number of vertebral fractures expected at this age (*Table 69*).

A cost-effectiveness acceptability curve (CEAC) for one intervention is a graphical method of displaying the probability that the cost per QALY of an intervention is equal to, or below, a given threshold level, compared with no treatment. This approach allows for some quantification of the uncertainty surrounding the mean cost per QALY value for an intervention. For example, in *Figure*

TABLE 68 *Assumed efficacy of alendronate in women with previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.53 (0.42 to 0.67)	0.46 (0.23 to 0.91)	0.48 (0.31 to 0.75)	Assumed no effect

TABLE 69 *Cost-effectiveness of alendronate in women with previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (95% CI)
50	252,496	716.40	148,924	4.43	33,621 (23,871 to 77,272)
60	288,019	686.61	138,752	3.49	39,733 (28,022 to 72,990)
70	281,796	556.04	94,979	5.61	16,934 (9,742 to 44,277)
80	492,576	397.91	4,527	6.49	697 (Dominating to 30,663)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

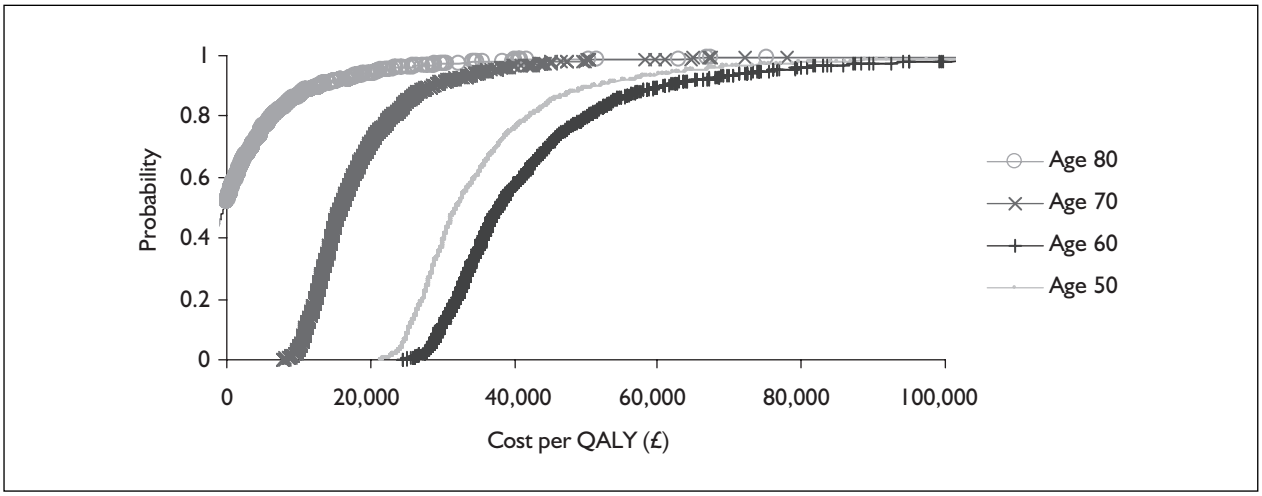

FIGURE 33 *CEACs for alendronate in women with previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

33, it is estimated that at 70 years of age the probability that the cost per QALY would be below £20,000 is approximately 70%. The value at which a line intersects the *y* axis is the proportion that a treatment is dominant. In *Figure 33*, at the age of 80 years the treatment is dominant approximately 50% of the time.

It is seen that at 80 years of age the cost per QALY value is very rarely above £20,000.

Risedronate

The efficacy data for risedronate seen in women with severe osteoporosis were used for this analysis (*Table 70*).

The cost per QALY ratio decreases as the age increases owing to the greater incidence of fractures (*Table 71*). The cost per QALY values range from £46,596 at 60 years to £5002 at 80 years of age.

TABLE 70 *Assumed efficacy of risedronate in women with previous fractures and* T*-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis or osteoporosis)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.63 (0.51 to 0.78)	0.60 (0.42 to 0.88)	0.68 (0.43 to 1.08)	0.46 (0.23 to 0.94)

TABLE 71 *Cost-effectiveness of risedronate in women with previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (95% CI)
50	248,703	715.40	145,131	3.43	42,268 (30,154 to 78,619)
60	284,666	686.02	135,399	2.91	46,596 (33,166 to 84,694)
70	290,414	555.14	103,596	4.71	22,001 (13,991 to 43,226)
80	514,540	396.70	26,490	5.28	5,022 (Dominating to 27,253)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

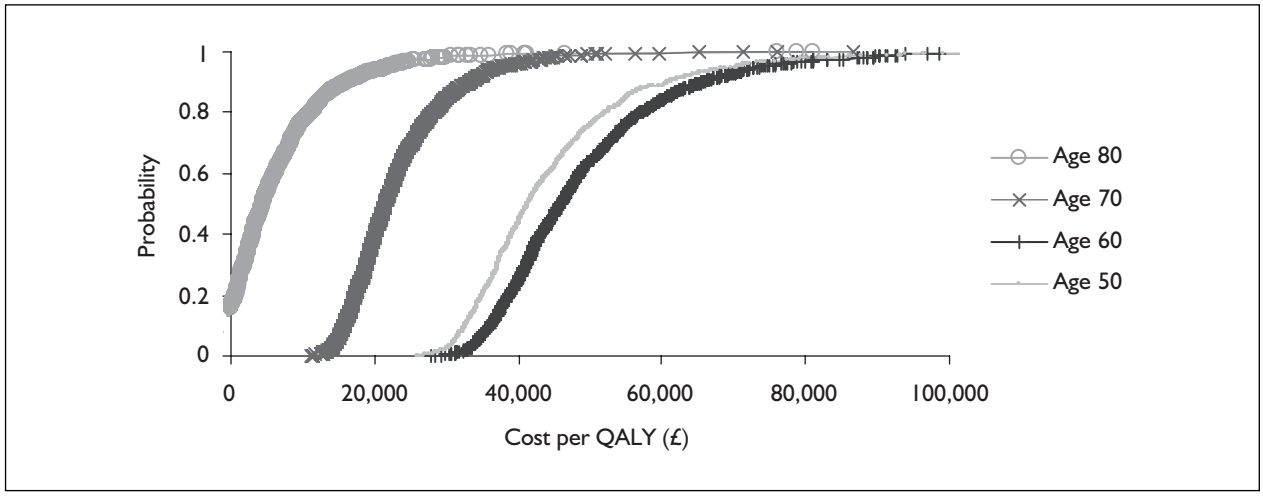

FIGURE 34 *CEACs for risedronate in women with previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis)*

Figure 34 shows that the cost per QALY ratio at 80 years of age is very rarely greater than £20,000.

Etidronate

Efficacy data on preventing vertebral fractures for etidronate were similar for women with severe osteoporosis and women with severe osteoporosis, osteoporosis or osteopenia. The data from the combined group were used (*Table 72*) owing to the reduced confidence intervals. Because of the extremely wide confidence intervals for efficacy around hip fractures (0.05 to 5.34) and other non-vertebral fractures (0.12 to 3.82), it was assumed that the drug has no effect on these sites.

Etidronate was more cost-effective at 70 years than at 80 years of age, owing to the greater incidence of vertebral fractures at 70 years, which is the only fracture site that etidronate has been assumed to affect (*Table 73*). At 70 years the average cost per

TABLE 72 *Assumed efficacy of etidronate in women with previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis or osteoporosis assuming no effect on non-vertebral fractures)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.40 (0.20 to 0.83)	Assumed no effect	Assumed no effect	Assumed no effect

TABLE 73 *Cost-effectiveness of etidronate in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis, and no effect on non-vertebral fractures)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (95% CI)
50	209,100	713.30	105,528	1.34	78,960 (62,236 to 123,556)
60	252,998	684.24	103,730	1.16	89,079 (70,276 to 139,219)
70	276,196	553.44	89,378	3.01	29,742 (22,952 to 47,849)
80	563,001	392.97	74,951	1.54	48,521 (36,882 to 79,718)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

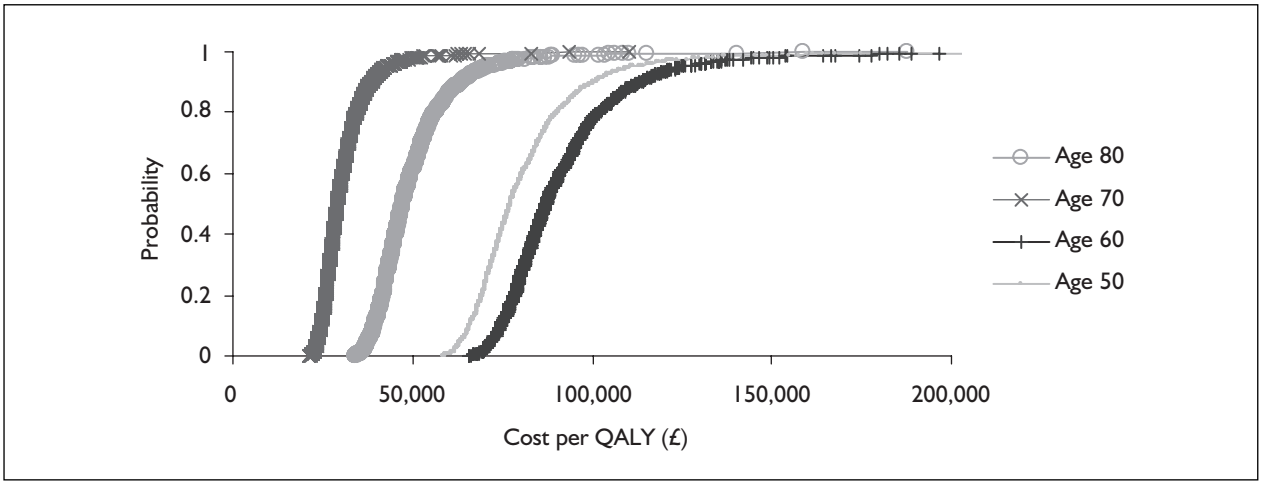

FIGURE 35 *CEACs for etidronate in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis, and no effect on non-vertebral fractures)*

QALY of etidronate was below £30,000, at 80 years the cost per QALY was greater than £40,000, and the value was greater than £70,000 at both 50 and 60 years of age.

Additional analyses were undertaken for etidronate, using observational data from van Staa and colleagues.[222] In line with the etidronate submission,[38] the analyses used a 15% reduction in hip fractures and an 8% reduction in wrist fracture. In these analyses the cost per QALY ratios fell to £43,903, £51,182, £18,554 and £13,226 at the ages of 50, 60, 70 and 80 years, respectively. The efficacy figures were the upper bound of the reported 95% confidence intervals. These were taken as non-varying parameters and as such a confidence interval around the cost-effectiveness of etidronate was not calculated for this scenario.

The CEACs are quite tight (*Figure 35*). However, excluding the results from 70 years of age,

TABLE 74 *Assumed efficacy of raloxifene in women with previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis or osteoporosis, and assuming no effect on non-vertebral fractures)*

	Vertebral	Hip	Wrist	Proximal humerus	Breast cancer
RR (95% CI)	0.65 (0.53 to 0.79)	Assumed no effect	Assumed no effect	Assumed no effect	0.38 (0.24 to 0.58)

TABLE 75 *Cost-effectiveness of raloxifene in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis, and no effect on non-vertebral fractures)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (95% CI)
50	247,798	716.74	144,226	4.78	31,189 (24,974 to 42,183)
60	266,744	688.79	117,477	5.68	20,696 (16,154 to 31,933)
70	314,697	554.70	127,880	4.26	29,993 (24,487 to 40,860)
80	573,901	395.47	85,851	4.05	21,183 (16,247 to 32,452)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

etidronate never has a cost per QALY below £40,000. When the observational data were included the cost per QALY was below £20,000 at both 70 and 80 years of age.

Raloxifene

[*Commercial-in-confidence information removed.*]

The efficacy data for raloxifene were taken from patients with severe osteoporosis and osteoporosis, owing to the similarity of results compared with severe osteoporosis alone, and the reduced confidence intervals (*Table 74*). Because of the wide confidence intervals that straddled unity it was assumed that the intervention had no effect on non-vertebral fractures. Raloxifene has been proven to have a significant effect in reducing breast cancer events, data for which were taken from Cauley and colleagues,[143] assuming the reduction seen in all breast cancer events. It was also seen that raloxifene has a significant effect on the incidence of cardiovascular events in patients at high risk; however, this effect was not significant for the entire population.

Assuming that raloxifene impacts only on vertebral fracture and breast cancer, the cost per QALY is below £30,000 at 60 years of age and above (*Table 75*). At 50 years of age it is above but close to £30,000.

A key factor in the cost-effectiveness value for raloxifene is the impact on breast cancer. This evaluation has assumed a relationship between low BMD and reduced incidence of breast cancer, as reported in large epidemiological studies,[32,33] which result in the incidence being reduced by 47% the incidence at 50 years, declining to a 10% reduction at 80 years of age. The raloxifene submission[39] assumes no link, which will greatly reduce the cost per QALY of the intervention in the younger age groups.

Raloxifene has a cost per QALY value that is rarely greater than £40,000 (*Figure 36*)

Caveat on raloxifene results

Great caution must be taken when interpreting the results for raloxifene, as the main constituent of the health gain was through reduction in breast cancer incidents rather than fracture reductions. Additional analyses were undertaken to evaluate separately the beneficial effects of the reduction of vertebral fractures and the reduction in the number of breast cancer cases. The effect of breast cancer reduction was far greater than the effect of vertebral

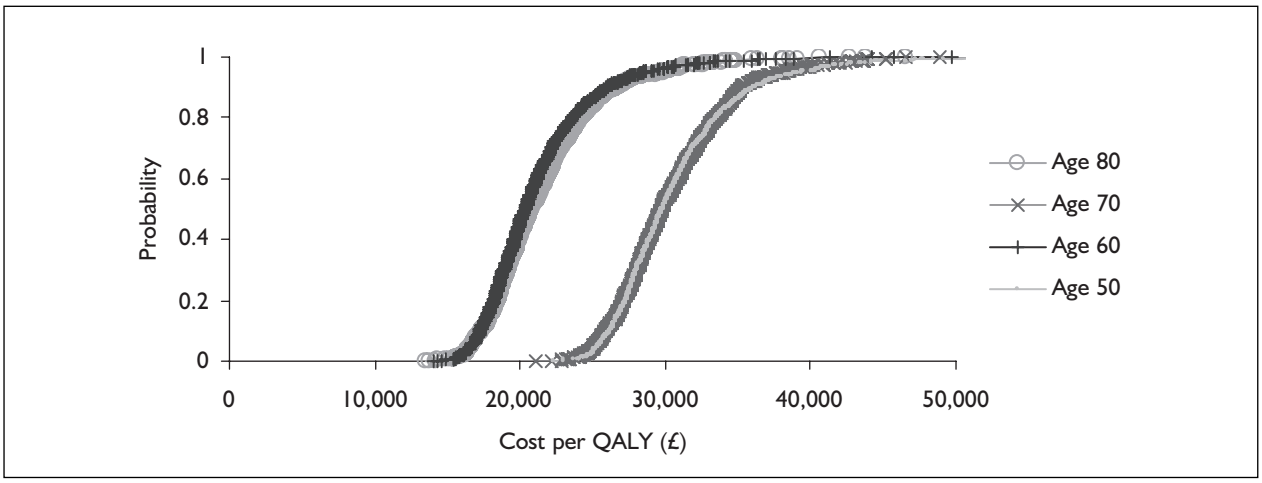

FIGURE 36 *CEACs for raloxifene in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis, and no effect on non-vertebral fractures)*

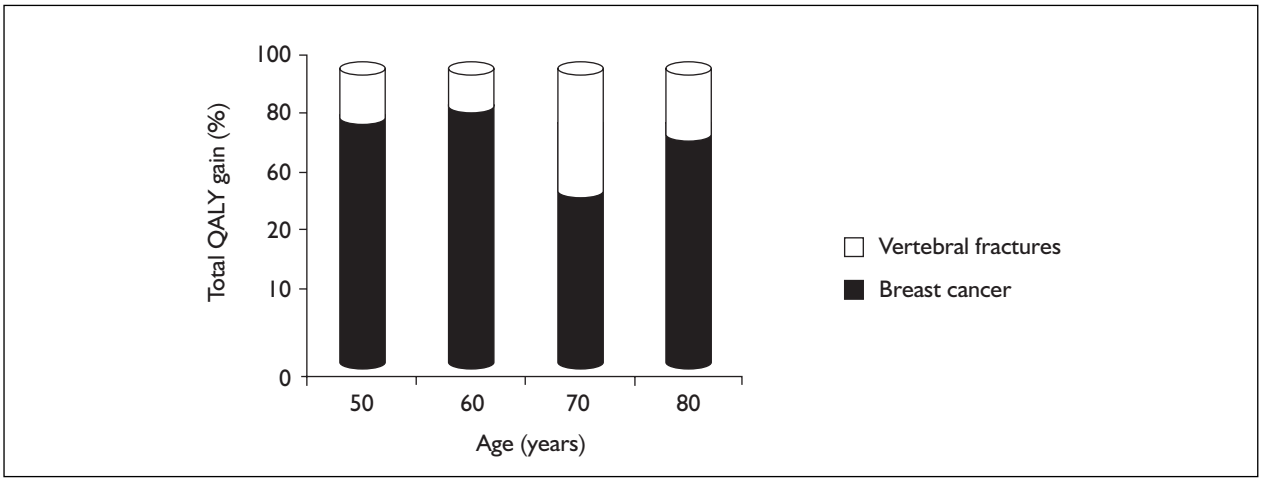

FIGURE 37 *Comparative effects of reduced vertebral fracture and reduced breast cancer incidence due to raloxifene treatment*

fracture reduction at the ages of 50, 60 and 80 years. At 70 years of age, where the incidence of vertebral fractures was greatest, the health gains from vertebral fracture reduction and breast cancer reduction were more similar (*Figure 37*).

The model was developed as an osteoporosis model and the breast cancer reduction was initially designed as an extra feature of this model. As such, average figures were used for the costs of breast cancer (set to approximately £8500), the mortality associated with breast cancer (approximately 32% with an associated cost of £12,000) and the reduction in QALYs due to a non-fatal event (assumed to be a multiplier of 0.62). If it is the case that the reduction in breast cancer events comprised those that were less likely to be fatal or costly, or both, then the results for raloxifene would dramatically change. Similarly, if the duration for the breast cancer to manifest itself was a long period, then assuming that the impacts were instantaneous, as the appraisal model does, would greatly overestimate the cost-effectiveness of the intervention.

To ascertain the true cost-effectiveness of raloxifene a model accurately simulating the experiences of breast cancer patients, including the different stages of severity, is required.

Assuming no effect on breast cancer or non-vertebral fractures greatly affected the cost per QALY ratio, rising to over £100,000 at 50, 60 and 80 years, and above £70,000 at 70 years of age.

Teriparatide

Efficacy data from RCTs for teriparatide were found only for patients with severe osteoporosis

TABLE 76 *Assumed efficacy of teriparatide in women with previous fractures and* T*-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.35 (0.22 to 0.55)	0.50 (0.09 to 2.73)	0.54 (0.22 to 1.35)	0.80 (0.22 to 2.98)

TABLE 77 *Cost-effectiveness of teriparatide in women with previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (95% CI)
50	661,316	714.41	557,744	2.45	227,976 (110,368 to Dominated)
60	702,620	685.18	553,353	2.06	268,104 (129313 to Dominated)
70	717,187	554.37	530,370	3.94	134,728 (69,716 to Dominated)
80	974,697	395.37	486,629	3.95	123,205 (45,654 to Dominated)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

(*Table 76*). The data for hip, wrist and proximal humerus had very wide confidence intervals and a second analysis was undertaken assuming that the intervention had no effect at these sites.

[*Commercial-in-confidence information removed.*]

The modelling assumptions were very favourable towards teriparatide as the model assumed 3.5 years of full sustained effect after cessation of treatment followed by a period of 1 year linear decline to a no treatment level. This assumption resulted in the estimated cost per QALY being lower than expected.

The average cost per QALY ratio for teriparitide does not fall below £100,000 at any age (*Table 77*).

Since the efficacy data on hip fracture had a wide confidence that spans unity, the CEACs are wide (*Figure 38*), with the drug being dominated approximately 10% of the time. This value cannot be seen on the graph as the *x* axis has been cropped at £250,000.

In the second analysis, which assumes that teriparatide has no effect on hip, wrist and proximal humerus fractures (*Table 78*), the average cost per QALY ratio for teriparatide does not fall below £200,000 at any age (*Table 79*). The cost-effectiveness ratio is better at 70 than at 80 years of age owing to the higher incidence of vertebral fractures at this age.

Figure 39 shows that the cost per QALY ratio does not fall below £150,000 at any age.

Oestrogen (HRT)

Efficacy data for oestrogen were taken from patients with severe osteoporosis (*Table 80*). No data were available individually for hip, wrist and proximal humerus fractures. The confidence interval around non-vertebral fractures was high and it was assumed that the intervention would only affect vertebral fractures. Efficacy data from RCTs for other patient groups were so wide that it was assumed there was no effect at any fracture site, which would result in the intervention never being cost-effective. The increased risk of breast cancer was taken from Beral and colleagues.[29]

As oestrogen has been licensed for many years a secondary analysis was undertaken allowing observational data on fractures to be used. These data were taken from Cauley and colleagues,[223] assuming multivariate adjusted values for women with a history of osteoporosis. It was assumed that oestrogen had no effect on CHD owing to the

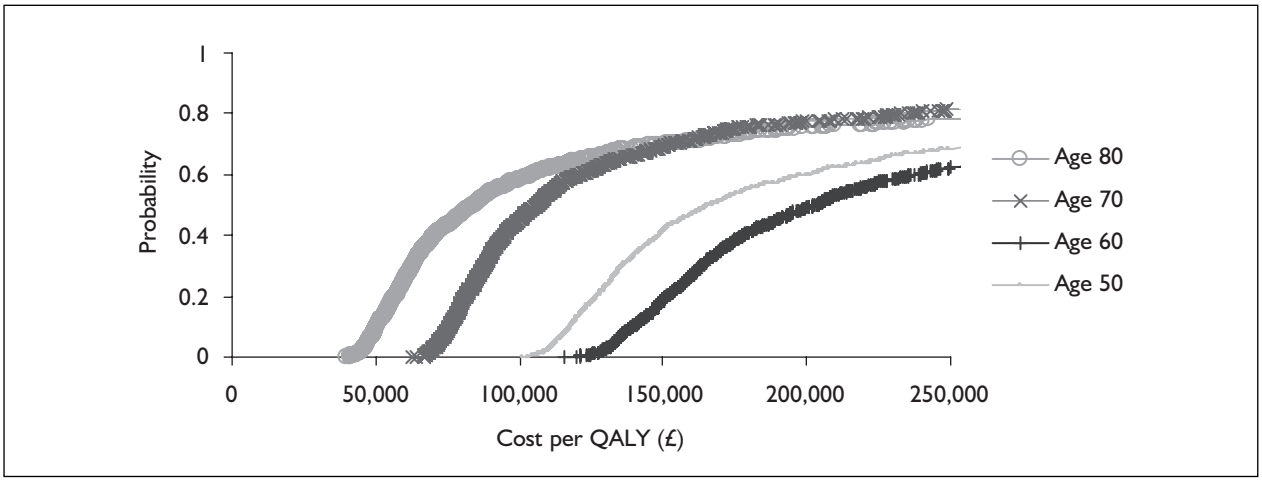

FIGURE 38 *CEACs for teriparatide in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis)*

TABLE 78 *Assumed efficacy of teriparatide in women with previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis and assuming no effect on hip, wrist or proximal humerus fractures)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.35 (0.22 to 0.55)	Assumed no effect	Assumed no effect	Assumed no effect

TABLE 79 *Cost-effectiveness of teriparatide in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis, and no effect of hip, wrist or proximal humerus fracture)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (95% CI)
50	669,651	712.97	566,079	1.00	564,864 (465,181 to 800,512)
60	714,601	684.02	565,334	0.90	625,603 (515,257 to 886,445)
70	742,189	552.95	555,371	2.51	221,130 (181,709 to 314,315)
80	1,036,163	392.80	548,113	1.38	396,184 (325,143 to 564,116)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

non-significant effect reported by Beral and colleagues.[29] The point estimate was, however, greater than unity; if this value were true the cost per QALY of oestrogen would rise markedly.

Oestrogen has a relatively small acquisition price. Assuming data on efficacy from RCTs only, it is dominated at all ages except for 70 years, where it has a cost-effectiveness ratio above £60,000 (*Table 81*). This is due to the higher risk of vertebral fractures at 70 years.

Owing to the wide confidence interval around vertebral fractures which spans unity and the adverse effect on breast cancer, oestrogen is dominated more than 65% of the time at 50, 60 and 80 years, and 35% of the time at 70 years of age (*Figure 40*).

In the secondary analysis, which incorporates observational data (*Table 82*), the average cost-effectiveness ratio is dramatically different across ages (*Table 83*). The adverse effects on breast

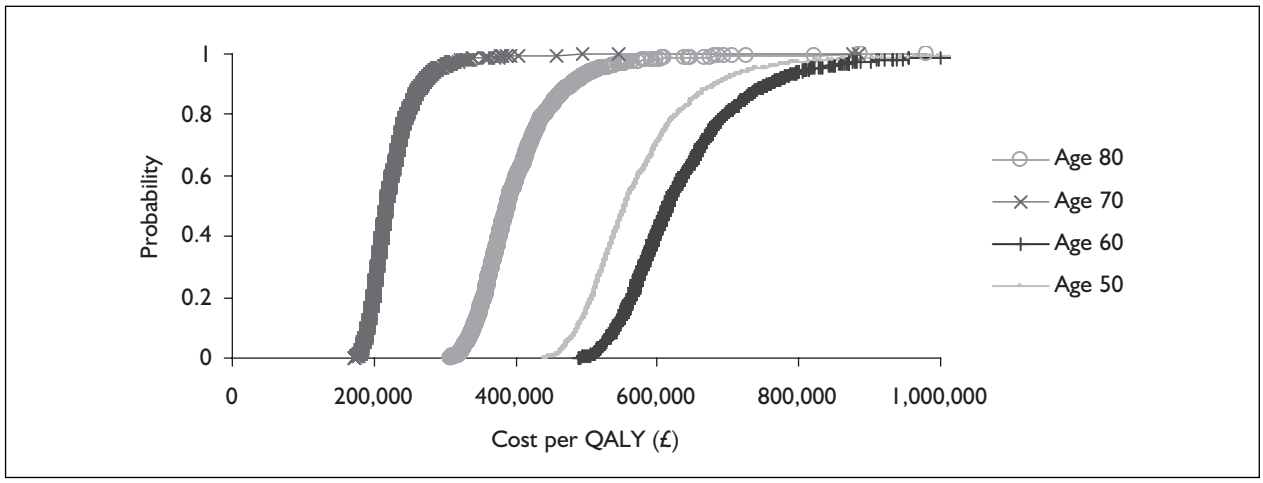

FIGURE 39 *CEACs for teriparatide in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis, and no affect on hip, wrist and proximal humerus fractures)*

TABLE 80 *Assumed efficacy of oestrogen in women with previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis)*

	Vertebral	Hip	Wrist	Proximal humerus	Breast cancer
RR (95% CI)	0.58 (0.26 to 1.30)	Assumed no effect	Assumed no effect	Assumed no effect	1.27 (1.02 to 1.56)

TABLE 81 *Cost-effectiveness of oestrogen in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (95% CI)
50	165,726	710.99	62,155	–0.98	Dominated (69,857 to Dominated)
60	221,180	681.58	71,913	–1.54	Dominated (98,744 to Dominated)
70	238,285	551.17	51,468	0.74	69,585 (15,177 to Dominated)
80	542,228	390.96	54,178	–0.46	Dominated (33,874 to Dominated)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

cancer are more pronounced at 50 and 60 years of age, owing to the relatively low incidence of hip fracture. At 50 years the ratio is over £600,000 and at 60 years of age it is dominated by no treatment. At 70 and 80 years of age the ratio is £24,585 and £13,258, respectively, owing to the effect on hip fracture reduction. The confidence intervals around these results are very large, and at 70 and 80 years of age they span from dominating to dominated.

By incorporating observational data the CEACs become much flatter owing to the wide confidence interval surrounding the efficacy of hip fracture (*Figure 41*). Oestrogen is dominated by no treatment on approximately 20% of occasions, at 70 and 80 years of age.

Summary of treatment results assuming a woman at the threshold of osteoporosis and with a prior fracture

Results given are for a cohort of 100 women.

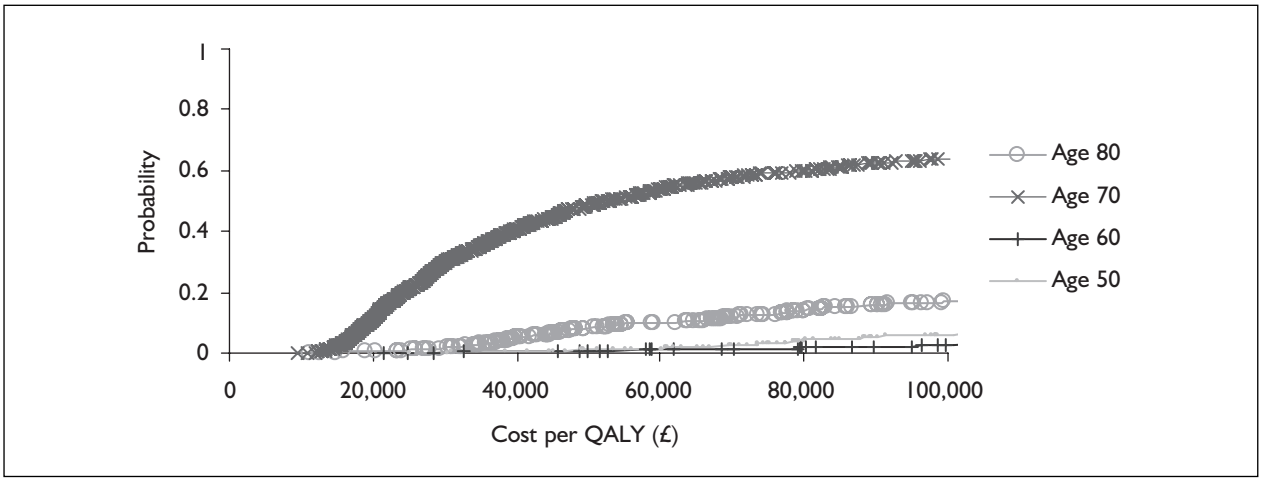

FIGURE 40 *CEACs for oestrogen in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis)*

TABLE 82 *Assumed efficacy of oestrogen in women with previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis and observational data)*

	Vertebral	Hip	Wrist	Proximal humerus	Breast cancer
RR (95% CI)	0.58 (0.26 to 1.30)	0.86 (0.42 to 1.75)	0.32 (0.13 to 0.78)	0.63 (0.45 to 0.89)	1.27 (1.02 to 1.56)

TABLE 83 *Cost-effectiveness of oestrogen in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis and using observational data)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (95% CI)
50	159,623	712.06	56,051	0.09	616,891 (11,169 to Dominated)
60	211,140	682.56	61,873	–0.56	Dominated (13,237 to Dominated)
70	225,156	551.99	38,339	1.56	24,584 (Dominating to Dominated)
80	509,406	393.03	21,356	1.61	13,258 (Dominating to Dominated)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

50 years of age
The most cost-effective drug for women aged 50 years at the threshold of osteoporosis is raloxifene (*Table 84*). The average cost per QALY ratio is £31,189.

60 years of age
At 60 years of age the most cost-effective drug is raloxifene (*Table 85*). The cost per QALY ratio is approximately £20,696.

70 years of age
At 70 years of age the most cost-effective drug is alendronate, with an average cost per QALY ratio under £20,000 (*Table 86*). Risedronate has an average cost per QALY of £22,000. Etidronate has an average cost per QALY below £20,000 if observational data are incorporated.

80 years of age
At 80 years of age, both alendronate and

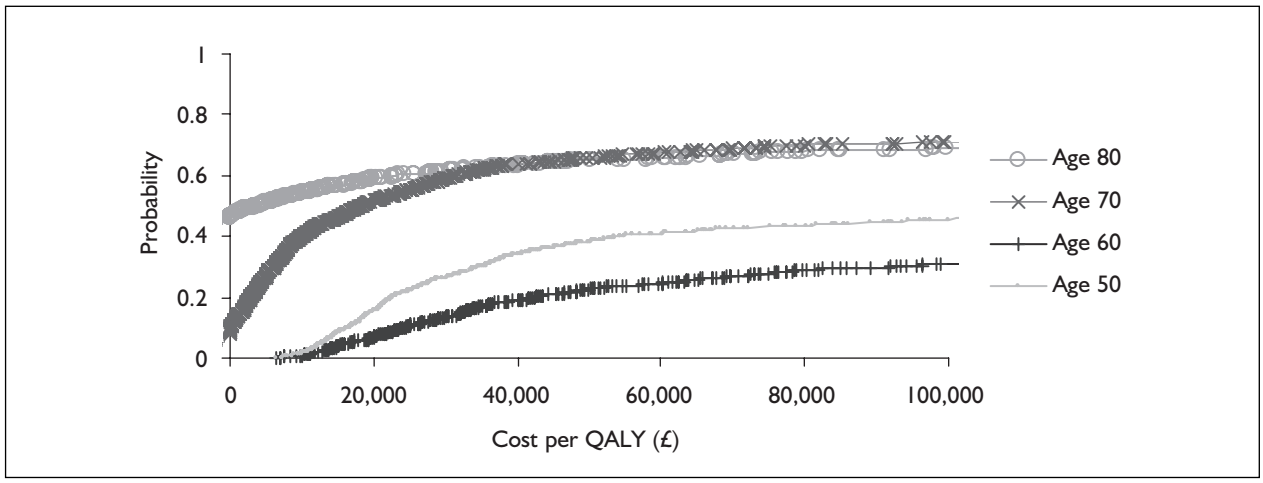

FIGURE 41 *CEACs for oestrogen in women with previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis and using observational data)*

TABLE 84 *Cost-effectiveness for each treatment at 50 years of age*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	95% CI[a]
Alendronate	148,924	4.43	33,621	23,871 to 77,272
Risedronate	145,131	3.43	42,268	30,154 to 78,619
Etidronate	105,528	1.34	78,960	62,236 to 123,556
Etidronate[b]	100,443	2.29	43,903	Not calculated
Raloxifene*	144,226	4.78	31,189	24,974 to 42,183
Teriparatide	557,744	2.45	227,976	110,368 to Dominated
Teriparatide[c]	566,079	1.00	564,864	465,181to 800,512
Oestrogen	62,155	–0.98	Dominated	69,857 to Dominated
Oestrogen[d]	56,051	0.09	616,891	11,169 to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

TABLE 85 *Cost-effectiveness for each treatment at 60 years of age*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average Cost per QALY[a]	95% CI[a]
Alendronate	138,752	3.49	39,733	28,022 to 72,990
Risedronate	135,399	2.91	46,596	33,166 to 84,694
Etidronate	103,730	1.16	89,079	70,276 to 139,219
Etidronate[b]	96,718	1.89	51,182	Not calculated
Raloxifene*	117,477	5.68	20,696	16,154 to 31,933
Teriparatide	553,353	2.06	268,104	129,313 to Dominated
Teriparatide[c]	565,334	0.90	625,603	515,257 to 886,445
Oestrogen	71,913	–1.54	Dominated	98,744 to Dominated
Oestrogen[d]	61,873	–0.56	Dominated	13,237 to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

TABLE 86 *Cost-effectiveness for each treatment at 70 years of age*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	95% CI[a]
Alendronate	94,979	5.61	16,934	9,742 to 44,277
Risedronate	103,596	4.71	22,001	13,991 to 43,226
Etidronate	89,378	3.01	29,742	22,952 to 47,849
Etidronate[b]	74,150	4.00	18,554	Not calculated
Raloxifene*	127,880	4.26	29,993	24,487 to 40,860
Teriparatide	530,370	3.94	134,728	69,716 to Dominated
Teriparatide[c]	555,371	2.51	221,130	181,709 to 314,315
Oestrogen	51,468	0.74	69,585	15,177 to Dominated
Oestrogen[d]	38,339	1.56	24,584	Dominating to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

TABLE 87 *Cost-effectiveness for each treatment at 80 years of age*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	95% CI[a]
Alendronate	4,527	6.49	697	Dominating to 30,663
Risedronate	26,490	5.28	5,022	Dominating to 27,253
Etidronate	74,951	1.54	48,521	36,882 to 79,718
Etidronate[b]	39,628	3.00	13,226	Not calculated
Raloxifene*	85,851	4.05	21,183	16,247 to 32,452
Teriparatide	486,629	3.95	123,205	45,654 to Dominated
Teriparatide[c]	548,113	1.38	396,184	325,143 to 564,116
Oestrogen	54,178	–0.46	Dominated	33,874 to Dominated
Oestrogen[d]	21,356	1.61	13,258	Dominating to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

risedronate have cost per QALYs under £6,000 (*Table 87*). If observational data are included for etidronate it also has a cost per QALY below £15,000. If observational data on fracture are included for oestrogen the average cost per QALY is also below £15,000, but there is a very wide confidence interval around this figure. Raloxifene has a cost per QALY slightly above £20,000.

However, caution must be applied when interpreting these results, since the efficacy assumptions are from a weak evidence base, as women at this age only represent a small minority of patients in RCTs.

Incremental analyses

The intervention with the lowest cost per QALY ratio is not always the intervention that is optimal for society to use. As a hypothetical example, it is assumed that society is willing to pay £30,000 per QALY, and that the options are no treatment, intervention A and intervention B. Intervention A has a marginal cost of £500 and marginal QALY of 0.1 compared with no treatment. These values are £50,000 and 2 for intervention B. Thus, the cost per QALY ratio, compared with no treatment, is £5000 and £25,000, respectively. Comparing interventions A and B, the incremental cost of intervention B is £45,000 and incremental QALY is 1.9. The ICER of intervention B compared with A is 45,000/1.9 = £23,684, which is below the threshold that society is willing to pay, and thus intervention B is the optimal treatment despite having a higher cost per QALY ratio than intervention A.

TABLE 88 *Optimal order of interventions at each age band for women at the threshold of osteoporosis and with a prior fracture, assuming a maximum cost per QALY threshold of £30,000*

Age (years)			
50	**60**	**70**	**80**
No treatment	Raloxifene* No treatment	Alendronate Etidronate[a] Risedronate Oestrogen[b] Etidronate Raloxifene* No treatment	Alendronate Risedronate Etidronate[a] Raloxifene* Oestrogen[b] No treatment

* See caveat on all raloxifene results.
[a] Assuming observational data on hip, wrist and proximal humerus fracture.
[b] Assuming observational data on hip, wrist and proximal humerus fracture, and breast cancer.

Optimal interventions are therefore calculated by ranking the interventions in order of ascending health gain and initially comparing the two least effective treatments. If the incremental cost per QALY between the more effective treatment and the lesser is below the cost per QALY threshold, the more effective treatment is selected as optimal. Similar comparisons are then iteratively conducted between the current optimal treatment and the next most effective treatment, until the most effective intervention is reached, and the optimal treatment is calculated.

The optimal order of interventions at each age band was calculated assuming a cost per QALY threshold of £30,000. These are presented in *Table 88*. These results were calculated assuming that the treatments are mutually exclusive (e.g. a woman would not take both raloxifene and risedronate). In cost-effectiveness terms the intervention ranked highest should be identified as the first line treatment. If, however, a woman cannot tolerate this intervention, the next intervention should be adopted, until the no treatment option is reached.

CEACs for all interventions

A CEAC plotted with more than one intervention differs substantially from the CEAC of one intervention against no treatment. A defining characteristic is that the summation of the probabilities of each treatment being optimal is equal to 100%, and that a line for no treatment is explicitly drawn as opposed to being implied in the single intervention diagram.

CEACs are calculated by calculating the net benefit of each treatment at different thresholds of cost per QALY (λ). The net benefit for an intervention is calculated as the marginal increase in QALYs compared with no treatment multiplied by λ, with the marginal increase in costs compared with no treatment being subtracted. The net benefit of no treatment (as the option against which all interventions are compared) is set by definition to zero.

The option that gave the greatest net benefit for each of the 1000 Monte Carlo samples was recorded and summated to estimate the proportion of times that each intervention would be the optimal selection. The 1000 samples were randomly shuffled for each intervention to avoid the situation where selections from the lower tail of the efficacy distributions for one treatment would be associated with similar selections for the remaining interventions.

The default scenarios were used to calculate the CEACs presented in *Figures 42–45*. For clarity reasons, any intervention that did not have a probability of being optimal greater than 2.5% was omitted from the figures.

It can be seen from the multiple intervention CEACs and assuming a cost per QALY threshold of £30,000 that the intervention with the most probability of being optimal is raloxifene at 50 years, no treatment at 60 years, and alendronate at 70 and 80 years of age. These analyses are presented for completeness of health economic analyses; however, it should be noted that although alendronate appears to be favoured over risedronate no head-to-head trials have been conducted, and that the trials on which efficacy data are based differ in some respects, including the type of patients involved.

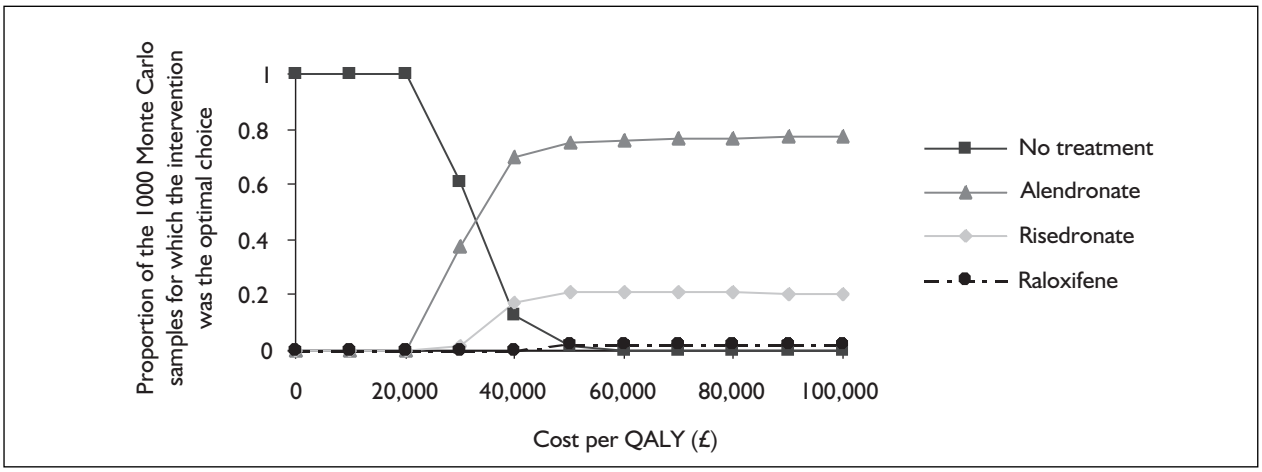

FIGURE 42 *CEACs for all interventions at 50 years of age, for women at 50 years of age, for women at the threshold of osteoporosis with a previous fragility fracture*

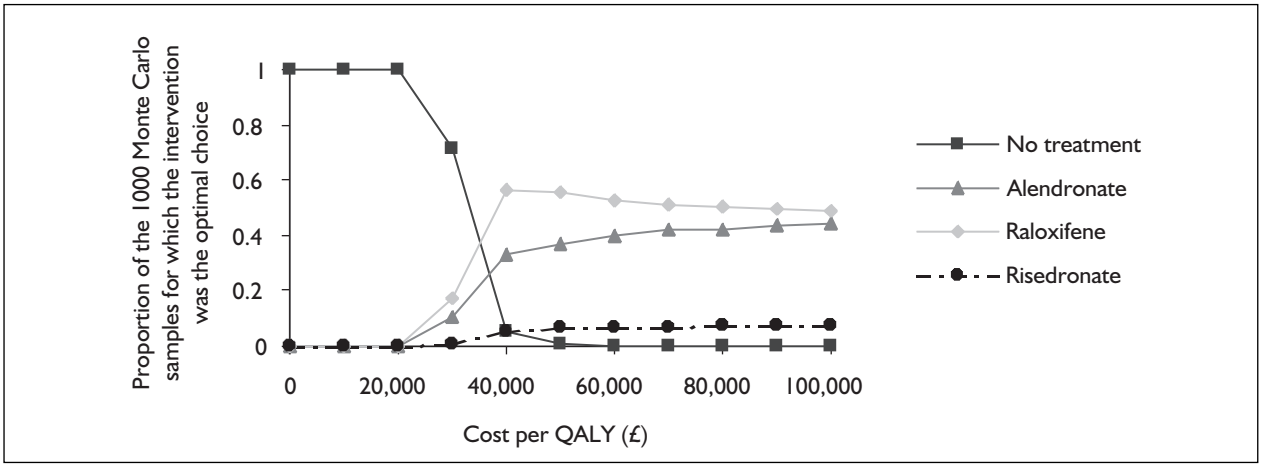

FIGURE 43 *CEAC for all interventions at 60 years of age, for women at the threshold of osteoporosis with a previous fragility fracture*

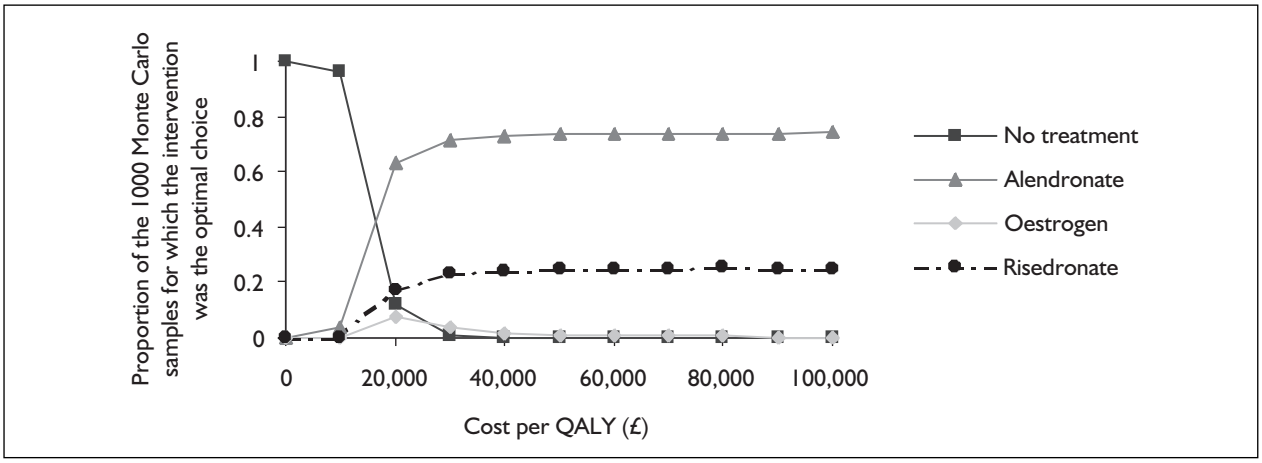

FIGURE 44 *CEACS for all interventions at 70 years of age, for women at the threshold of osteoporosis with a previous fragility fracture*

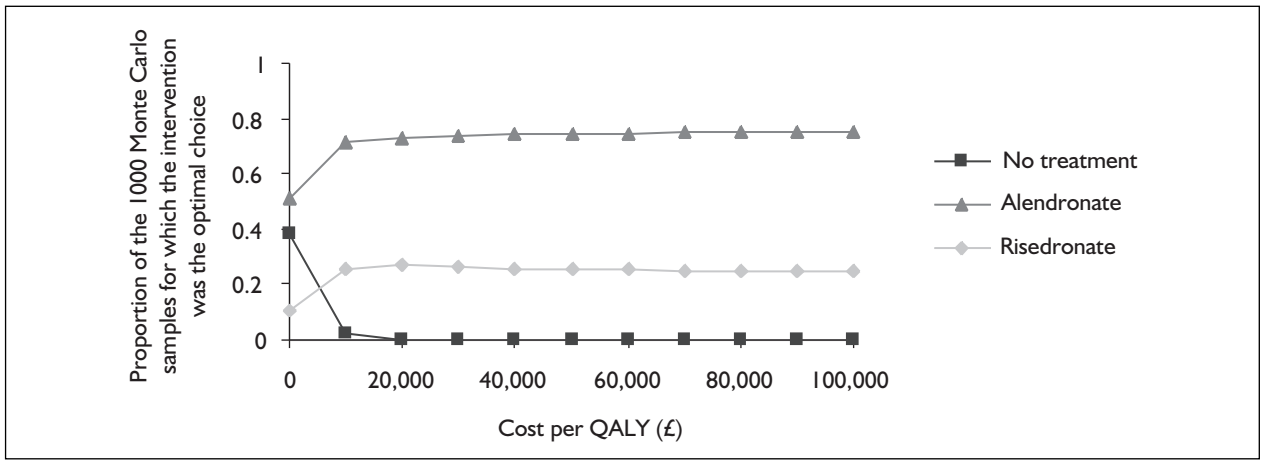

FIGURE 45 *CEAC for all interventions at 80 years of age, for women at the threshold of osteoporosis with a previous fragility fracture*

Sensitivity analyses

Sensitivity analyses were conducted around the following parameters, one at a time:

- incorporating the effects of morphometric fractures
- assuming that the effect on vertebral fracture was much greater in the first year, by assuming a multiplier of 0.63 rather than 0.83
- analysing the assumption of a 1-year fall time, rather than 5 years.

None of these factors was seen to change the cost per QALY ratios to any great extent. The full analyses are given in Appendix 15. The impact of these changes was to adjust the cost per QALY of all the interventions; as such, the ranking of the interventions was expected to remain constant.

Further sensitivity analyses were undertaken to estimate the cost-effectiveness ratio at the age of 65 years, as there was a wide difference between the cost-effectiveness ratios at 60 years and at 70 years, which straddled the ranges of cost-effectiveness that have been hypothesised as being cost-effective within the UK.[224]

These results were imputed from the Gaussian process models formulated at 60 years since the individual patient model was not run at 65 years of age. The Gaussian model at 60 years of age was run having altered the fracture, breast cancer and CHD rates to approximate those at 65 years rather than 60 years of age. Factors such as all-cause mortality rates and proportion of fatalities following hip fracture would be underestimated in the 60-year-old model; however, as these affect the cost-effectiveness of an intervention in different directions, it is expected that any bias via this approach would be small. The results are given in *Table 89*.

As expected, the cost-effectiveness results for each drug at the age of 65 years fell between those of 60 years and 70 years of age. The one exception was for raloxifene, which is explained by the lower assumed breast cancer rate at 65 years compared with 60 and 70 years of age.

Evaluating the effect of double fracture risk

The default analyses were conducted assuming that a woman has a *T*-score at the threshold of osteoporosis. By definition, the average osteoporotic woman will have a *T*-score lower than –2.5 SD, and other factors such as low body mass index, corticosteroid use, current smoking or a history of maternal hip fracture will increase the risk of fracture beyond that explained by *T*-score alone.

To assess the impact that these factors would have, additional analyses were conducted assuming that the risk of fracture at each site was doubled. With no other non-skeletal factors the doubling of risk at the hip would be associated with a *T*-score of –3.22, compared with a *T*-score of –2.5.

The values associated with the no treatment option changed owing to the assumed increase in fracture risk. These are presented in *Table 90*.

50 years of age

The most cost-effective drug for women aged 50 years at the threshold of osteoporosis is alendronate, where the average cost per QALY ratio is £14,484 (*Table 91*). Risedronate also has an average cost per QALY below £20,000.

TABLE 89 *Interpolated cost-effectiveness for each treatment at 65 years of age*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]
Alendronate	132,601	4.04	32,811
Risedronate	130,056	3.40	38,303
Etidronate	102,923	1.60	64,273
Etidronate[b]	94,487	2.31	40,877
Raloxifene*	138,120	4.15	33,260
Teriparatide	514,666	2.55	202,201
Teriparatide[c]	529,123	1.29	409,097
Oestrogen	67,781	0.10	675,105
Oestrogen[d]	57,065	1.26	45,422

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

TABLE 90 *Costs incurred and QALYs accrued from no treatment in women with previous fractures and T-scores of –2.5, assuming double fracture risk*

Age (years)	Cost incurred (£)	QALYs accrued
50	134,830	706.18
60	193,083	678.10
70	276,662	542.45
80	704,417	381.15

TABLE 91 *Cost-effectiveness for each treatment at 50 years of age when the fracture risk is doubled*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Alendronate	128,315	8.86	14,484	9,528 to 36,901
Risedronate	128,238	6.87	18,674	12,509 to 37,200
Etidronate	102,474	2.67	38,337	29,980 to 60,622
Etidronate[b]	92,303	4.58	20,173	Not calculated
Raloxifene*	142,385	5.56	25,594	21,218 to 34,912
Teriparatide	546,999	4.89	111,792	52,690 to Dominated
Teriparatide[c]	563,668	2.00	281,231	231,390 to 399,047
Oestrogen	60,249	–0.15	Dominated	24,733 to Dominated
Oestrogen[d]	48,043	1.99	24,106	2,094 to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

60 years of age

The most cost-effective drug at 60 years of age is alendronate, with an average cost per QALY value of £15,902 (*Table 92*). The cost per QALY ratios for risedronate and raloxifene are also below £20,000.

70 years of age

At 70 years of age the most cost-effective drug is alendronate, with an average cost per QALY below £3000 (*Table 93*). Risedronate and etidronate (assuming observational data) have an average cost per QALY below £10,000. Etidronate,

TABLE 92 *Cost-effectiveness for each treatment at 60 years of age when the fracture risk is doubled*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Alendronate	111,064	6.98	15,902	9,677 to 42,059
Risedronate	111,748	5.81	19,228	12,314 to 38,778
Etidronate	101,024	2.33	43,377	33,987 to 68,416
Etidronate[b]	86,998	3.78	23,091	Not calculated
Raloxifene*	115,789	6.36	18,302	14,380 to 26,890
Teriparatide	539,241	4.13	130,633	60,434 to Dominated
Teriparatide[c]	563,203	1.81	311,622	256,455 to 442,031
Oestrogen	70,225	–0.81	Dominated	34,018 to Dominated
Oestrogen[d]	50,144	1.14	43,833	742 to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

TABLE 93 *Cost-effectiveness for each treatment at 70 years of age when the fracture risk is doubled*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Alendronate	33,336	11.22	2,972	Dominating to 18,612
Risedronate	91,899	9.42	9,758	4,560 to 23,547
Etidronate	79,432	6.01	13,216	9,826 to 22,264
Etidronate[b]	48,975	7.99	6,127	Not calculated
Raloxifene*	121,853	6.03	20,206	15,831 to 28,558
Teriparatide	497,252	7.87	63,158	29,436 to Dominated
Teriparatide[c]	547,249	5.02	108,948	89,240 to 155,541
Oestrogen	79,549	2.61	30,453	10,244 to Dominated
Oestrogen[d]	53,294	4.25	12,534	Dominating to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

excluding observational data, and oestrogen have values below £15,000; however, the confidence intervals for oestrogen are very wide. Raloxifene has a value slightly above £20,000.

80 years of age
At 80 years of age both alendronate and Risedronate dominate no treatment (*Table 94*). Etidronate has an average cost per QALY below £20,000, but dominates no treatment if observational data are incorporated. Raloxifene has a cost per QALY below £16,000. Oestrogen dominates no treatment if observational data are incorporated, but has an average cost per QALY above £90,000 if these data are excluded. The confidence intervals around the cost per QALY for oestrogen are very wide.

The optimal order of interventions at each age band was calculated assuming a cost per QALY threshold of £30,000. The results are presented in *Table 95*.

If it is assumed that teriparatide does not have an effect on hip fracture, then it does not have an average cost per QALY below £100,000 at any age. It does not have a cost per QALY below £50,000 at any age, even when the beneficial effects on non-vertebral fractures are included.

Evaluating the effect of quadruple fracture risk
Additional analyses were conducted assuming that the risk of fracture at each site was quadrupled. With no other non-skeletal factors the doubling of risk at the hip would be associated with a *T*-score

TABLE 94 *Cost-effectiveness for each treatment at 80 years of age when the fracture risk is doubled*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Alendronate	–130,551	12.98	Dominating	Dominating to 8,107
Risedronate	–80,297	10.55	Dominating	Dominating to 4,911
Etidronate	61,658	3.09	19,985	14,141 to 35,467
Etidronate[b]	–8,988	5.99	Dominating	Not calculated
Raloxifene*	77,652	4.96	15,652	11,606 to 23,268
Teriparatide	413,779	7.90	52,381	11,673 to Dominated
Teriparatide[c]	536,747	2.77	193,984	158,477 to 277,918
Oestrogen	45,903	0.50	92,130	8,324 to Dominated
Oestrogen[d]	–19,742	4.65	Dominating	Dominating to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

TABLE 95 *The optimal order of interventions at each age band for women at the threshold of osteoporosis and with a prior fracture when the fracture risk is doubled*

Age (years)			
50	**60**	**70**	**80**
Alendronate	Alendronate	Alendronate	Alendronate
Risedronate	Raloxifene*	Etidronate[a]	Risedronate
Etidronate[a]	Risedronate	Risedronate	Etidronate[a]
Raloxifene*	Etidronate[a]	Etidronate	Oestrogen[b]
Oestrogen[b]	No treatment	Oestrogen[b]	Raloxifene*
No treatment		Raloxifene*	Etidronate
		No treatment	No treatment

* See caveat on all raloxifene results.
[a] Assuming observational data on hip, wrist and proximal humerus fracture.
[b] Assuming observational data on hip, wrist and proximal humerus fracture, and breast cancer.

of –3.95 SD, compared with a *T*-score of –2.5 SD. Since all interventions bar teriparitide had scenarios where the criterion for cost-effectiveness was met at double risk, only teriparitide was analysed at quadruple risk.

The values associated with the no treatment option changed owing to the assumed increase in fracture risk. These are presented in *Table 96*.

50 years of age
At 50 years of age, teriparatide has an average cost per QALY above £50,000 regardless of the efficacy assumptions (*Table 97*).

60 years of age
At 60 years of age, teriparatide has an average cost per QALY above £50,000 regardless of the efficacy assumptions (*Table 98*).

70 years of age
At 70 years of age, teriparatide has an average cost per QALY below £30,000. If it is assumed to have no effect on non-vertebral fractures this figure rises to above £50,000 (*Table 99*).

80 years of age
At 80 years of age, teriparatide has an average cost per QALY below £20,000 when it is assumed to affect all fracture rates (*Table 100*). The confidence intervals around these cost per QALY values are wide and include 'dominated'. If it is assumed only to affect vertebral fracture this figure rises to above £90,000.

If it is assumed that teriparatide does not have an effect on hip fracture then it does not have a cost per QALY below £50,000 at any age. Even assuming a beneficial effect on hip fractures the

TABLE 96 *Costs incurred and QALYs accrued from no treatment in women with previous fractures and T-scores of –2.5, assuming quadruple fracture risk*

Age (years)	Cost incurred (£)	QALYs accrued
50	197,345	694.60
60	280,713	668.07
70	456,063	526.48
80	1,137,151	360.60

TABLE 97 *Cost-effectiveness for each treatment at 50 years of age when the fracture risk is quadrupled*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Teriparatide	525,509	9.79	53,700	23,754 to Dominated
Teriparatide[b]	558,846	4.01	139,413	114,495 to 198,315

[a] Compared with calcium and vitamin D.
[b] Assuming effect on vertebral fractures only.

TABLE 98 *Cost-effectiveness for each treatment at 60 years of age when the fracture risk is quadrupled*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average Cost per QALY[a]	90% CI[a]
Teriparatide	511,019	8.26	61,898	26,065 to Dominated
Teriparatide[b]	558,942	3.61	154,632	127,054 to 219,824

[a] Compared with calcium and vitamin D.
[b] Assuming effect on vertebral fractures only.

TABLE 99 *Cost-effectiveness for each treatment at 70 years of age when the fracture risk is quadrupled*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Teriparatide	431,308	15.75	27,391	9,261 to Dominated
Teriparatide[b]	531,273	10.05	52,884	43,031 to 76,174

[a] Compared with calcium and vitamin D.
[b] Assuming effect on vertebral fractures only.

TABLE 100 *Cost-effectiveness for each treatment at 80 years of age when the fracture risk is quadrupled*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Teriparatide	268,079	15.80	16,968	Dominating to Dominated
Teriparatide[b]	514,015	5.53	92,884	75,144 to 134,819

[a] Compared with calcium and vitamin D.
[b] Assuming effect on vertebral fractures only.

TABLE 101 *Costs incurred and QALYs accrued from no treatment in women without a previous fracture and* T-scores *of –2.5*

Age (years)	Cost incurred (£)	QALYs accrued
70	158,225	563.98
80	265,242	411.66

TABLE 102 *Assumed efficacy of alendronate in women without previous fractures and* T-scores *of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.53 (0.46 to 0.67)	0.46 (0.23 to 0.91)	0.48 (0.31 to 0.75)	Assumed no effect

TABLE 103 *Cost-effectiveness of alendronate in women without previous fractures and* T-scores *of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (90% CI)
70	275,761	566.87	117,535	2.90	40,460 (27,995 to 76,967)
80	309,044	415.25	43,802	3.60	12,181 (888 to 66,984)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment.

cost per QALY is only lower than £30,000 at 70 and 80 years of age.

Estimations of the cost-effectiveness of each intervention in women at the threshold for osteoporosis without a prior fracture

Since the presence of a prior fracture is associated with an increase in fracture risk,[15] each intervention will have a markedly increased cost per QALY ratio when used in patients who have not suffered a fracture.

Since no intervention was seen to have cost-effectiveness ratios below £30,000 at the ages of 50 and 60 years in patients with fractures, the analysis of women without a previous fracture was confined to the ages of 70 and 80 years. Each intervention was assessed in turn. The costs incurred and the QALYs accrued under a policy of no treatment are given in *Table 101*.

Alendronate

In the absence of efficacy data in women with osteoporosis only, efficacy data were taken from women with severe osteoporosis, osteoporosis or osteopenia (*Table 102*).

The cost per QALY ratios are higher in patients without a prior fracture and are below £30,000 at 80 years, but not at 70 years of age (*Table 103* and *Figure 46*).

Risedronate

Risedronate was one of the few interventions with data on efficacy in patients with osteoporosis only. These data were on hip fracture only and were seen to be comparable to those for women with severe osteoporosis. These latter data were used owing to the confidence intervals being significantly reduced. The efficacy data for vertebral fracture were taken from patients with severe osteoporosis, osteoporosis or osteopenia (*Table 104*).

The cost per QALY value falls below £30,000 at 80 years of age (*Table 105*).

Figure 47 shows that at 70 years of age the cost per QALY of risedronate is very rarely below £40,000.

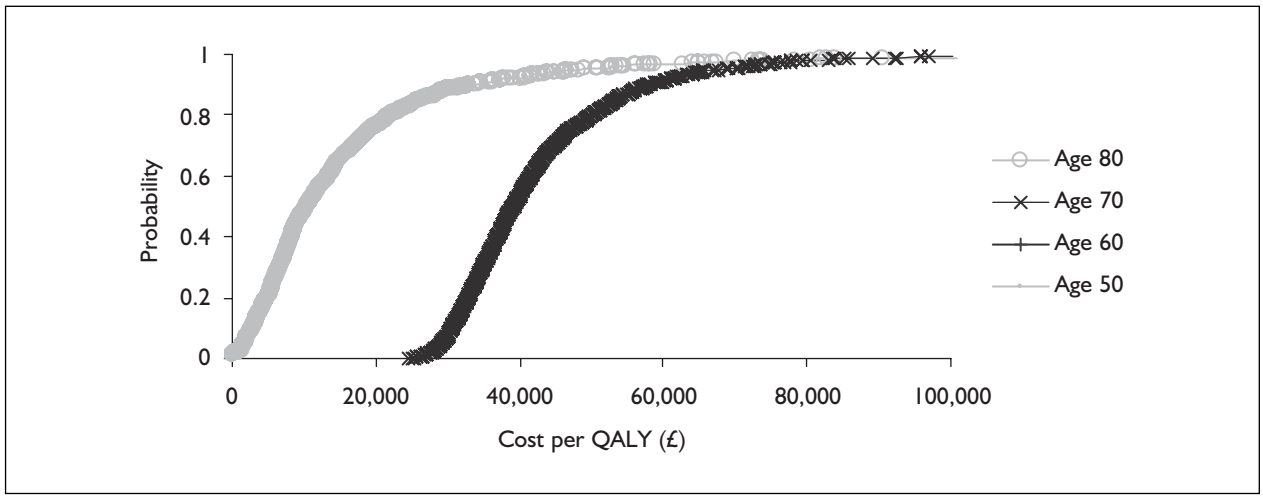

FIGURE 46 *CEACs for alendronate in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

TABLE 104 *Assumed efficacy of risedronate in women without previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis, osteoporosis or osteopenia)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.62 (0.50 to 0.76)	0.66 (0.48 to 0.89)	0.68 (0.43 to 1.08)	0.46 (0.23 to 0.94)

TABLE 105 *Cost-effectiveness of risedronate in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis, osteoporosis or osteopenia)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (90% CI)
70	283,495	565.23	125,270	1.27	98,855 (56,051 to 314,357)
80	328,394	415.32	63,152	3.55	17,240 (7,230 to 40,528)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment.

Etidronate

In the absence of data from patients with osteoporosis only, data were taken from patients with severe osteoporosis, osteoporosis or osteopenia (*Table 106*). Because of the extremely wide confidence intervals around hip (0.05 to 5.34) and other non-vertebral fractures (0.12 to 3.82), it was assumed that the drug has no effect on these sites.

Etidronate is more cost-effective at 70 years than at 80 years of age owing to the greater incidence of vertebral fractures at 70 years, which is the only fracture site that etidronate has been assumed to affect. At 70 years of age the average cost per QALY of etidronate was above £40,000, whereas at 80 years the cost per QALY was greater than £70,000 (*Table 107*).

An additional analysis was undertaken assuming that etidronate reduces hip fractures by 15% and wrist fractures by 8%, these values being the upper bound on the 95% confidence interval reported by van Staa and colleagues.[222] Using these efficacy figures, the cost per QALY improved to £33,677 and £28,678 at 70 and 80 years of age, respectively. These efficacy data were not varied and thus no confidence interval for the cost-

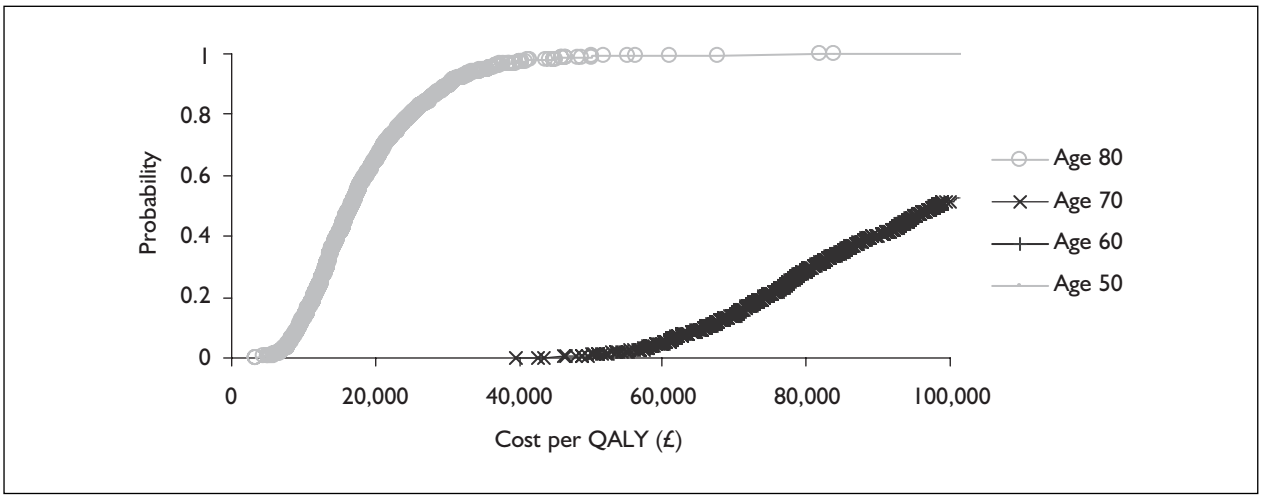

FIGURE 47 *CEACs for risedronate in women without previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

TABLE 106 *Assumed efficacy of etidronate in women without previous fractures and* T*-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis or osteoporosis, and assuming no effect on non-vertebral fractures)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.40 (0.20 to 0.83)	Assumed no effect	Assumed no effect	Assumed no effect

TABLE 107 *Cost-effectiveness of etidronate in women without previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis, and no effect on non-vertebral fractures)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (90% CI)
70	250,155	566.01	91,930	2.04	45,071 (34,884 to 72,214)
80	343,962	412.75	78,720	1.09	72,007 (55,478 to 116,176)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment.

effectiveness of etidronate was calculated in this scenario.

At the age of 80 years, etidronate never has a cost per QALY below £50,000 and at 70 years it is never below 30,000 (*Figure 48*). However, when observational data are incorporated the cost per QALY falls below £30,000 at 80 years of age.

Raloxifene

[*Commercial-in-confidence information removed.*]

The efficacy data for the effect of Raloxifene on vertebral fractures were taken from patients with osteoporosis alone (*Table 108*). Because of the non-significant effect on non-vertebral fractures it was assumed that raloxifene only had an effect on vertebral fractures. Data on the reduction in breast cancer were taken from Cauley and colleagues, assuming the risk of preventing all breast cancer events.[143]

The average cost per QALY is below £20,000 at 70 years and below £30,000 at 80 years of age (*Table 109*). These values do not change greatly in the absence of a prior fracture owing to the large effect of breast cancer reduction. As with all raloxifene results these data should be interpreted

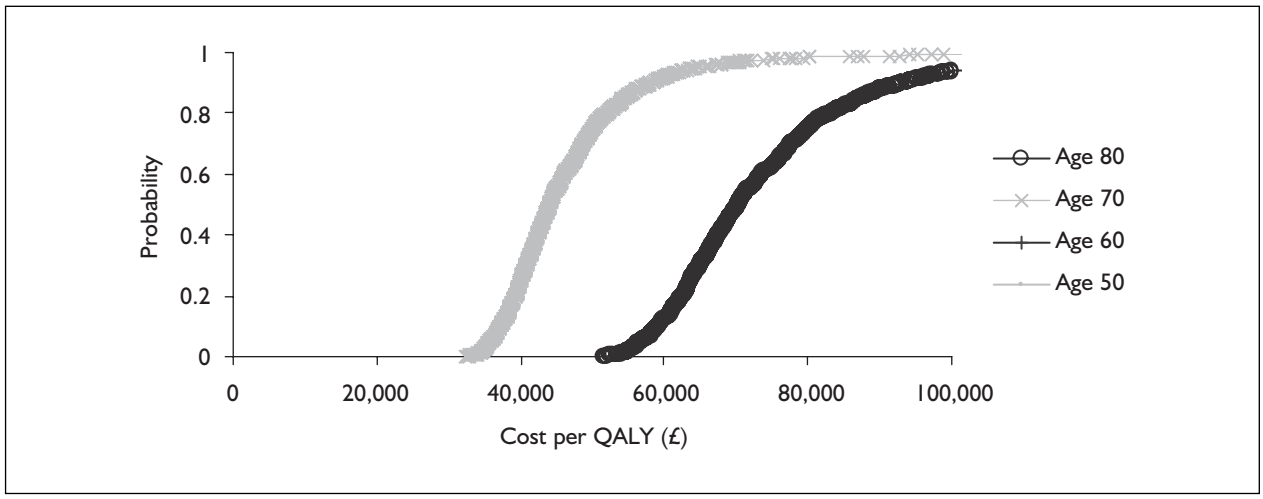

FIGURE 48 *CEACs for etidronate in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis, and no effect on non-vertebral fractures)*

TABLE 108 *Assumed efficacy of raloxifene in women without previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis or osteoporosis)*

	Vertebral	Hip	Wrist	Proximal humerus	Breast cancer
RR (95% CI)	0.53 (0.35 to 0.79)	Assumed no effect	Assumed no effect	Assumed no effect	0.38 (0.24 to 0.58)

TABLE 109 *Cost-effectiveness of raloxifene in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal Costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (90% CI)
70	251,910	568.99	93,685	5.02	18,664 (13,830 to 29,010)
80	352,262	414.82	87,020	3.17	27,483 (21,076 to 41,821)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment.

with caution. Refer to the caveat on raloxifene results.

Figure 49 shows that the cost per QALY ratio is very seldom greater than £50,000. As with all raloxifene results these data should be interpreted with caution. Refer to the caveat on raloxifene results.

Teriparatide

Efficacy data from RCTs for teriparatide were found only for patients with severe osteoporosis (*Table 110*). The data for hip, wrist and proximal humerus had very wide confidence intervals and a second analysis was undertaken assuming that the intervention had no effect at these sites.

The modelling assumptions were very favourable towards teriparatide as the model assumed 3.5 years of full sustained effect after cessation of treatment followed by a period of 1 year linear decline to a no treatment level. This assumption will result in the estimated cost per QALY being lower than expected.

Owing to the acquisition price of the drug the average cost-effectiveness ratio is not below £200,000 cost per QALY at 70 or 80 years of age (*Table 111*).

Since the efficacy on hip fracture has a wide confidence interval that spans unity, the CEACs

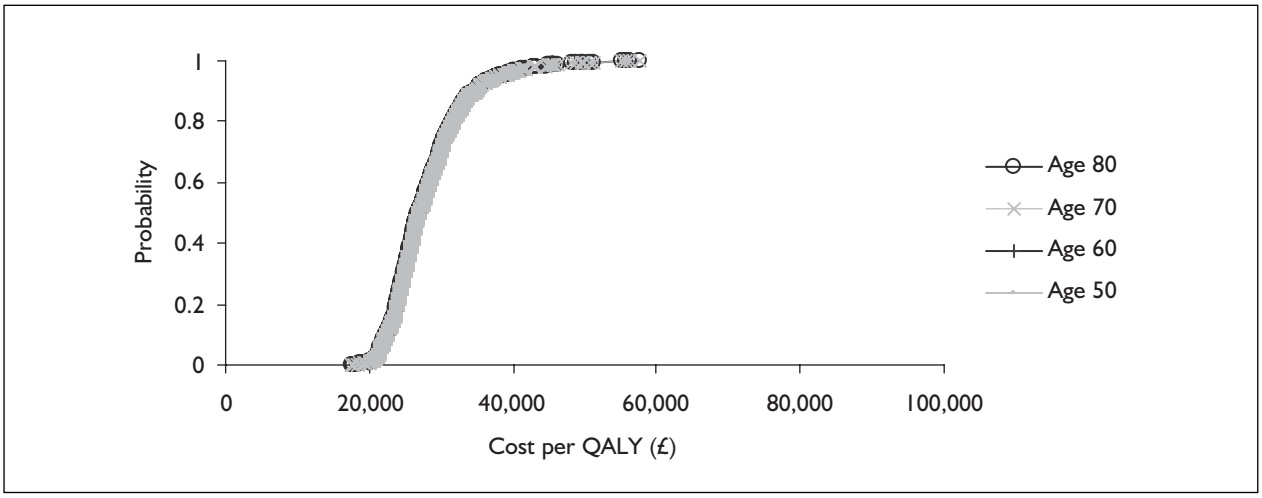

FIGURE 49 *CEACs for raloxifene in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis and no effect on non-vertebral fractures)*

TABLE 110 *Assumed efficacy of teriparatide in women without previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.35 (0.22 to 0.55)	0.50 (0.09 to 2.73)	0.54 (0.22 to 1.35)	0.80 (0.22 to 2.98)

TABLE 111 *Cost-effectiveness of teriparatide in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients without severe osteoporosis)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (90% CI)
70	700,239	566.16	542,041	2.19	247,660 (118,502 to Dominated)
80	772,144	413.98	506,902	2.33	218,020 79,026 to Dominated)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment.

are wide, with the drug being dominated approximately 10% of the time (*Figure 50*).

In the second analysis, teriparatide was assumed to have no effect on hip, wrist and proximal humerus fractures (*Table 112*). Owing to the acquisition price of the drug the average cost-effectiveness ratio is not below £300,000 cost per QALY at any age (*Table 113*).

The cost-effectiveness ratio is better at 70 than at 80 years of age owing to the higher incidence of vertebral fractures at this age. However, at both ages the cost per QALY is very high (>£300,000). By assuming no effect on non-vertebral fractures, teriparatide is never dominated, but the ranges of cost-effectiveness values are high (>£100,000) (*Figure 51*).

Oestrogen (HRT)

Efficacy data for oestrogen were taken from patients with severe osteoporosis, osteoporosis or osteopenia (*Table 114*). No data were available individually for hip, wrist and proximal humerus fractures. The confidence interval around non-vertebral fractures was high and it was assumed that the intervention would only affect vertebral fractures. Efficacy data from RCTs for other

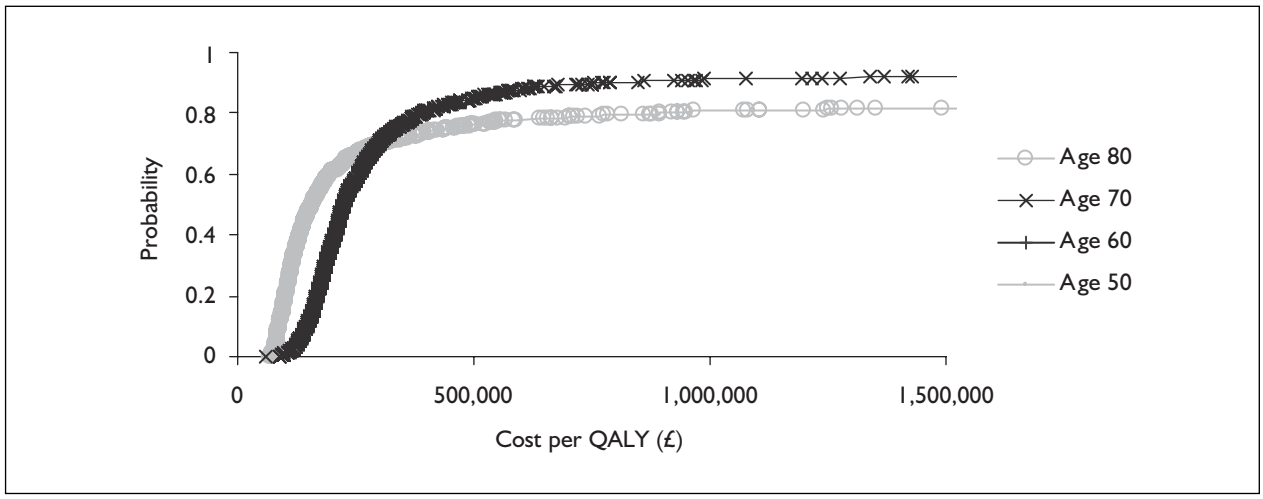

FIGURE 50 *CEACs for teriparatide in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis)*

TABLE 112 *The assumed efficacy of teriparatide in women without previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis and assuming no effect on hip, wrist or proximal humerus fractures)*

	Vertebral	Hip	Wrist	Proximal humerus
RR (95% CI)	0.35 (0.22 to 0.55)	Assumed no effect	Assumed no effect	Assumed no effect

TABLE 113 *Cost-effectiveness of teriparatide in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis or osteoporosis, and no effect of hip, wrist or proximal humerus fracture)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal Costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (90% CI)
70	715,854	565.64	557,629	1.68	332,440 (273,196 to 472,439)
80	816,570	412.62	551,329	0.96	573,427 (471,157 to 815,234)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment.

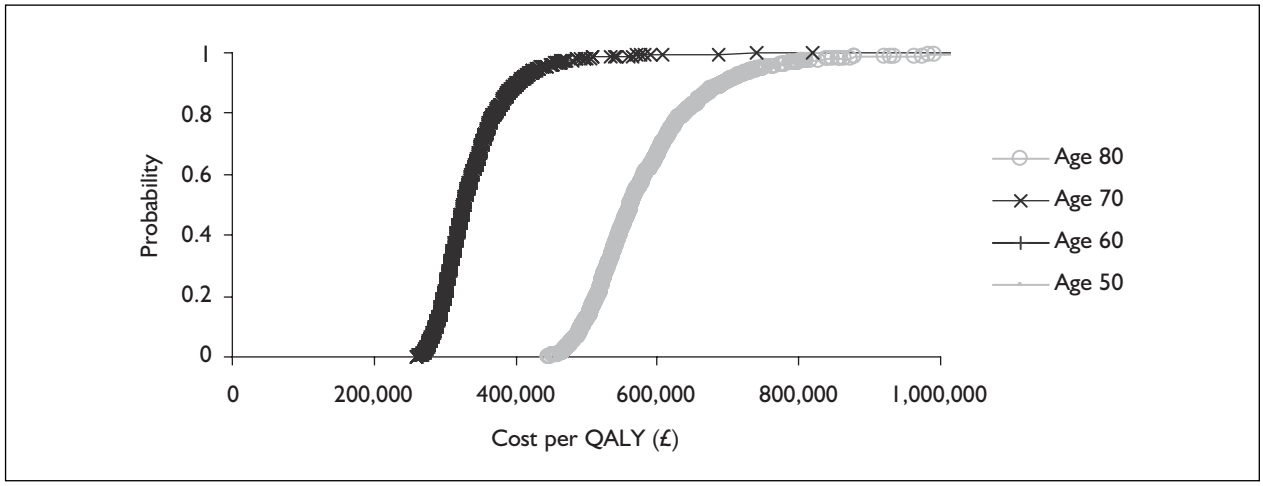

FIGURE 51 *CEACs for teriparatide in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis, and no effect of hip, wrist or proximal humerus fracture)*

TABLE 114 *Assumed efficacy of oestrogen in women without previous fractures and* T*-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis)*

	Vertebral	Hip	Wrist	Proximal humerus	Breast cancer
RR (95% CI)	0.71 (0.24 to 2.12)	Assumed no effect	Assumed no effect	Assumed no effect	1.27 (1.02 to 1.56)

TABLE 115 *Cost-effectiveness of oestrogen in women without previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (90% CI)
70	229,495	562.87	71,270	–1.09	Dominated (33,811 to Dominated)
80	322,487	410.92	57,245	–0.74	Dominated (54,772 to Dominated)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment.

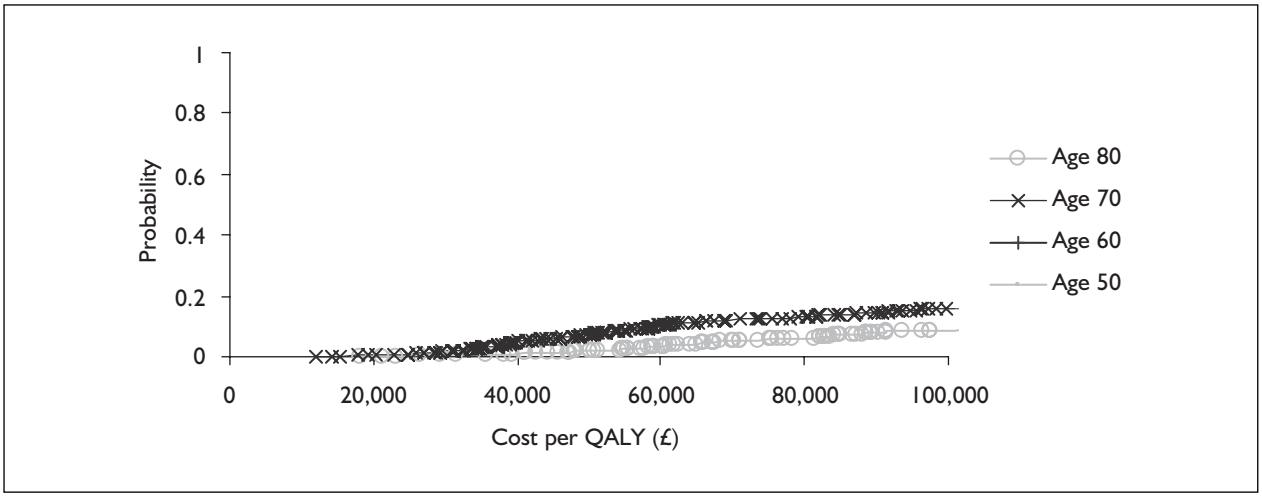

FIGURE 52 *CEACs for oestrogen in women without previous fractures and* T*-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis)*

patient groups were so wide that it was assumed there was no effect at any fracture site, which would result in the intervention never being cost-effective. The increased risk of breast cancer has been taken from Beral and colleagues.[29]

As oestrogen has been licensed for many years, a secondary analysis was undertaken allowing observational data to be used. These data were taken from Cauley and colleagues, assuming the multivariate adjusted values for women with a history of osteoporosis.[223]

Assuming data on efficacy from RCTs only, the average cost-effectiveness ratio is dominated by no treatment at all ages (*Table 115*). This is due to the adverse breast cancer effect and the lower incidence of fracture in patients without a prior fracture.

Owing to the wide confidence interval around vertebral fractures which spans unity, oestrogen is dominated approximately 70% of the time (*Figure 52*). This value is not seen on the graph as the *x* axis has been cropped at £100,000.

In the secondary analysis, observational efficiency data was incorporated (*Table 116*). At 70 years of age the cost per QALY ratio is dominated; at 80 years, where the fracture rates are greater, the

TABLE 116 *Assumed efficacy of oestrogen in women without previous fractures and T-scores of –2.5 (using the relative risks seen in patients with severe osteoporosis and observational data)*

	Vertebral	Hip	Wrist	Proximal humerus	Breast cancer
RR (95% CI)	0.71 (0.24 to 2.12)	0.86 (0.42 to 1.75)	0.32 (0.13 to 0.78)	0.63 (0.45 to 0.89)	1.27 (1.02 to 1.56)

TABLE 117 *Cost-effectiveness of oestrogen in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis and using observational data)*

Age (years)	Cost incurred (£)[a]	QALYs accrued	Marginal costs (£)[b]	Marginal QALYs[b]	Cost per QALY (£) (90% CI)
70	222,317	562.55	64,091	–1.41	Dominated (16,575 to Dominated)
80	294,296	412.44	29,055	0.78	37,307 (Dominating to Dominated)

[a] Including drug acquisition costs, GP consultations and BMD scans.
[b] Compared with no treatment.

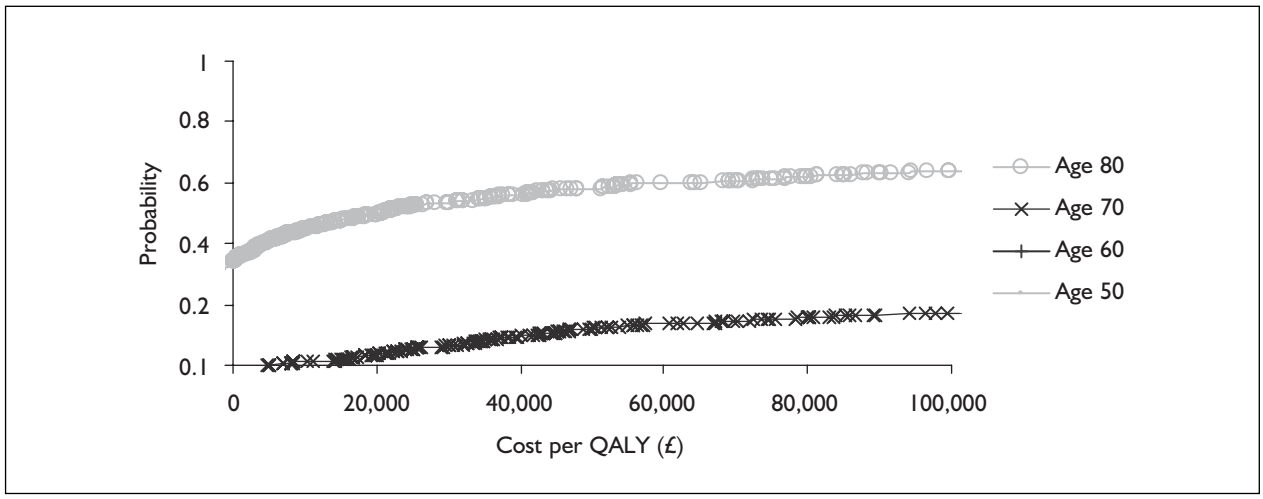

FIGURE 53 *CEACs for oestrogen in women without previous fractures and T-scores of –2.5 (assuming the relative risks seen in patients with severe osteoporosis and using observational data)*

adverse effects on breast cancer are less prominent and the cost per QALY ratio is £37,307 (*Table 117*). The confidence intervals around these results are very large, and at 80 years of age it spans from dominating to dominated.

By incorporating observational data the CEACs become much flatter owing to the wide confidence interval surrounding the efficacy of hip fracture (*Figure 53*). Oestrogen is dominated by no treatment on approximately 70% of occasions at 70 years and on 30% of occasions at 80 years of age.

Summary of treatment results assuming a woman at the threshold of osteoporosis and without a prior fracture

Results given are for a cohort of 100 women.

70 years of age

The most cost-effective drug at 70 years of age is raloxifene, with an average cost per QALY ratio under £20,000; however, this result must be treated with caution owing to the majority of health gains being accrued from breast cancer reduction. No other treatment has a cost per QALY below £30,000 (*Table 118*).

TABLE 118 *Cost-effectiveness for each treatment at 70 years of age, in women at the threshold of osteoporosis and with no prior fracture*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Alendronate	117,535	2.90	40,460	27,995 to 76,967
Risedronate	125,270	1.27	98,855	56,051 to 314,357
Etidronate	91,930	2.04	45,071	34,884 to 72,214
Etidronate[b]	82,299	2.44	33,677	Not calculated
Raloxifene*	93,685	5.02	18,664	13,830 to 29,010
Teriparatide	542,041	2.19	247,660	118,502 to Dominated
Teriparatide[c]	557,629	1.68	332,440	273,196 to 472,439
Oestrogen	71,270	–1.09	Dominated	33,811 to Dominated
Oestrogen[d]	64,091	–1.41	Dominated	16,575 to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

TABLE 119 *Cost-effectiveness for each treatment at 80 years of age, in women at the threshold of osteoporosis and with no prior fracture*

Intervention	Marginal cost (£)[a]	Marginal QALY[a]	Average cost per QALY[a]	90% CI[a]
Alendronate	43,802	3.60	12,181	888 to 66,984
Risedronate	63,152	3.55	17,240	7,230 to 40,528
Etidronate	78,720	1.09	72,007	55,478 to 116,176
Etidronate[b]	53,958	1.88	28,678	Not calculated
Raloxifene*	87,020	3.17	27,483	21,076 to 41,821
Teriparatide	506,902	2.33	218,020	79,026 to Dominated
Teriparatide[c]	551,329	0.96	573,427	471,157 to 815,234
Oestrogen	57,245	–0.74	Dominated	54,772 to Dominated
Oestrogen[d]	29,055	0.78	37,307	Dominating to Dominated

* See caveat on all raloxifene results.
[a] Compared with no treatment in women with sufficient calcium and vitamin D intakes.
[b] Incorporating observational data on hip and wrist fractures.
[c] Assuming skeletal effect on vertebral fractures only.
[d] Incorporating observational data on hip, wrist and proximal humerus fractures.

80 years of age

At 80 years of age, alendronate is estimated to have a cost per QALY below £15,000. This value is below £20,000 for risedronate. Raloxifene has a cost per QALY below £30,000, as does etidronate if observational data are considered. All other interventions have cost per QALY values in excess of £30,000 (*Table 119*).

Incremental analyses

The optimal order of interventions at each age band was calculated, assuming a cost per QALY threshold of £30,000. The results are presented in *Table 120*.

TABLE 120 *Optimal order of interventions at each age band for women at the threshold of osteoporosis and without a prior fracture, assuming a maximum cost per QALY threshold of £30,000*

Age (years)	
70	**80**
Raloxifene*	Alendronate
No treatment	Risedronate
	Raloxifene*
	Etidronate[a]
	No treatment

* See caveat on all raloxifene results.
[a] Assuming observational data on hip and wrist fractures.

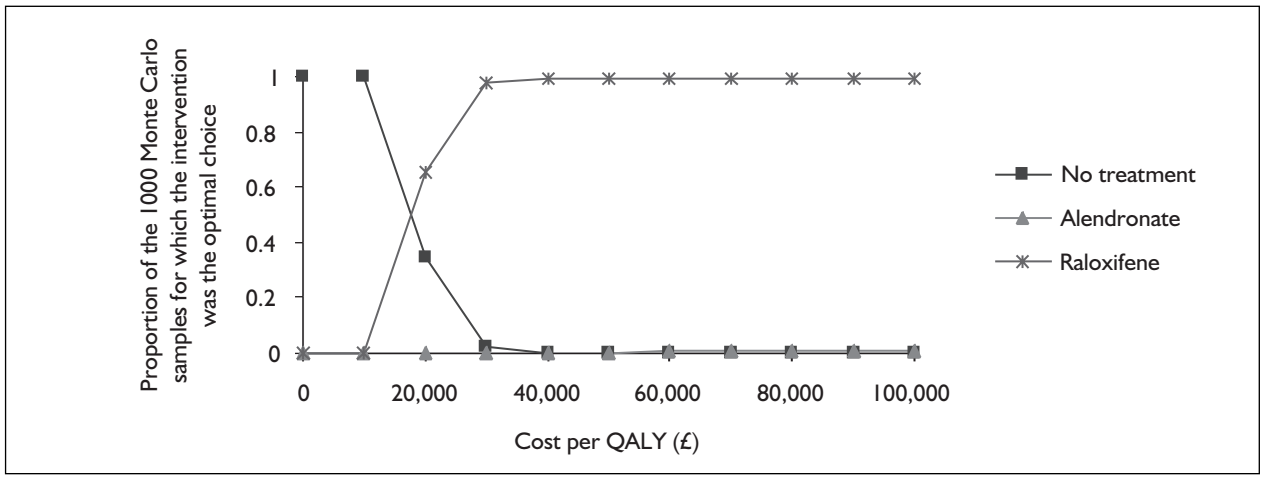

FIGURE 54 *CEAC for all interventions at 70 years of age, for women at the threshold of osteoporosis without a previous fragility fracture*

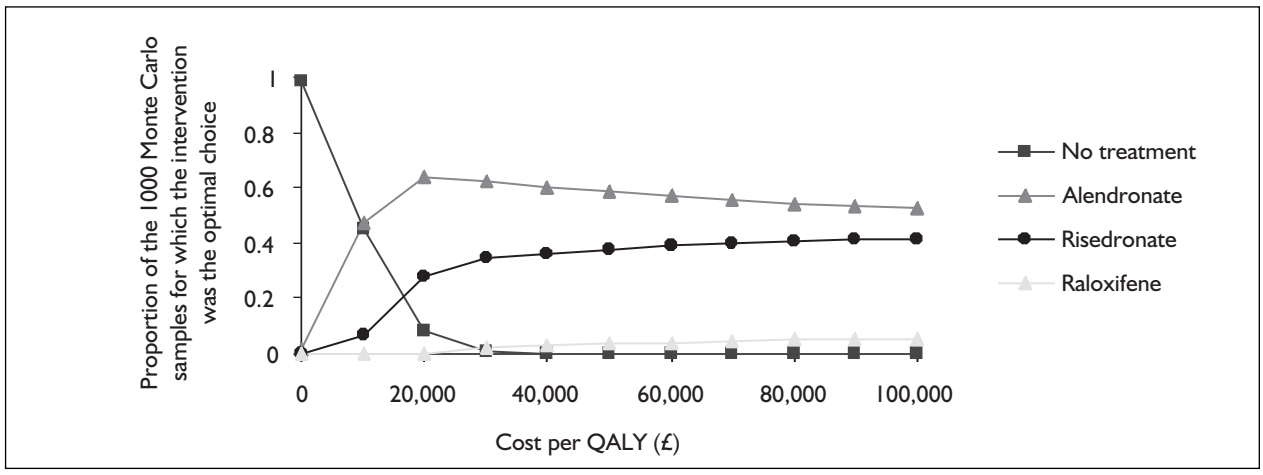

FIGURE 55 *CEAC for all interventions at 80 years of age, for women at the threshold of osteoporosis without a previous fragility fracture*

CEACs for all interventions

The default scenarios were used to calculate the CEACs, apart from raloxifene, where it was assumed that the intervention had no effect on non-vertebral fractures. For reasons of clarity, any intervention that did not have a probability of being optimal greater than 2.5% was omitted from the figures.

It can be seen from the multiple intervention CEACs in *Figures 54* and *55* that, assuming a cost per QALY threshold of £30,000, the intervention with the most probability of being optimal at 70 years of age is raloxifene. However, this conclusion is tempered by the caveat on raloxifene results discussed earlier. At 80 years of age alendronate is the intervention most likely to be optimal.

It was assumed that the effects of including death due to vertebral fractures and morphometric fractures, and the reduction in fall time would be less marked in a patient subset without a prior fracture than in a subset of those with a previous fracture. As such, these analyses were not undertaken for the prevention group.

No analyses were undertaken assuming that the fracture rates were double those for women at the threshold of osteoporosis with no other risk factors. The rationale for omitting these analyses is that these results would be similar to those in patients at the threshold where a fracture had been sustained, since the majority of relative risks for subsequent fractures given by Klotzbuecher and colleagues[15] are close to 2.

The output from this model was compared with that of the submission models[38–40] and a discussion of the differences in the results is given in Appendix 16.

TABLE 121 *Expected number of women suffering from osteoporosis and severe osteoporosis*

Age (years)	No. of women suffering severe osteoporosis	No. of women suffering osteoporosis	No. of women who do not have osteoporosis
50–54	6,700	16,400	1,332,300
55–64	305,300	137,100	2,036,600
65–74	437,500	106,800	1,223,900
⩾75	652,100	198,700	1,530,400

TABLE 122 *Estimated cost (£ million) over a 10-year period of treating all women with severe osteoporosis (costs include GP consultations and BMD scans)*

	Age (years)			
	50–54	55–64	65–74	⩾75
Alendronate	15.2	173.3	449.0	902.9
Risedronate	14.5	165.6	428.7	861.6
Etidronate[a]	9.7	110.8	284.5	568.9
Raloxifene	13.5	153.8	396.8	795.9

[a] The acquisition costs for etidronate when observational data are assumed are slightly greater owing to a marginally increased survival rate within the 5-year treatment period.

Calculating the expected cost to the NHS of treating patients with severe osteoporosis

Work was undertaken to analyse the impact on NHS resources were each intervention prescribed exclusively to all patients with osteoporosis. The costs presented assume 100% compliance, with each treatment being taken for 5 years, or until patient death. The effect of compliance on these figures can be estimated assuming that the total expenditure is proportionate to the compliance level.

These calculations were not undertaken for teriparatide, given the very small subset of patients at whom the intervention is targeted.

The assumed prevalence of osteoporosis was shown in *Figure 1* (see Chapter 2). The estimated proportion of these patients who have suffered a fracture is provided in Appendix 1. The number of women in England and Wales aged between 50 and 110 years[11] was multiplied by these figures to estimate the absolute number of patients with osteoporosis and established osteoporosis. The results are summarised in *Table 121*.

The acquisition cost for each intervention of treating all women with severe osteoporosis for a 5-year period is given in *Table 122*. These costs are discounted at 6% and include the cost of BMD scans in years 2 and 5, and the costs of two GP visits per annum.

The estimated net monetary expenditure for each intervention when fractures and breast cancer events avoided are included is given in *Table 123*. It was assumed that the average savings within the age band are equal to those of the middle age, except in the age group 50–54 years, where savings equivalent to 50-year-old women were assigned.

The estimated net expenditure when it is assumed that the fracture rates are doubled, owing to either a T-score of –3.22 or non-skeletal reasons, is given in *Table 124*.

The cost for each intervention of treating all women with osteoporosis, but without a prior fracture, for a 5-year period is given in *Table 125*. These costs are discounted at 6% and include the cost of BMD scans in years 2 and 5, and the costs of two GP visits per annum.

The estimated net monetary expenditure for each intervention when fractures and breast cancer events avoided are included is given in *Table 126*. It has been assumed that the average savings within the age band are equal to those of the middle age, except in the age group 50–54 years,

TABLE 123 *Estimated net cost (£ million) over a 10-year period for each intervention of treating all women with severe osteoporosis*

	Age (years)			
	50–54	**55–64**	**65–74**	**⩾75**
Alendronate	13.4	144.6	272.6	29.4
Risedronate	13.0	141.1	297.3	171.8
Etidronate	9.5	108.1	256.5	486.1
Etidronate[a]	9.0	122.4	367.0	556.8
Raloxifene*	12.9	100.8	212.8	257.0

* See caveat on all raloxifene results.
[a] Assuming observational data.

TABLE 124 *Estimated net cost (£ million) over a 10-year period for each intervention of treating all women with severe osteoporosis (assuming that the fracture risk is doubled in all patients)*

	Age (years)			
	50–54	**55–64**	**65–74**	**⩾75**
Alendronate	11.5	115.7	95.7	–846.7
Risedronate	11.5	116.4	263.7	–520.8
Etidronate	9.2	105.3	228.0	399.9
Etidronate[a]	8.3	90.6	140.6	–58.3
Raloxifene*	12.8	120.6	349.7	503.6

* See caveat on all raloxifene results.
[a] Assuming observational data.

TABLE 125 *Estimated cost (£ million) over a 10-year period for each intervention of treating all women with osteoporosis and no prior fracture*

	Age (years)	
	65–74	**⩾75**
Alendronate	202.2	254.4
Risedronate	193.2	242.8
Etidronate[a]	128.8	160.5
Raloxifene*	178.7	224.5

* See caveat on all raloxifene results.
[a] The acquisition costs for etidronate when observational data are assumed are slightly greater owing to a marginally increased survival rate within the 5-year treatment period.

TABLE 126 *Estimated net cost (£ million) over a 10-year period for each intervention of treating all women with osteoporosis and no prior fracture*

	Age (years)	
	65–74	**⩾75**
Alendronate	150.5	80.0
Risedronate	160.4	115.3
Etidronate	117.7	143.7
Etidronate[a]	119.9	158.8
Raloxifene*	105.4	98.5

* See caveat on all raloxifene results.
[a] Assuming observational data.

where savings equivalent to 50-year-old women were assigned. Costs were discounted at 6% per annum.

The estimated net expenditure when it is assumed that the fracture rates are doubled, owing to either a *T*-score of –3.22 or non-skeletal factors, is given in *Table 127*. These values have been calculated assuming that the costs recouped from fractures avoided and breast cancer events avoided by doubling the risk of a patient with osteoporosis will equal the costs recouped from a person with severe osteoporosis at the same age.

TABLE 127 *Estimated net cost (£ million) for each intervention of treating all women with osteoporosis and no prior fracture assuming that the fracture risk is doubled*

	Age (years)	
	65–74	**⩾75**
Alendronate	121.6	48.4
Etidronate	114.4	136.8
Etidronate[a]	94.9	156.7
Raloxifene*	163.7	72.3

* See caveat on all raloxifene results.
[a] Assuming observational data.

Chapter 5
Discussion

A cost-effectiveness analysis was undertaken on interventions for osteoporosis, with systematic reviews undertaken of costs, efficacy and utilities. The model was populated with data drawn from the UK where possible. The principal findings of this report are that there are effective treatments for women suffering osteoporosis and that these can be given cost-effectively under some circumstances. Conversely, there are effective treatments that cannot be given cost-effectively under some circumstances.

Owing to resource constraints analyses were only undertaken at the threshold of osteoporosis and at double this fracture risk. Where interventions were cost-effective at double risk, but not at single risk, it does not mean that a doubled risk is absolutely necessary for cost-effectiveness. In circumstances where the cost per QALY value at single risk is marginally above an assumed cost-effectiveness ratio, smaller increased risk may well produce cost-effective scenarios.

The calculations of cost-effectiveness allowed a provisional incremental order of interventions to be established, with bisphosphonates being the preferred choice in patients at high risk. In patients at lower risk raloxifene becomes the agent of choice; however, this is dependent on the effects of breast cancer, which may have been modelled inaccurately.

There was a need to assume the efficacy of interventions in patient populations of a different age to those enrolled in the RCT. Although it may seem appropriate to assume that the relative risk of fracture is constant across the age ranges, this has yet to be proven in RCTs to be correct. Conversely, a trial by McClung[221] showed that risedronate had a non-significant efficacy in the elderly, which contrasts with RCTs in patients of lower ages. Caution therefore must be applied when analysing the results produced for patients aged 80 years.

The results were calculated assuming that women who receive no treatment have sufficient intakes of calcium and vitamin D. If patients were deficient in calcium and vitamin D then the initiation of an intervention, with accompanying calcium and vitamin D, would produce better results than those estimated, hence the results produced may be conservative.

The results produced at the threshold of osteoporosis were provided as an indication of whether all patients with this disease should be treated. As reported by Kanis and colleagues,[207] the RRs for patients across the entire osteoporosis spectrum are likely to have double this risk. If a decision is made to treat all patients with osteoporosis then the analyses assuming double risk may be the most appropriate results to consider.

The cost-effectiveness results for each intervention are summarised and presented graphically (*Figures 56–62*). The following scenarios were analysed at the ages of 50, 60, 70 and 80 years for each intervention:

- women at the threshold of osteoporosis with a prior fracture
- women at the threshold of osteoporosis with a prior fracture, assuming that the fracture risk is doubled at each site
- women at the threshold of osteoporosis without a prior fracture; this analysis was only presented at the ages of 70 and 80 years.

It was assumed that when the fracture risk is doubled for women at the threshold of osteoporosis and no prior fracture, the results will be broadly similar to those for women at the threshold of osteoporosis and with a prior fracture.

To aid clarity in the figures presented, on any occasion where the intervention dominates no treatment in women with sufficient intake of calcium and vitamin D, an illustrative value of –£10,000 cost per QALY is shown.

The submission for etidronate[38] incorporates observational data from van Staa and colleagues.[222] Including a 15% reduction in hip fractures and an 8% reduction in wrist fracture markedly improves the cost-effectiveness ratio (*Figures 58* and *59*).

The results for raloxifene are dependent on the assumption regarding the efficacy on hip, wrist

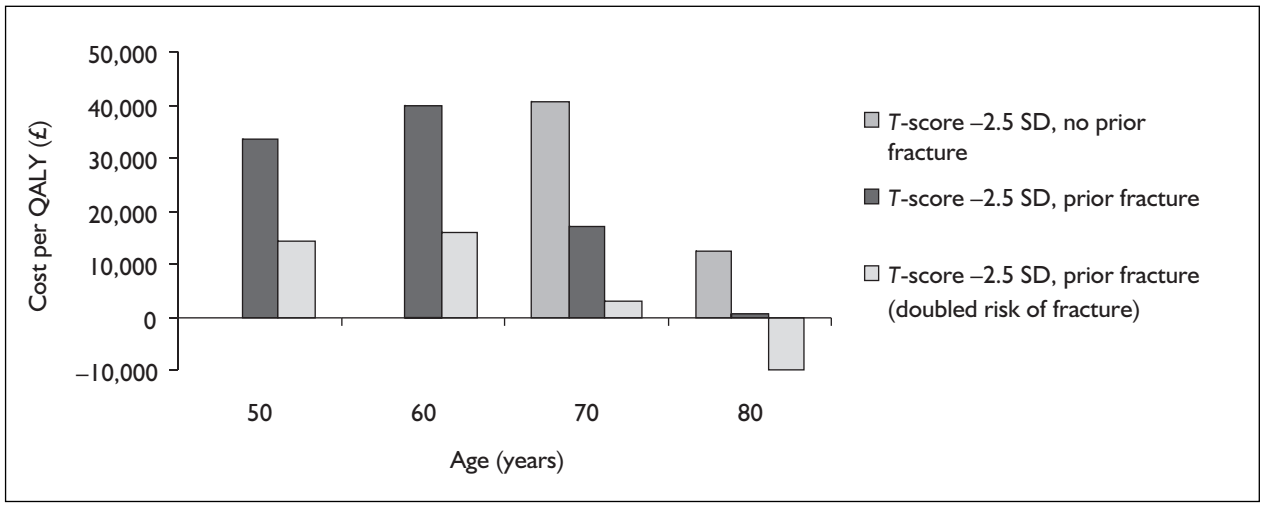

FIGURE 56 *Estimated cost-effectiveness of alendronate*

Risedronate

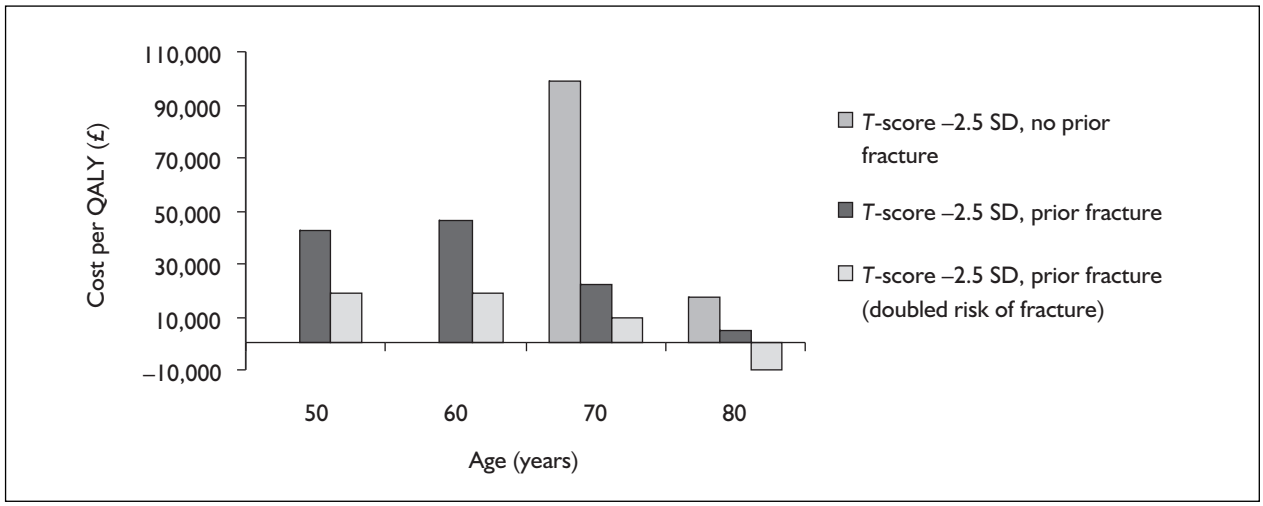

FIGURE 57 *Estimated cost-effectiveness of risedronate*

and proximal humerus fractures (*Figure 60*). However, the key factor that influences the cost-effectiveness of raloxifene is the effect on breast cancer. Caution must be applied when interpreting these results as the appraisal model was not intended to be a dedicated model of breast cancer, and the simplifying assumptions made may change the accuracy of the results.

A critical component of the cost-effectiveness of teriparatide is the assumed efficiency regarding hip fracture (*Figures 61* and *62*). A crucial component, however, is the assumed efficacy regarding hip fracture. Teriparatide has been shown to have an average relative risk of 0.50 (90% CI 0.09 to 2.73). Analyses were undertaken using this distribution, but were also undertaken assuming that teriparatide has no effect on the incidence of hip fracture. It is recommended that a further trial of teriparatide be undertaken to reduce the wide uncertainty around the reduction in the incidence of hip fracture.

[*Commercial-in-confidence information removed.*]

For each intervention, a scenario was found where the cost per QALY ratio is below £50,000. For some interventions the conditions required to meet such a threshold are more stringent than for other interventions.

For alendronate and risedronate the cost per QALY at 70 years of age or older is less than £25,000 for severe osteoporotics. For patients

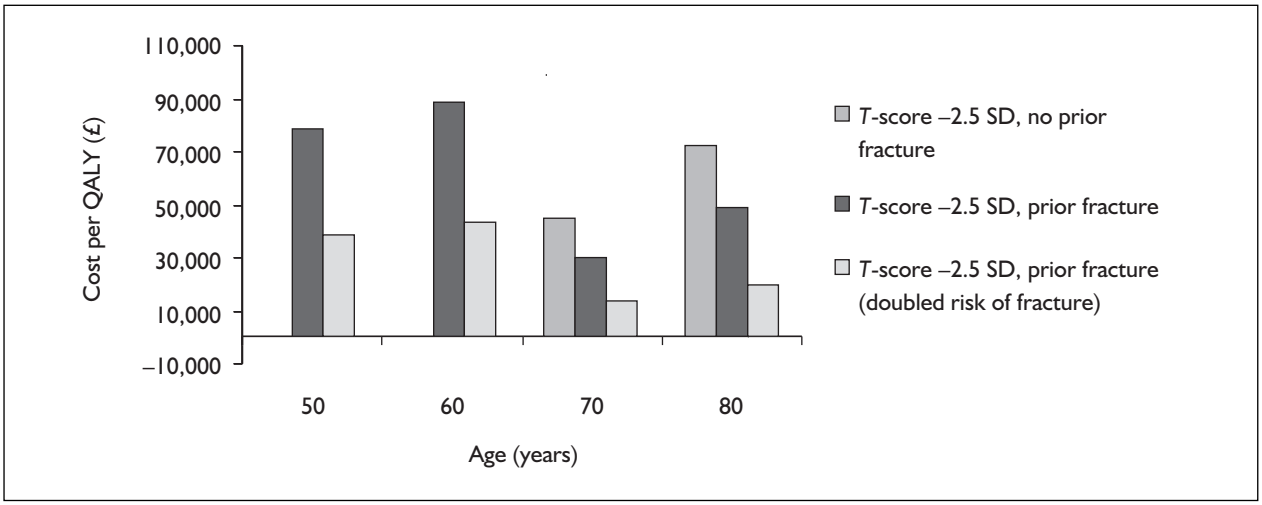

FIGURE 58 *Estimated cost-effectiveness of etidronate*

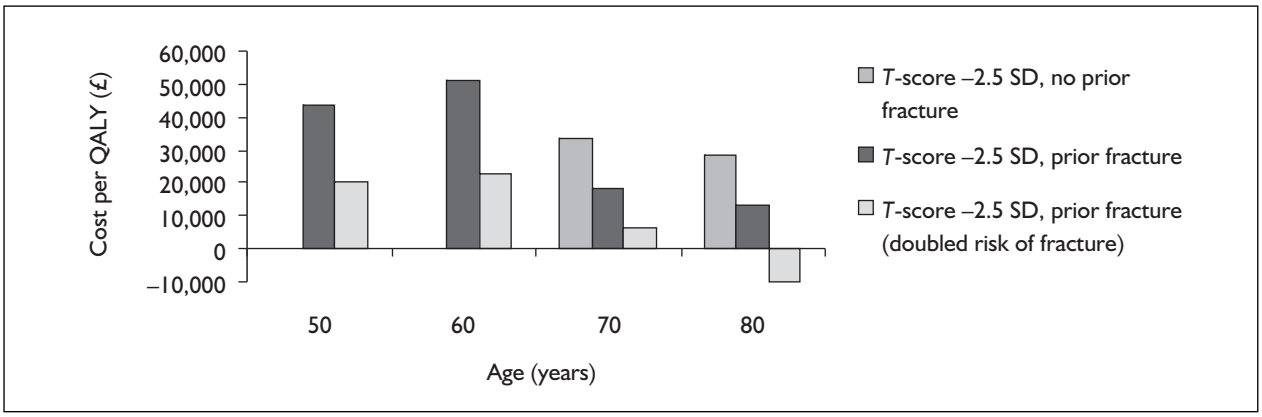

FIGURE 59 *Estimated cost-effectiveness of etidronate when including observational data*

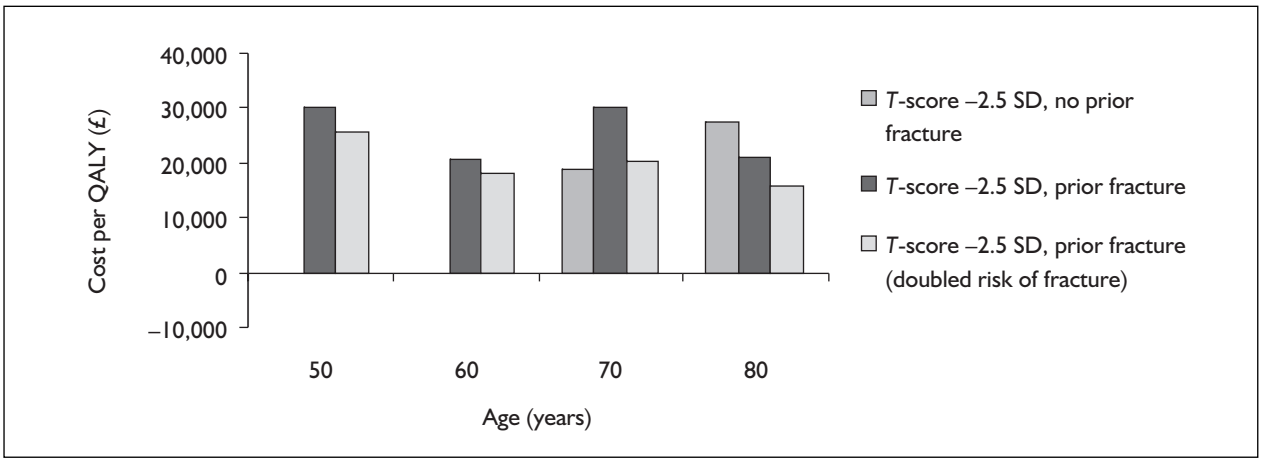

FIGURE 60 *Estimated cost-effectiveness of raloxifene (assuming no effect on hip, wrist or proximal humerus fracture)*

without a previous fracture these interventions become cost-effective at 80 years or older. Where the risk is doubled, owing to a lower *T*-score or other factors, these ratios improve, and the cost per QALY values for severe osteoporotics are approximately £20,000 at all ages.

The cost-effectiveness of etidronate is largely dependent on whether observational data should be used to estimate efficacy. Using RCT data only, the cost per QALY for women with severe osteoporosis is below £30,000 only at 70 years of age. When observational data are incorporated the

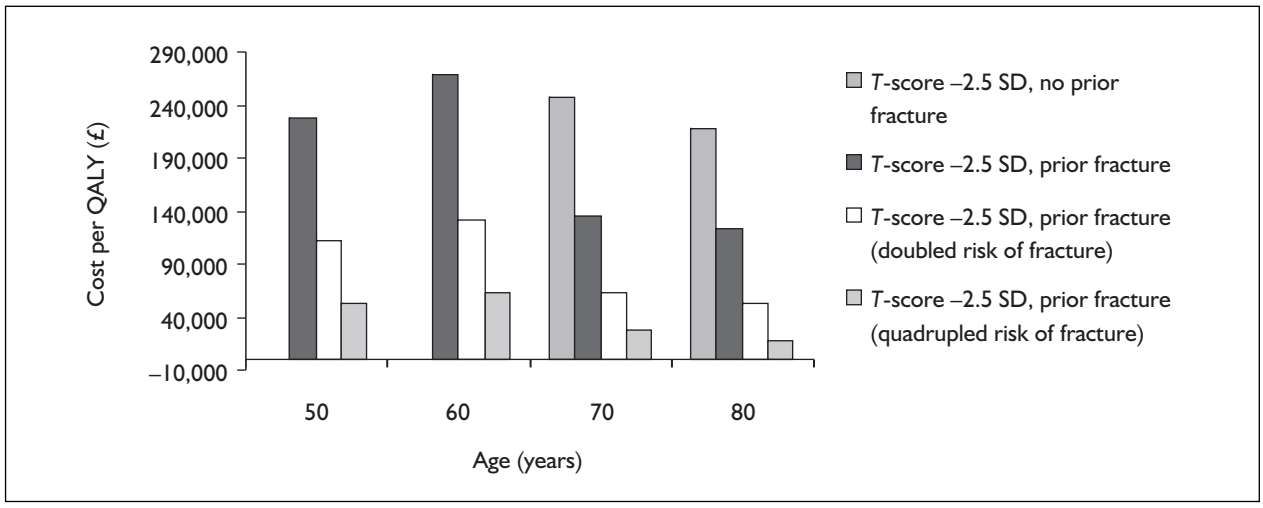

FIGURE 61 *Estimated cost-effectiveness of teriparatide, using RCT data*

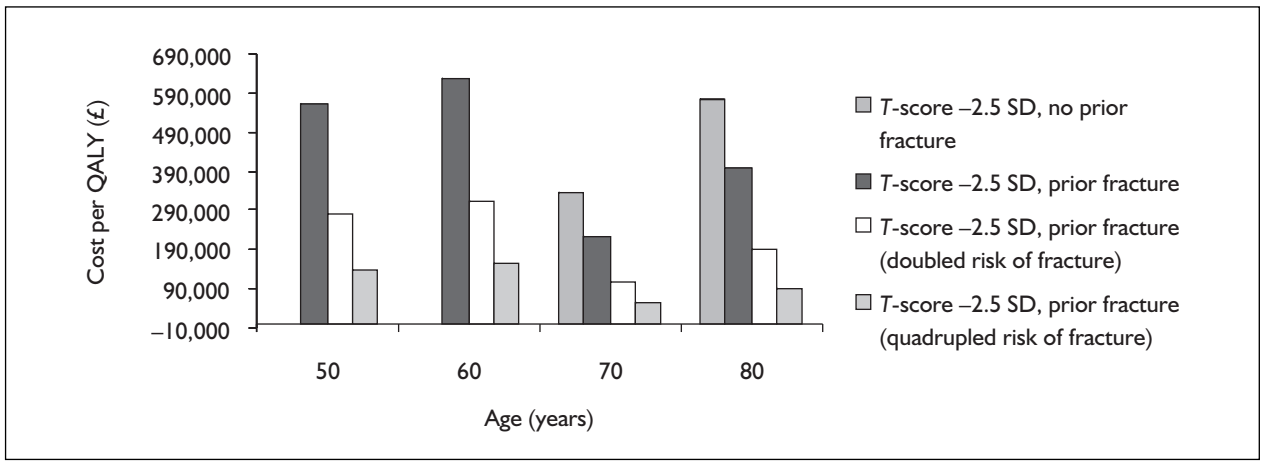

FIGURE 62 *Estimated cost-effectiveness of teriparatide (assuming no effect on hip, wrist or proximal humerus fracture)*

ages at which cost-effectiveness is met are 70 and 80 years. An RCT to estimate the true efficacy of etidronate would allow a more accurate assessment of the cost per QALY value to be estimated.

The cost-effectiveness ratio derived for raloxifene is impacted on greatly by the effect on breast cancer. Without this effect the cost per QALY ratios rose from £30,000 at 60 years of age to greater than £100,000. This creates uncertainty as the appraisal model has used simplifying assumptions and may not be an accurate representation of the implications of breast cancer.

For teriparatide the cost per QALY only falls below £30,000 when it is assumed that the effect of teriparatide on hip fracture is beneficial (RR 0.50, 95% CI 0.09 to 2.73) and that women aged 70 and 80 years are at high risk of future fractures. An example of such a risk would be quadruple that of a woman at the threshold of osteoporosis and with a prior fracture.

Chapter 6
Conclusions

Alendronate and risedronate produced results that would generally be considered as cost-effective at 70 and 80 years of age. Etidronate would have similar values if observational data were included in the efficacy analysis, but is only likely to be considered cost-effective at 70 years of age, when observational data are excluded. The cost-effectiveness of raloxifene reached levels that are generally considered by policy makers to represent acceptable value for money, at 60 years of age, but this result depends on the inclusion of health benefits from the reduced incidence of breast cancer. Teriparatide is unlikely to be considered cost-effective at any age.

When a doubled risk is assumed, alendronate and risedronate are likely to be considered cost-effective at all ages. When observational data are included, the same is true for etidronate. When observational data are excluded, etidronate appears less cost-effective, and is likely to be considered acceptable value for money only at 70 and 80 years of age. The results for raloxifene again suggest acceptable cost-effectiveness at all ages, but with the result being greatly influenced by the impact on breast cancer. Again, the cost-effectiveness of teriparatide is estimated at levels that are not generally considered to represent acceptable value for money by policy makers.

Analyses were undertaken to establish the conditions under which teriparatide might be considered cost-effective. It was estimated that a quadrupling of fracture risk in women aged 70 and 80 years would be needed for teriparatide to reach generally accepted levels of cost-effectiveness. However, owing to uncertainty in the efficacy of teriparatide in treating hip fracture, this result has wide confidence intervals consistent with the extreme cases of teriparatide being either cost-saving and beneficial or not beneficial and more costly.

For patients without a fracture, the three bisphosphonates (assuming observational data for etidronate) have a cost per QALY ratio of less than £30,000 only at 80 years of age, or at 70 years when it is assumed that the risk of fracture is doubled.

For patients at a high risk of fracture, doubled risk with a prior fracture, or 70 or 80 years of age with a prior fracture, alendronate and risedronate produced the most cost-effective results. If the observational data from etidronate were to be included then this intervention would produce similar results.

In patients with a lower risk of fracture, raloxifene is the optimal treatment; however, this is due far more to its effects on breast cancer than on vertebral fracture reduction.

Owing to its higher acquisition cost, teriparitide is cost-effective only in patients with a very high fracture risk, and this intervention has a high incremental cost per QALY compared with alendronate or risedronate.

Chapter 7

Need for further research

A key research recommendation is that the evidence base for the efficacy of interventions in women aged 80 years and over be strengthened. At present this age range has the potential to provide substantial savings for the NHS, assuming that the efficacies seen in patients at younger ages are applicable. If, as seen in the RCT reported by McClung,[221] interventions do not significantly reduce the number of hip fractures at 80 years of age and over, the conclusions on the cost-effectiveness at this age would be dramatically different.

The cost-effectiveness data provide a provisional hierarchical order of cost-effectiveness, but this may not be robust owing to the lack of head-to-head trials between interventions. Without such trials either the provisional order should be taken or no distinction made between drugs with similar characteristics, such as alendronate and risedronate.

To model accurately the cost-effectiveness of raloxifene it is recommended that its efficacy on breast cancer is assessed using a dedicated breast cancer model. The model used in this report was initially developed to assess the cost-effectiveness of interventions that reduce osteoporotic fractures, with a simplified model of breast cancer additionally incorporated. In this respect alone, raloxifene had high cost per QALY ratios, which were estimated at significantly lower levels when breast cancer was included. The robustness of these results cannot be guaranteed.

The advancement of osteoporosis modelling should be continued. It is clear that the risks associated with being osteoporotic are not constant, as the risks at the age of 70 years will be much greater than at 50 years. The decision to treat should not be based on *T*-score alone, but should ideally be based on the absolute risk of fracture for a patient in the forthcoming year.

Acknowledgements

This work has been built on the foundations of work undertaken for the NCCHTA, whose authors included Professor John Kanis, Dr Neill Calvert, Professor John Brazier and Dr Eugene McCloskey. Dr Jean Peters assisted in sifting abstracts. Professor John Brazier advised on the health state utility values used in the model and read and commented on a draft version of the report. Mr Stephen Walters advised on the meta-analysis of the efficacy data. All responsibility for the contents of the report remains with the authors.

This research was commissioned by the NHS R&D Executive HTA Programme. 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.

Contributions of authors

Matt Stevenson (Operational Research Analyst) carried out the review of the background information and the cost-effectiveness analyses. Myfanwy Lloyd-Jones (Research Fellow) carried out the clinical effectiveness review. Enrico de Nigris (Research Assistant) undertook the review of the utility values. Jeremy Oakley (Lecturer) produced the meta-model from the individual patient model data. Sarah Davis (Operational Research Analyst) ran the meta-model and collated and compiled the final set of results given the changes we had to make following the release of new data.Naomi Brewer (Information Officer) undertook the electronic literature searches.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the four schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost-effectiveness of healthcare interventions for the NHS R&D HTA Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence. ScHARR-TAG is part of a wider collaboration of six units from other regions. The other units are: Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

References

1. Department of Health. *Dietary reference values for food energy and nutrients for the United Kingdom*. Vol. 41. London: HMSO; 1991.
2. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 2003;**94**:646–50.
3. Keene GS, Parker MJ, Pryor GA. Mortality and morbidity after hip fractures. *BMJ* 1993; **307**:1248–50.
4. Torgerson DJ, Dolan P. The cost of treating osteoporotic fractures in the United Kingdom female population – the author replies. *Osteoporos Int* 2000;**11**:551–2.
5. Burge RT, Worley D, Johansen A, Bhattacharyya S, Bose U. The cost of osteoporotic fractures in the UK: projections for 2000–2020. *Journal of Medical Economics* 2001;**4**:51–2.
6. World Health Organization. *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis*. Report No. 843. Geneva: WHO; 1994.
7. Kanis JA, Melton LJ III, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res* 1994;**9**:1137–41.
8. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, *et al*. A meta-analysis of BMD as a predictor of fracture risk. *J Bone Miner Res*; in press.
9. Oden A, Dawson A, Dere W, Johnell O, Jonsson B, Kanis JA. Lifetime risk of hip fractures is underestimated. *Osteoporos Int* 1998;**8**:599–603.
10. Holt G, Khaw KT. Prevalence of osteoporotic bone mineral density at the hip in Britain differs substantially from the US over 50 years of age: implications for clinical densitometry. *Br J Radiol* 2002;**75**:736–42.
11. Office for National Statistics. *National population projections 1998-based*. Series PP2, No. 22. London: The Stationery Office; 2000.
12. Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15,000 adults: the influence of age and gender. *J Bone Joint Surg Br* 1998;**80**:243–8.
13. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, *et al*. Long-term risk of osteoporotic fracture in Malmö. *Osteoporos Int* 2000;**11**:669–74.
14. Kanis JA, Johnell O, Oden A, De Laet C, Jonsson B, Dawson A. Ten-year risk of osteoporotic fracture and the effect of risk factors on screening strategies. *Bone* 2002;**30**:251–8.
15. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA III, 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**:721–39.
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. Meyer HE, Tverdal A, Falch JA, Pedersen JI. Factors associated with mortality after hip fracture. *Osteoporos Int* 2000;**11**:228–32.
18. Poor G, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Determinants of reduced survival following hip fractures in men. *Clin Orthop* 1995;(319):260–5.
19. Todd CJ, Freeman C, Camilleri-Ferrante C, Laxton C, Murrell P, Palmer C, *et al*. Cambridge Health Services Research Group. *Anglian audit of hip fracture 2*. Cambridge: Cambridge Health Services Research Group, University of Cambridge; 1999.
20. Parker MJ, Anand JK. What is the true mortality of hip fractures? *Public Health* 1991;**105**:443–6.
21. 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.
22. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. *Osteoporos Int* 2000;**11**:556–61.
23. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1999;**159**:1215–20.
24. Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. *J Clin Endocrinol Metab* 2000;**85**:1895–900.
25. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, *et al*. Mortality after osteoporotic fracture. *Osteoporos Int* 2004;**15**(1): 38–42.
26. Jonsson B, Christiansen C, Johnell O, Hedbrandt J, Karlsson G. Cost-effectiveness of

fracture prevention in established osteoporosis. *Scand J Rheumatol* 1996;**25**:30–8.

27. Office for National Statistics. *Mortality series*. DH2 No. 25. London: The Stationery Office; 1998.
28. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HA. Coronary event and case fatality rates in an English population: results of the Oxford Myocardial Infarction Incidence Study. The Oxford Myocardial Infarction Incidence Study Group. *Heart* 1998;**80**:40–4.
29. Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet* 2002; **360**:942–4.
30. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, *et al*., MORE Investigators (Multiple Outcomes of Raloxifene Evaluation). Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 2002;**287**:847–57.
31. Office for National Statistics. *Cancer survival trends in England and Wales 1971–1995. Deprivation and NHS region*. London: HMSO; 2001.
32. 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. Study of Osteoporotic Fractures Research Group. *JAMA* 1996;**276**:1404–8.
33. 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.
34. Government Actuary Department. *Expectations of life: United Kingdom females* – 1999. London; Government Actuary Office; 1999.
35. Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. Study of Osteoporotic Fractures Research Group. *Lancet* 1991;**338**:355–8.
36. 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.
37. Van Der Klift M, Pols HA, Geleijnse JM, Van Der Kuip DA, Hofman A, De Laet CE. Bone mineral density and mortality in elderly men and women: the Rotterdam Study. *Bone* 2002;**30**:643–8.
38. Procter & Gamble Pharmaceuticals. The clinical and cost-effectiveness of Didronel PMO in the prevention of osteoporotic fractures. Submission to the National Institute for Clinical Excellence; 2002.
39. Eli Lilly and Company. The clinical effectiveness and cost effectiveness of Evista (raloxifene) in the prevention and treatment of osteoporosis. Submission to the National Institute for Clinical Excellence; 29 November 2002.
40. Eli Lilly and Company. The clinical effectiveness and cost effectiveness of Forsteo (teriparatide) in the treatment of osteoporosis. Submission to the National Institute for Clinical Excellence; 29 November 2002.
41. British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary*. 2002. URL: http://www.bnf.org/. Accessed 6 January 2003.
42. Merck Sharp & Dohme. The clinical and cost effectiveness of alendronate (Fosamax®) for the treatment of osteoporosis and prevention of fractures. Report for submission to the National Institute for Clinical Excellence; 29 November 2002.
43. Alliance for Better Bone Health: Aventis UK and Procter & Gamble Pharmaceuticals UK. The clinical and cost effectiveness of risedronate in the prevention of osteoporotic fracture. Submission to the National Institute for Clinical Excellence; 2 December 2002.
44. European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products. *Summary of opinion for Forsteo*. URL: http://www.emea.eu.int/pdfs/human/opinion/60660 2en.pdf. Accessed 12 December 2002.
45. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, *et al*., for the FIT Research Group. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab* 2000;**85**:4118–24.
46. Cranney A, Tugwell P, Wells G, Guyatt G. Systematic reviews of randomized trials in osteoporosis: introduction and methodology. *Endocr Rev* 2002;**23**:497–507.
47. Voss S, Quail D, Dawson A, Backstrom T, Aguas F, Erenus M, *et al*. A randomised, double-blind trial comparing raloxifene HCl and continuous combined hormone replacement therapy in postmenopausal women: effects on compliance and quality of life. *BJOG* 2002;**109**:874–85.
48. Shintani M, Beppu K, Hara Y. Effect of etidronate therapy on lumber spine bone mineral density in women with osteopenia or osteoporosis [in Japanese]. *Acta Obstet Gynecol Jpn* 1998;**50**:186–8.
49. Aitken JM, Hart DM, Lindsay R. Oestrogen replacement therapy for prevention of osteoporosis after oophorectomy. *BMJ* 1973; **3**:515–18.
50. Alexandersen P, Riis BJ, Christiansen C. Monofluorophosphate combined with hormone replacement therapy induces a synergistic effect on bone mass by dissociating bone formation and

resorption in postmenopausal women: a randomized study. *J Clin Endocrinol Metab* 1999; **84**:3013–20.

51. Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. *Osteoporos Int* 1998;**8**:255–60.

52. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, *et al*. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. *J Clin Endocrinol Metab* 2000;**85**:720–6.

53. Caniggia A, Delling G, Nuti R, Lore F, Vattimo A. Clinical, biochemical and histological results of a double-blind trial with 1,25-dihydroxyvitamin D_3, estradiol and placebo in post-menopausal osteoporosis. *Acta Vitaminologica et Enzymologica* 1984;**6**:117–28.

54. Chesnut CH III, 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.

55. Delmas PD, Confavreux E, Garnero P, Fardellone P, de Vernejoul MC, Cormier C, Arce JC. A combination of low doses of 17 beta-estradiol and norethisterone acetate prevents bone loss and normalizes bone turnover in postmenopausal women. *Osteoporos Int* 2000; **11**:177–87.

56. 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.

57. Eiken P, Pors NS, Kolthoff N. Effects on bone mass after eight years of hormonal replacement therapy. *British Journal of Obstetrics and Gynaecology* 1997; **104**:702–7.

58. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab* 2001;**86**:3618–28.

59. Genant HK, Lucas J, Weiss S, Akin M, Emkey R, McNaney-Flint H, *et al*. Low-dose esterified estrogen therapy: effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. Estratab/Osteoporosis Study Group. *Arch Intern Med* 1997;**157**:2609–15.

60. Greenspan SL, Schneider DL, McClung MR, Miller PD, Schnitzer TJ, Bonin R, *et al*. Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002; **136**:742–6.

61. 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.

62. Herd RJM, Balena R, Blake GM, Ryan PJ, Fogelman I. The prevention of early postmenopausal bone loss by cyclical etidronate therapy: a 2-year, double-blind, placebo-controlled study. *Am J Med* 1997;**103**:2–99.

63. Johnston CC Jr, Bjarnason NH, Cohen FJ, Shah A, Lindsay R, Mitlak BH, *et al*. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women: three-year data from 2 double-blind, randomized, placebo-controlled trials. *Arch Intern Med* 2000;**160**:3444–50.

64. Lees B, Stevenson JC. The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17 beta and dydrogesterone. *Osteoporos Int* 2001;**12**:251–8.

65. Lindsay R, Tohme JF. Estrogen treatment of patients with established postmenopausal osteoporosis. *Obstet Gynecol* 1990;**76**:290–5.

66. McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J, Weinstein RS, *et al*. Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. *Ann Intern Med* 1998;**128**:253–61.

67. Meunier PJ, Confavreux E, Tupinon I, Hardouin C, Delmas PD, Balena R. Prevention of early postmenopausal bone loss with cyclical etidronate therapy (a double-blind, placebo-controlled study and 1-year follow-up). *J Clin Endocrinol Metab* 1997;**82**:2784–91.

68. Mortensen L, Charles P, Bekker P. J, Digennaro J, Johnston CC Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab* 1998;**83**:396–402.

69. Orr-Walker BJ, Evans MC, Clearwater JM, Horne A, Grey AB, Reid IR. Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women. *Arch Intern Med* 2000;**160**:2161–6.

70. Pouilles JM, Tremollieres F, Roux C, Sebert JL, Alexandre C, Goldberg D, *et al*. Effects of cyclical etidronate therapy on bone loss in early postmenopausal women who are not undergoing hormonal replacement therapy. *Osteoporos Int* 1997;**7**:213–18.

71. Ravn P, Bidstrup M, Wasnich RD, Davis JW, McClung MR, Balske A, *et al*. Alendronate and estrogen–progestin in the long-term prevention of bone loss: four-year results from the Early Postmenopausal Intervention Cohort study. A randomized, controlled trial. *Ann Intern Med* 1999;**131**:935–42.

72. Recker RR, Davies KM, Dowd RM, Heaney RP. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. *Ann Intern Med* 1999;**130**:897–904.

73. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Effect of calcium supplementation on bone loss in postmenopausal women. *N Engl J Med* 1993;**328**:460–4.

74. Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ III. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *J Bone Miner Res* 1998;**13**:168–74.

75. Weiss SR, Ellman H, Dolker M. A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. Transdermal Estradiol Investigator Group. *Obstet Gynecol* 1999;**94**:330–6.

76. Gillespie WJ, Avenell A, Henry DA, O'Connell DL, Robertson J. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *The Cochrane Library* 2001;**2**:2ROM.

77. 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. *British Journal of Obstetrics and Gynaecology* 1988; **95**:3–16.

78. Berlin JA. Does blinding of readers affect the results of meta-analyses? *Lancet* 1997;**350**:185–6.

79. 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.

80. Windeler J, Lange S. Events per person year – a dubious concept. *BMJ* 1995;**310**:454–6.

81. Ross PD, Davis JW, Epstein RS, Wasnich RD. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. *Ann Intern Med* 1991;**14**:919–23.

82. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res* 1999;**4**:821–8.

83. 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.

84. Bjarnason NH, Christiansen C. Early response in biochemical markers predicts long-term response in bone mass during hormone replacement therapy in early postmenopausal women. *Bone* 2000;**26**:561–9.

85. Cheng S, Sipila S, Puolakka H, Suominen H. Effects of hormone replacement therapy and high impact physical activity on bone/muscle ratio in postmenopausal women. *Osteoporos Int* 2000; **11**(Suppl 2):175.

86. 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, von Herrath D, editors. *Vitamin D. Chemical, biochemical and clinical update*. Berlin: Walter de Gruyter; 1985. pp. 1004–5.

87. Gallagher JC, Riggs BL, Recker RR, Goldgar D. The effect of calcitriol on patients with postmenopausal osteoporosis with special reference to fracture frequency. *Proceedings of the Society for Experimental Biology and Medicine* 1989;**191**:287–92.

88. Herrington DM, Reboussin DM, Broshnihan KB, Sharp PC, Shumaker SA, Snyder TE, *et al*. Effects of estrogen replacement on the progression of coronary artery atherosclerosis. *N Engl J Med* 2000;**343**:522–9.

89. Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, Doody R, *et al*. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000;**283**:1007–15.

90. Nachtigall LE, Nachtigall RH, Beckman M. Estrogen replacement therapy I: a 10-year prospective study in the relationship to osteoporosis. *Obstet Gynecol* 1979;**53**:277–81.

91. Writing Group for the PEPI Trial. Effect of hormone therapy on bone mineral density. *JAMA* 1996;**276**:1389–96.

92. Strickler R, Stovall DW, Merritt D, Shen W, Wong M, Silfen SL. Raloxifene and estrogen effects on quality of life in healthy postmenopausal women: a placebo-controlled randomized trial. *Obstet Gynecol* 2000;**96**:359–65.

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. Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, *et al*. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002; **87**:4528–35.

95. Bone HG, Downs RW Jr, Tucci JR, Harris ST, Weinstein RS, Licata AA, *et al*. Dose–response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. *J Clin Endocrinol Metab* 1997;**82**:265–74.

96. 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 Medica Italiana – Archivio per le Scienze Mediche* 1998;**157**:105–9.

97. Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. *Int J Clin Pract* 2001;**55**:505–9.

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. Fracture Intervention Trial Research Group. *Lancet* 1996;**348**:1535–41.

99. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Conner 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. 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. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995;**333**:1437–43.

101. 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.

102. 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. Foxamax International Trial Study Group. *Osteoporos Int* 1999;**9**:461–8.

103. Rossini M, Gatti D, Zamberlan N, Braga V, Dorizzi R, Adami S. Long-term effects of a treatment course with oral alendronate of postmenopausal osteoporosis. *J Bone Miner Res* 1994;**9**:1833–7.

104. Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, *et al*. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. *J Clin Endocrinol Metab* 2000;**85**:3109–15.

105. Tucci JR, Tonino RP, Emkey RD, Peverly CA, Kher U, Santora AC. Effect of three years of oral alendronate treatment in postmenopausal women with osteoporosis. *Am J Med* 1996;**101**:488–501.

106. Nevitt MC, Thompson DE, Black DM, Rubin SR, Ensrud K, Yates AJ, Cummings SR. Effect of alendronate on limited-activity days and bed-disability days caused by back pain in postmenopausal women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Arch Intern Med* 2000;**160**:77–85.

107. Hosking D, Chilvers CE, Christiansen C, Ravn P, Wasnich R, Ross P, *et al*. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med* 1998;**338**:485–92.

108. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, *et al*. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 2002;**23**:508–16.

109. 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.

110. Watts N, Freedholm D, Daifotis A. The clinical tolerability profile of alendronate. *Int J Clin Pract Suppl* 1999;**101**:51–61.

111. Marcus R, Wong M, Heath H III, Stock JL. Antiresorptive treatment of postmenopausal osteoporosis: comparison of study designs and outcomes in large clinical trials with fracture as an endpoint. *Endocr Rev* 2002;**23**:16–37.

112. 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.

113. MacKay FJ, Wilton LV, Pearce GL, Freemantle SN, Mann RD. United Kingdom experience with alendronate and oesophageal reactions. *Br J Gen Pract* 1998;**48**:1161–62.

114. Donahue JG, Chan KA, Andrade SE, Beck A, Boles M, Buist DS, *et al*. Gastric and duodenal safety of daily alendronate. *Arch Intern Med* 2002;**162**:936–42.

115. Greenspan SL, Bone G III, Schnitzer TJ, Watts NB, Adami S, Foldes AJ, *et al*. Two-year

results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res* 2002;**17**:1988–96.

116. Buist DS, LaCroix AZ, Black DM, Harris F, Blank J, Ensrud K, *et al*. Inclusion of older women in randomized clinical trials: factors associated with taking study medication in the fracture intervention trial. *J Am Geriatr Soc* 2000;**48**:1126–31.

117. 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**(Suppl 2):46.

118. Ishida Y, Soh H, Tsuchida M, Kawahara S, Murata H. Comparison of the effectiveness of hormone replacement therapy, bisphosphonate, calcitonin, vitamin D, and vitamin K in postmenopausal osteoporosis: a one-year prospective, randomized, controlled trial. *Bone* 2001;**28**:S224.

119. Iwamoto J, Takeda T, Ichimura S. Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate. *J Orthop Sci* 2001;**6**:487–92.

120. 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 Rheumatol* 1997;**16**:354–60.

121. 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.

122. 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.

123. 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.

124. 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.

125. Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. *Am J Med* 1998;**104**:219–26.

126. 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.

127. 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.

128. Storm T, Kollerup G, Thamsborg G, Genant HK, Sorensen OH. Five years of clinical experience with intermittent cyclical etidronate for postmenopausal osteoporosis. *J Rheumatol* 1996; **23**:1560–4.

129. Wimalawansa SJ. Combined therapy with estrogen and etidronate has an additive effect on bone mineral density in the hip and vertebrae: four-year randomized study. *Am J Med* 1995;**99**:36–42.

130. Cranney A, Guyatt G, Krolicki N, Welch V, Griffith L, Adachi JD, *et al*., Osteoporosis Research Advisory Group. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 2001;**12**:140–51.

131. 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.

132. 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. Vertebral Efficacy With Risedronate Therapy (VERT) study group. *JAMA* 1999;**282**:1344–52.

133. 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.

134. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, *et al*., Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001;**344**:333–40.

135. 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. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int* 2000;**11**:83–91.

136. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, *et al*. The efficacy and tolerability of risedronate once a week for the

treatment of postmenopausal osteoporosis. *Calcif Tissue Int* 2002;**71**:103–11.

137. Lufkin EG, Whitaker MD, Nickelsen T, Argueta R, Caplan RH, Knickerbocker RK, Riggs BL. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res* 1998;**13**:1747–54.

138. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, *et al*. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) investigators. *JAMA* 1999; **282**:637–45.

139. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, *et al*. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002;**87**:3609–17.

140. Chapurlat RD, Ewing SK, Bauer DC, Cummings SR. Influence of smoking on the antiosteoporotic efficacy of raloxifene. *J Clin Endocrinol Metab* 2001;**86**:4178–82.

141. Delmas PD, Mitlak BH, Christiansen C. Effects of raloxifene in postmenopausal women. *N Engl J Med* 1998;**338**:1313–14.

142. Davies GC, Huster WJ, Lu Y, Plouffe L, Lakshmanan M. Adverse effects reported by postmenopausal women in controlled trials with raloxifene. *Obstet Gynecol* 1999;**93**:558–65.

143. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, *et al*. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. *Breast Cancer Res Treat* 2001;**65**:124–34.

144. Walsh BW, Kuller LH, Wild RA, Paul S, Farmer M, Lawrence JB, *et al*. Effects of raloxifene on serum lipis and coagulation factors in healthy postmenopausal women. *JAMA* 1998;**279**:1445–51.

145. 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. Multiple Outcomes of Raloxifene Evaluation. *JAMA* 1999;**281**:2189–97.

146. Khovidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. *Ann Intern Med* 1999;**130**:431–9.

147. Kayser J, Ettinger B, Pressman A. Postmenopausal hormonal support: discontinuation of raloxifene versus estrogen. *Menopause* 2001;**8**:328–32.

148. Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, Lindsay R. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 2001;**16**:925–31.

149. Fujita T, Inoue T, Morii H, Morita R, Norimatsu H, Orimo H, *et al*. Effect of an intermittent weekly dose of human parathyroid hormone (1-34) on osteoporosis: a randomized double-masked prospective study using three dose levels. *Osteoporos Int* 1999;**9**:296–306.

150. Minshall ME, Silverman SL, Shen W, Xie S. The impact of incident vertebral and non-vertebral fractures on health related quality of life (HRQOL) in established postmenopausal osteoporosis: results from the rhPTH(1-34) randomized, placebo-controlled trial in postmenopausal women. *J Bone Miner Res* 2001;**16**:S541.

151. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, *et al*. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;**344**:1434–41.

152. Reeve J, Mitchell A, Tellez M, Hulme P, Green JR, Wardley-Smith B, Mitchell R. Treatment with parathyroid peptides and estrogen replacement for severe postmenopausal vertebral osteoporosis: prediction of long-term responses in spine and femur. *J Bone Miner Metab* 2001;**19**:102–14.

153. Crandall C. Parathyroid hormone for treatment of osteoporosis. *Arch Intern Med* 2002;**162**:2297–309.

154. Pfeifer M, Begerow B, Minne HW, Schlotthauer T, Pospeschill M, Scholz M, Lazarescu AD. Vitamin D status, trunk muscle strength, body sway, falls, and fractures among 237 postmenopausal women with osteoporosis. *Exp Clin Endocrinol Diabetes* 2001; **109**:87–92.

155. Dechant KL, Goa KL. Calcitriol. A review of its use in the treatment of postmenopausal osteoporosis and its potential in corticosteroid-induced osteoporosis. *Drugs Aging* 1994;**5**:300–17.

156. Royal College of Physicians. *Osteoporosis. Clinical guidelines for prevention and treatment*. London: Royal College of Physicians of London; 1999.

157. McNagny SE. Prescribing hormone replacement therapy for menopausal symptoms. *Ann Intern Med* 1999;**131**:605–16.

158. Orimo H, Shiraki M, Hayashi T, Nakamura T. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D_3. *Bone and Mineral* 1987;**3**:47–52.

159. Recker RR, Hinders S, Davies KM, Heaney RP, Stegman MR, Lappe JM, Kimmel DB. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* 1996;**11**:1961–6.

160. Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992; **326**:357–62.

161. Tilyard MW. 1,25-Dihydroxyvitamin D_3 (calcitriol) in the treatment of postmenopausal osteoporosis. In Cohn DV, Gennari C, Tashjien AH Jr. editors. *Calcium regulating hormones and bone metabolism: basic and clinical aspects*. Vol. II. Amsterdam; Excerpta Medica; 1992. pp. 395–9.

162. Komulainen MH, Kroger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, Saarikoski S. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. *Maturitas* 1998;**31**:45–54.

163. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med* 1995;**98**:331–5.

164. Curhan G, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplementary calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med* 1997;**126**:497–504.

165. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994;**308**:1081–2.

166. Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, *et al*. Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the decalyos II study. *Osteoporos Int* 2002;**13**:257–64.

167. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999;**69**:842–56.

168. Aloia JF, Vaswani A, Ellis K, Yuen K, Cohn SH. A model for involutional bone loss. *J Lab Clin Med* 1985;**106**:630–7.

169. Arthur RS, Piraino B, Candib D, Cooperstein L, Chen T, West C, Puschett J. Effect of low-dose calcitriol and calcium therapy on bone histomorphometry and urinary calcium excretion in osteopenic women. *Mineral and Electrolyte Metabolism* 1990;**16**:385–90.

170. 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.

171. 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.

172. Ott SM, Chesnut, CH III. Calcitriol treatment is not effective in postmenopausal osteoporosis. *Ann Intern Med* 1989;**110**:267–74.

173. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, *et al*. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;**117**:1–9.

174. Zarcone R, Carfora E, Sergio F, Bellini P, Longo M, Tartaglia E, Tomasillo G. [Estrogen therapy in women with postmenopausal osteoporosis] [in Italian]. *Minerva Ginecol* 1997; **49**:355–9.

175. Davies KM, Recker RR, Heaney RP. Revisable criteria for vertebral deformity. *Osteoporos Int* 1993;**3**:265–70.

176. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001;**285**:2891–7.

177. Bjarnason NH, Byrjalsen I, Hassager C, Haarbo J, Christiansen C. Low doses of estradiol in combination with gestodene to prevent early postmenopausal bone loss. *Am J Obstet Gynecol* 2000;**183**:550–60.

178. Cauley JA, Black DM, Barrett-Connor E, Harris F, Shields K, Applegate W, Cummings SR. Effects of hormone replacement therapy on clinical fractures and height loss: the Heart and Estrogen/Progestin Replacement Study (HERS). *Am J Med* 2001; **110**:442–50.

179. Mosekilde L, Beck-Nielsen H, Sorensen OH, Nielsen SP, Charles P, Vestergaard P, *et al*. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women – results of the Danish Osteoporosis Prevention Study. *Maturitas* 2000;**36**:181–93.

180. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–33.

181. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA, HERS Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy. Results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA* 2002; **287**:591–7.

182. Grady D, Cummings SR. Postmenopausal hormone therapy for prevention of fractures: how good is the evidence? *JAMA* 2001;**285**:2909–10.

183. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, *et al*. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;**117**:1016–37.

184. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;**85**:304–13.

185. Barrett-Connor E. Hormone replacement therapy. *BMJ* 1998;**317**:457–61.

186. MacLennan A, Lester S, Moore V. Oral estrogen replacement therapy versus placebo for hot flushes: a systematic review. *Climacteric* 2001; **4**:58–74.

187. Greendale GA, Reboussin BA, Hogan P, Barnabei VM, Shumaker S, Johnson S, Barrett-Connor E. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol* 1998;**92**:982–8.

188. Whooley MA, Grady D, Cauley JA. Postmenopausal estrogen therapy and depressive symptoms in older women. *J Gen Intern Med* 2000;**15**:535–41.

189. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998;**279**:688–95.

190. Burkman RT, Collins JA, Greene RA. Current perspectives on benefits and risks of hormone replacement therapy. *Am J Obstet Gynecol* 2001; **185**:S13–23.

191. Rozenberg S, Vandromme J, Kroll M, Pastijn A, Liebens F. Compliance to hormone replacement therapy. *Int J Fertil Menopaus Stud* 1995; **40** Suppl 1:23–32.

192. Ryan PJ, Harrison R, Blake GM, Fogelman I. Compliance with hormone replacement therapy (HRT) after screening for post menopausal osteoporosis. *British Journal of Obstetrics and Gynaecology* 1992;**99**:325–8.

193. 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.

194. 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.

195. Castelo-Branco C, Figueras F, Sanjuan A, Vicente JJ, Martinez-de-Osaba MJ, Pons F, *et al*. Long-term compliance with estrogen replacement therapy in surgical postmenopausal women: benefits to bone and analysis of factors associated with discontinuation. *Menopause* 1999;**6**:307–11.

196. Doren M, Reuther G, Minne HW, Schneider HPG. Superior compliance and efficacy of continuous combined oral estrogen–progestogen replacement therapy in postmenopausal women. *Am J Obstet Gynecol* 1995;**173**:1446–51.

197. 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.

198. Bravo G, Gauthier P, Roy PM, Payette H, Gaulin P, Harvey M, *et al*. Impact of a 12-month exercise program on the physical and psychological health of osteopenic women. *J Am Geriatr Soc* 1996; **44**:756–62.

199. Winegard K, Papaioannou A, Parkinson W, Ferko N, Adachi JD, McCartney N. Twelve month efficacy of home-based exercise for improving the quality of life of elderly women with symptomatic osteoporosis related vertebral fractures. *J Bone Miner Res* 2001;**16**:S409.

200. McMurdo MET, Mole PA, Paterson CR. Controlled trial of weight bearing exercise in older women in relation to bone density and falls. *BMJ* 1997; **314**:569.

201. Preisinger E, Kerschan SK, Wober C, Kollmitzer J, Ebenbichler G, Hamwi A, *et al*. The effect of calisthenic home exercises on postmenopausal fractures – a long-term observational study. *Maturitas* 2001;**40**:61–7.

202. Sinaki M, Itoi E, Wahner HW, Wollan P, Gelzcer R, Mullan BP, *et al*. Stronger back muscles reduce the incidence of vertebral fractures: a prospective 10 year follow-up of postmenopausal women. *Bone* 2002;**30**:836–41.

203. Preisinger E, Alacamlioglu Y, Pils K, Saradeth T, Schneider B. Therapeutic exercise in the prevention of bone loss. A controlled trial with women after menopause. *Am J Phys Med Rehabil* 1995;**74**:120–3.

204. 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.

205. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, *et al*. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med* 2002;**347**:716–25.

206. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83.

207. 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).

208. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;**13**:322–38.

209. Sox HC, Blatt MA, Higgins MC, Marton KI. *Medical decision making*. Boston, MA: Butterworth-Heinemann; 1998.

210. O'Hagan A. Curve fitting and optimal design for prediction (with discussion). *Journal of the Royal Statistical Society* 1978; Series B:1–42.

211. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost effectiveness in health and medicine*. London: OUP; 1996.

212. National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. Introduction. *Osteoporos Int* 1998;**8**:S7–80.

213. 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. York: University of York; 1999; Discussion Paper No. 169, 1–59.

214. Torgerson DJ, Reid DM. The economics of osteoporosis and its prevention. A review. *Pharmacoeconomics* 1997;**11**:126–38.

215. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;**316**:736–41.

216. Murray C, Walters SJ, Brazier JE. Utility following a fracture in a group of elderly women. *Qual Life Res* 2002;**11**:642.

217. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, Kanis J. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. *J Bone Miner Res* 2000;**15**:1384–92.

218. Dolan P, Torgerson D, Kakarlapudi TK. Health-related quality of life of Colles' fracture patients. *Osteoporos Int* 1999;**9**:196–9.

219. 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** Suppl 2:8–22.

220. Netton A, Curtis L. *Unit costs of health and social care*. Kent: PSSRU; 2002.

221. McClung M. The effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001;**344**:11720–1.

222. van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. *Bone* 2001;**29**:517–22.

223. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 1995;**122**:9–16.

224. Raftery J. NICE: faster access to modern treatments? Analysis of guidance on health technologies. *BMJ* 2001;**323**:1300–3.

225. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993;**8**:1137–48.

226. Liberman UA, Hirsch LJ. Esophagitis and alendronate. *N Engl J Med* 1996;**335**:1069–70.

227. Orimo H, Sugioka Y, Fukunaga M, Muto Y, Hotokebuchi T, Gorai I, *et al*. Diagnostic criteria of primary osteoporosis. *J Bone Miner Metab* 1998; **16**:139–50.

228. Melton LJ III, Lane AW, Cooper C, Eastell R, O'Fallon WM, Riggs BL. Prevalence and incidence of vertebral deformities. *Osteoporos Int* 1993; **3**:113–19.

229. Komulainen M, Kroger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, *et al*. Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D-3 in early postmenopausal women: a population-based 5-year randomized trial. *J Clin Endocrinol Metab* 1999;**84**:546–52.

230. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, *et al*. Vitamin D_3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;**327**:1637–42.

231. Zethraeus N. *Costs and quality of life associated with osteoporosis related fractures – based on a Swedish pilot study*. Report. Stockholm: Centre for Health Economics; 2002.

232. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**280**:605–13.

233. Gabriel SE, Kneeland TS, Melton LJ III, 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.

234. Gold DT. The clinical impact of vertebral fractures: quality of life in women with osteoporosis. *Bone* 1996;**18**:185–9S.

235. Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE, Quine S. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. *BMJ* 2000; **320**:7231–345.

236. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;**35**:1095–108.

237. Fitzpatrick R, Ziebland S, Jenkinson C, Mowat A, Mowat A. A comparison of the sensitivity to change of several health status instruments in rheumatoid arthritis. *J Rheumatol* 1993;**20**:429–36.

238. Brazier J, Deverill M, Green C. A review of the use of health status measures in economic evaluation. *Journal of Health Services Research and Policy* 1999;**4**:174–84.

239. Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, Martin PA. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making* 1993; **13**:89–102.

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

241. Brazier JE, Green C, Kanis JA, Committee of Scientific Advisors, International Osteoporosis Foundation. A systematic review of health state utility values for osteoporosis-related conditions. *Osteoporos Int* 2002;**13**:768–76.

242. Cranney A, Coyle D, Pham BA, Tetroe J, Wells G, Jolly E, Tugwell P. The psychometric properties of patient preferences in osteoporosis. *J Rheumatol* 2001;**28**:132–7.

243. Johnell O, Kanis J, deLaet C, Jonsson B, Zethraeus N, Oden A. Sequential changes in quality of life after osteoporotic fracture. *Osteoporos Int* 2002;**13**:S70.

244. Tosteson AN, Gabriel SE, Grove MR, Moncur MM, Kneeland TS, Melton LJ III. Impact of hip and vertebral fractures on quality-adjusted life years. *Osteoporos Int* 2001;**12**:1042–9.

245. Grann VR, Panageas KS, Whang W, Antman KH, Neugut AI. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. *J Clin Oncol* 1998;**16**:979–85.

246. de Haes J, de Koning HJ, van Oortmarssen GJ, van Agt HME, de Bruyn AE, van der Maas PJ. The impact of a breast cancer screening programme on quality-adjusted life years. *Int J Cancer* 1991; **49**:538–44.

247. Oldridge N, Guyatt G, Jones N, Crowe J, Singer J, Feeny D, *et al*. Effects on quality of life with comprehensive rehabilitation after acute myocardial infarction. *Am J Cardiol* 1991; **67**:1084–9.

248. Tsevat J, Cook EF, Green ML, Matchar DB, Dawson NV, Broste SK, *et al.* Health values of the seriously ill. SUPPORT investigators. *Ann Intern Med* 1995;**122**:514–20.

249. Nease RF Jr, Kneeland T, O'Connor GT, Sumner W, Lumpkins C, Shaw L, *et al*. Variation in patient utilities for outcomes of the management of chronic stable angina. Implications for clinical practice guidelines. Ischemic Heart Disease Patient Outcomes Research Team. *JAMA* 1995;**273**:1185–90.

250. Kuntz KM, Tsevat J, Goldman L, Weinstein MC. Cost-effectiveness of routine coronary angiography after acute myocardial infarction. *Circulation* 1996; **94**:957–65.

251. Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, De Laet C, *et al*. The risk and burden of vertebral fractures in Sweden. *Osteoporos Int* 2004;**15**:20–6.

This version of HTA monograph volume 9, number 22 does not include the 164 pages of appendices. This is to save download time from the HTA website.

The printed version of this monograph also excludes the appendices.

View/download the appendices (662 kbytes).

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine

Dr Jeffrey Aronson
Reader in Clinical Pharmacology, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London

Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University

Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen

Professor Stuart Logan, Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter & Plymouth

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Professor Mark Sculpher, Professor of Health Economics, Centre for Health Economics, Institute for Research in the Social Services, University of York

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Birmingham

Ms Kate Thomas, Deputy Director, Medical Care Research Unit, University of Sheffield

Professor Simon G Thompson, Director, MRC Biostatistics Unit, Institute of Public Health, Cambridge

Ms Sue Ziebland, Senior Research Fellow, Cancer Research UK, University of Oxford

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre

Professor Imti Choonara, Professor in Child Health, University of Nottingham, Derbyshire Children's Hospital

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Stan Kaye, Professor of Medical Oncology, Consultant in Medical Oncology/Drug Development, The Royal Marsden Hospital

Ms Barbara Meredith, Project Manager Clinical Guidelines, Patient Involvement Unit, NICE

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Dr Aileen Clarke, Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, Institute of Community Health Sciences, Queen Mary, University of London

Mr Matthew William Cooke, Senior Clinical Lecturer and Honorary Consultant, Emergency Department, University of Warwick, Coventry & Warwickshire NHS Trust, Division of Health in the Community, Centre for Primary Health Care Studies, Coventry

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of Orthopaedic Surgery, South Tees Hospital NHS Trust

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint

Ms Maryann L. Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Professor James Neilson, Professor of Obstetrics and Gynaecology, Dept of Obstetrics and Gynaecology, University of Liverpool, Liverpool Women's Hospital

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Dr Vimal Sharma, Consultant Psychiatrist & Hon Snr Lecturer, Mental Health Resource Centre, Victoria Central Hospital, Wirrall

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Mary Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry, University Mental Health Group, Royal South Hants Hospital, Southampton

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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